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Systematic Review

Quercetin in Sports and Exercise: A review

JENNIFER A. KURTZ†[1], TRISHA A. VANDUSSELDORP‡[2], BRENT UKEN†[3], and JEFF OTIS‡[1]

[1]Department of Kinesiology and Health, Georgia State University, Atlanta, GA, USA; [2]Bonafide Health, LLC, Harrison, NY, USA; [2]Department of Health and Exercise Sciences, Jacksonville University, Jacksonville, FL, USA; [3]Department of Health Science, Rocky Mountain University, Provo, UT, USA

†Denotes graduate student author, ‡Denotes professional author

ABSTRACT

International Journal of Exercise Science 16(2): 1334-1384, 2023. This paper systematically reviews the latest evidence regarding Quercetin's (Q) effect following exercise performance, aerobic and anaerobic exercise, muscle-damaging bouts and highlights blood biomarkers associated with muscle damage and recovery. Google Scholar, Web of Science, and MedLine (PubMed) searches were conducted through July- December 2021. Peer-reviewed studies that investigated Q as a single ingredient or in combination with other ingredients at dosages of 500 mg - 3000 mg, ranging from 15 min-to-1 h prior to exercise bout or chronic dose (7 days - 8 weeks) of consumption were included. A total of 34 studies met the inclusion criteria for the review. Key results include significant performance improvements in the following: VO2max (*n* = 2), time to exhaustion (*n* = 4 articles), fatigue decrement (*n* = 1 article), muscle damage (*n* = 3 articles), strength, torque velocity, and neuromuscular performance (n = 3 articles), redox potential (*n* = 1 article), repeated sprint performance and oxygen extraction (*n* = 1). Q also caused a change in systemic biomarkers: decrease in creatine kinase (*n* = 2), c-reactive protein (n = 4), lactate dehydrogenase (*n* = 4), inflammatory markers (*n* = 3), lipid peroxidation (*n* = 3) in aerobic and anaerobic performance. Varied findings exist regarding the efficacy of Q supplementation on exercise performance and recovery outcomes. The source of Q, training status of subjects, and exercise protocol performed may contribute to the effectiveness of Q as an antioxidant, anti-inflammatory, or ergogenic agent in exercise.

KEY WORDS: Muscle damage, aerobic performance, anaerobic performance, oxidative stress

INTRODUCTION

Humans produce free radicals as part of normal metabolic processes and exercise. Free radicals (e.g., superoxide, hydroxyl radical, hydrogen peroxide, oxygen singlet, etc.) are reactive molecular species with unpaired electrons that oxidize and cause damage to other substances (e.g., proteins, lipids, DNA, carbohydrates, etc.) (10). Although these free radicals have positive effects in metabolic reactions such as mitochondrial biogenesis and hypertrophy, they are also known to cause negative effects. Such as, if the oxidative damage exists above a specific adaptation threshold for a chronic time, it has been associated with an increase in the

inflammatory response (30, 39, 44, 71), impaired exercise performance (e.g., force production), and induce muscle damage (48, 63, 71, 81, 94, 97), and accelerate fatigue (32, 48, 55, 71, 92, 93). Finding the optimal balance of negative-positive effects between physiological reactive oxygen species (ROS) and increasing adaptations is difficult to determine (7). Substances such as antioxidants help protect the cell from the harmful effects of free radicals.

Antioxidants are substances that may protect cells and provide oxidation-reduction balance from the damage caused by unstable molecules. In addition, they help provide a compatible physiological level of ROS to elicit long-term adaptations (e.g., mitochondrial biogenesis, hypertrophy) (7). Flavonoids are phenolic are antioxidant substances widely found in fruits and vegetables. The previous studies showed that the ingestion of flavonoids reduces the risk of cardiovascular diseases, liver damage, metabolic disorders, gene mutation and induces certain types of diseases such as diabetes (23, 101). These effects are due to the physiological activity of flavonoids in reducing oxidative stress, inhibiting low-density lipoproteins oxidation and platelet aggregation, and acting as vasodilators in blood vessels (10, 23). On the other hand, free radicals are constantly generated, resulting in extensive damage to tissues leading to various disease conditions such as cancer, Alzheimer's, renal diseases, cardiac abnormalities, etc., (23).

Plant-based diets (which contain flavonoids) or nutritional supplementation have grown in popularity to prevent free radical damage (10). Flavonoids have several subclasses: flavonols, flavones, isoflavones, anthocyanidins, and flavonols (10). Medicinal plants with antioxidant properties play a vital function in exhibiting beneficial effects and are employed as an alternative source of medicine to mitigate the disease associated with oxidative stress. Flavonoids have existed over one billion years, exist in a variety of foods (e.g., wine, citrus foods, green leafy vegetables), and possess a wide spectrum of biological activities that might be able to influence processes that are regulated in disease.

Quercetin (Q), a plant pigment, is an antioxidant flavonol belonging to the flavonoid group (10, 86). It is found in foods such as elderberries, citrus fruits, red wine, red onions, hot peppers, apples, berries, kale, and a large amount can be found in buckwheat tea and capers (10, 45, 101). Q is suggested to have antioxidant, anti-inflammatory, and cardioprotective effects, which may help reduce chronic inflammation and oxidative stress. The activity of Q and its protective effects against cardiovascular disorders, cancer, inflammation, oxidation, and anti-viral activities have been extensively documented in animal models (34, 41, 54, 58, 66, 102, 105). Q is an effective and potent free radical scavenger in the flavonoid family, and it is 6.24 times higher than Trolox, which has been used as an antioxidant reference (75, 85, 101). However, the combination of quercetin with metal ions (i.e., vanadium, copper, magnesium, iron, ruthenium, cobalt and cadmium, calcium, and rare earth elements) elicits a higher antioxidant activity (101). Quercetin when employed as an antioxidant becomes oxidized to generate quercetin–quinone (QQ). QQ is toxic because of its ability to arylate protein thiols (85). Protection against QQ may arise from binding with glutathione (GSH), the most abundant thiol (prevents uncontrolled oxidative reactions). In the presence of a low concentration of GSH QQ reaction, the Q quinones may become free to react with other thiol groups (e.g., protein sulfhydryls) and may cause ROS

(13, 85). The potentially toxic effects of QQ species have not yet been proven in humans. Further studies are needed to elucidate these exact mechanisms. The properties and structure of Q as a promising agent inhibit oxidative stress in damaging bouts of exercise. It appears that Q may increase aerobic performance to a greater extent than anaerobic performance. As such, there is an interest in its impact on exercise, especially regarding recovery from damaging bouts of exercise (88).

Structure, Pharmacokinetics, and Bioavailability of Quercetin

The structure of Q is glycosylated (sugar group at the 3-position). Glycosides consist of simple or several sugar groups which is the main compound that contributes to the potential beneficial effects of Q (40). Therefore, it is these glycosylated structures that are most common when assessing the antioxidant properties of Q. The structural composition of Q contains B ring *o*-dihydroxyl groups, 4-oxo group in conjugation with the 2,3-alkene, and 3- and 5-hydroxyl groups. Because of Q's structure, it can act as an antioxidant by donating electrons to stabilize reactive oxygen species (10). Q has served as a more powerful antioxidant than vitamins C and E (86). In different food products, onion-derived Q (containing Q glucoside) revealed a higher bioavailability than apple-derived Q (containing Q rhamnoside and Q galactoside) (85, 86).

Q shows relatively higher bioavailability than other phytochemicals, such as vitamins (carotenoids) and food polyphenols, such as flavonoids, phytoalexins, phenolic acids, indoles, and sulfur-rich compounds (20, 85, 86). Bioavailability is the extent to which absorption occurs. The average daily intake of Q in the diet has been estimated as 5–40 mg/day (85) with plasma concentrations between 0.06 and 7.6 µM (10), although these levels can increase up to 200–500 mg/day in individuals who consume high quantities of fruits and vegetables rich in Q (i.e., apples, onions, tomatoes) (85). However, Q in foods is not present with sugar groups, aglycon, but it is otherwise glycosylated. Q's bioavailability depends on the type of glycosides present in different food sources and food handling. For example, boiling can cause a significant decrease in Q bioavailability (10). Furthermore, storage effects (i.e., shelf life) can also affect Q content in digestion and absorption. High levels of ultraviolet-B rays (location grown) can also affect the flavanol content of Q. Thus, Q content varies with aglycons, geography, type, storage, boiling, and freezing (10, 31, 78).

The biochemical explanation for the higher bioavailability of Q glycosides (e.g., onion-derived than apple-derived Q) probably resides in either de-glycosylation processes at the intestinal level and/or carrier-mediated transport (40, 85). The biological activity of Q found in food is diminished during small-intestinal and hepatic metabolism (52) resulting in decreased potency after absorption into the blood compartment. In the small intestine, Q is conjugated to sugar molecules to form Q-glucuronides and can be further glucuronidated, sulfated, or methylated in the liver (73). However, the metabolism and bioavailability of Q are believed to substantially lower its bioactivity in vivo (72). Q glucosides can pass through the epithelial cell layer, but they have a lower efficiency than the Qaglycone (10). Therefore, the hydrolysis of the

glucoside to the aglycone accelerates the absorption of Q. Q absorption depends on the variety and position of the sugar groups attached.

After absorption, Q is metabolized in different organs, such as the small intestines, colon, liver, and kidney. Then, the molecule is conjugated to methyl and sulfate groups and glucuronic acid to generate its major conjugates in humans: 30-O-methyl Q (isorhamnetin), Q -3-O-glucuronide, 30-O-methyl Q -3-O-glucuronide, and Q -30-O-sulfate (43). According to some research, neither glycosides of Q nor free aglycone are present in plasma (95). The bioavailability of Q may be increased by incorporating conjugates, which further enhance its activity (i.e., antioxidant). However, it has been proposed Q does not necessarily need to be absorbed to exert an effect (10). The beneficial effects of Q in humans are largely dependent on its bioavailability after administration.

Q's dietary intake with other compounds' ingestion has been further examined, but little research exists on how this affects q Q's bioavailability. For example, Q combined with 30 mg of epigallocatechin 3-gallate (EGCG) from green tea extract, 100 mg of isoquercetin, and 100 mg of N3- PUFA (55 mg of EPA and 45 mg DHA) from fish oil in trained cyclists for two weeks improved Q bioavailability and extended its bioactive effects, as determined by experiments conducted by Quercegen Pharma (69). In addition, the absorption of Q is also influenced by gut microflora, which, in rats, converts more than 95% of the Q -40-glucoside to phenolic acids (85). As a result of its absorption and metabolism, total Q derived from the diet is present in plasma at the nanomolar range (< 100 nM) but can be increased to micromolar concentrations after supplementation (1 g, 28 days) (18, 85). These variations can be explained by evoking the different bioavailability of Q glycosides present in different foods and the polymorphism of intestinal enzymes in humans compared to animals (85). Q can be detected in plasma within 15–30 min of ingestion of a 250 or 500 mg Q chew preparation, reaching a peak concentration at approximately 120–180 min and returning to baseline levels at 24 h (9). Further, Q has a peak bioavailability time of 12 to 19 h (57). Q's bioavailability is largely dependent on co-ingestion with other nutrients, gut microbiota, and glycosides.

Q's half-life provides useful information serving as an antioxidant and anti-inflammatory in exercise. The half-lives of the molecule and its metabolites range between 11 and 28 h, which suggests the possibility of significantly increased plasma concentrations upon continuous supplementation (8, 9, 85). The plasma half-life of Q is 6–12 hr, and peak concentration has occurred in 1–3 hours (29). However, there does not appear to be a toxicity threshold and absorption rates from high dosages (> 3.5 g/day) of Q. With limited evidence existing in humans, Q and Q metabolites are widely distributed in rat tissues with the highest concentrations in the lung (3.98 and15.3 nmol/g tissue for 0.1% and 1% Q diet, respectively). Further studies are needed to elucidate the effects of Q degree and rate of absorption with varying dosages and forms.

Quercetin Toxicity and Safety

The International Agency for Research on Cancer stated that Q is not classifiable as carcinogenic to humans. Human studies have failed to show any adverse effects associated with the oral administration of Q in a single dose of up to 4 g (85)or after one month of 500 mg twice daily for 4-8 weeks (46, 76, 91). Clinical trials of Q currently recommend a dose of 1400 mg/m2, which corresponds to about 2.5 g for a 70 kg individual, administered via intravenous infusion at 3-week or weekly intervals (103). At higher doses, healthy individuals consumed up to 50 mg/kg (about 3.5 g/70 kg), renal toxicity was detected without signs of nephritis or obstructive uropathy (103). The consumption of Q in high doses (200-500mg, often found in diets rich in fruits and vegetables) is likely safe. However, no longer-term studies to date have been performed in humans. Previously mentioned, there does not appear to be a toxicity threshold from high Q dosages (> 3.5 g/day).

Mechanisms of Action: Quercetin in Exercise

Quercetin and Oxidative Stress

Several investigations have focused on Quercetin to decrease health-related concerns, such as decreasing high levels of oxidative stress and inflammation, and increasing lipid metabolism via transcription proteins, all of which improve sport and exercise. Related studies determined that Q acts as an antioxidant by inducing copper and ferrous iron through catechol in its chemical composition (101). In an animal study with rats, Q inhibited ferrous iron lipid peroxidation by binding ferrous and inhibiting iron overload in alcoholic liver disease (10, 101). Ferrous in compounds containing dihydroquercetin is inactive, unable to catalyze the decomposition of hydrogen peroxide, and thus unable to trigger further generation of free radicals (101).

Further, Q could inhibit oxidative damage by inhibiting lipid peroxidation (i.e., low-density lipoproteins (LDL)) by increasing the expression of LDL-R and reducing the secretion of proprotein convertase subtilisin/Kexin type 9 serine protease, which plays a role in cholesterol metabolism (10, 101). Further, Q combined with liposomes and glycerol nanoparticles could scavenge free radicals and protect human keratinocytes from hydrogen peroxide damage in vitro (59). A high antioxidant capacity of Q *in vivo* largely depends on a high concentration and gradient dependence. Q has been shown to manifest itself in the glutathione pathway to enhance antioxidant capacity (100). When reactive oxygen species are present, superoxide dismutase-2 captures the oxide molecule and converts it into hydrogen peroxide. Plasma glutathione peroxidase catalyzes the degradation of hydrogen peroxide to water molecules, which requires glutathione to provide reducing hydrogen (100). Thus, Q can assist with the glutathione pathway: regulating the levels and increasing glutathione synthesis (100). Increasing the glutathione pathway via Q may assist in antioxidant defense, nutrient metabolism, and regulation of cellular events (e.g., gene expression and protein synthesis). Although only performed in animal and cell studies, Q shows a promising supplement to minimize high levels of ROS through the glutathione pathway and enzyme activities.

Q can increase the expression of antioxidant enzymes, such as acetylcholinesterase and butyrylcholinesterase by the binding of the -OH groups on the side phenyl ring of Q to important amino acid residues at the active site of the two enzymes (100). It was reported that pretreatment with Q significantly enhanced the expression levels of endogenous antioxidant enzymes such as copper/ zinc superoxide dismutase (Cu/Zn SOD), manganese superoxide dismutase (Mn-SOD), catalase (CAT), and glutathione (GSH) peroxidase in the hippocampal CA1 pyramidal neurons of animals suffering from ischemic injury (100). This suggests that Q may be a potential neuroprotective agent for transient ischemia in animals. Further, Q can increase the expression of some antioxidant enzymes, such as glutathione transferase and aldo-ketoreductase, in rat liver (74). Q treatment in rats increased the levels of SOD and CAT and reduced the level of malondialdehyde after lipopolysaccharide-induced endotoxemia., suggesting that Q enhanced the antioxidant defense system (2).

The Q molecule is shown to have a protective effect by upregulating the expression of oxidative stress-related genes: superoxide dismutase-1 (SOD-1), CAT and glutathione synthetase (GSS) in menopausal rat ovaries in vivo and in vitro (98). Further, Q has been shown to activate, inhibit (e.g., p38MAPK/iNOS pathway), upregulate (e.g., SOD, TRAF3, GSH, CAT, Nrf12 or downregulate (e.g., MDA pathway, NIK, and NF-κB including IKK and RelB) many molecules in the antioxidant signaling pathway (101). Q inhibits oxidative stress by regulating the antioxidant defense systems by regulating the balance between oxidant and antioxidant effects. By influencing the signaling transduction pathways, Q may modulate the enzymes or antioxidant substances that enhance antioxidant capacity, preventing oxidative stress in high bouts of exercise. Due to Q's effect by stimulating genes responsible for antioxidative effects, Q may serve to be beneficial during sport and exercise as may assist in anti-inflammatory processes.

Quercetin and Inflammation

Q is confirmed to be a long-acting anti-inflammatory agent in animal and human cells by scavenging free radicals (10, 101). Free radicals can activate transcription factors to upregulate pro-inflammatory cytokines (10). It is validated in the treatment of respiratory and food allergies by inhibiting IL-8 and IL-6 (101). Further, it is shown to exert anti-inflammatory effects on endothelial and monocyte/macrophage systems in vitro (56). In animal models, Q inhibited the production of TNF-α induced by LPS in macrophages (38) and lung A549 cells LPS-induced IL-8 production (37). Furthermore, it has even been shown in glia cells that Q can suppress LPS-induced mRNA levels of TNF-α and interleukin1α: neuronal cell death is also reduced (15). Q can inhibit the enzymes that produce inflammation COX and LOX (69). The activity of COX-2 and iNOS was inhibited by Q by suppressing AP-1, NF-κB, and STAT-1 signaling in cytokine- or LPS-induced HUVECs and macrophages (42, 89). The expression of pro-inflammatory cytokines in calcium ionophore-and PMA-induced mast cells was attenuated by Q. Moreover, the TNF-α-stimulated NF-κB recruitment to proinflammatory gene promoters was also suppressed by Q in murine intestinal epithelial cells (77, 84). The TNF-α- or PMA-induced expression of ICAM-1 in human endothelial cells was decreased by Q (49). The LPS-stimulated

NF-κB and nitrite oxide production was also inhibited by Q in mice. The properties of Q in the inflammation process may assist in repair and recovery after exercise.

Quercetin and Lipid Metabolism

The research on improving lipid metabolism with supplements is surging, especially with plant polyphenols. Q is shown to improve lipid metabolism in animal models by modulating the AMPK/ PPARs signaling pathways via upstream (PI3K) and downstream enzymes (acetyl-CoA carboxylase). AMPK plays a key role in regulating lipid and glucose metabolism. AMPK signaling pathway coordinates glucose metabolism by regulating glycolysis and gluconeogenesis and controls lipid metabolism by acting on fatty acid synthesis and fatty acid oxidation (99). AMPK is shown to suppress the expression of NF-κB by increasing the expression of SIRT1, thereby minimizing the inflammatory response (104). A previous study reported that Q increased the phosphorylation of AMPK in cultured smooth muscle cells and aortic arteries, which also exhibited increased levels of acetyl CoA carboxylase, a downstream protein of AMPK, implicating the increased activity of AMPK following Q administration. Q supplementation has also been shown to increase the upstream proteins of AMPK, namely PI3K and PKB, fatty acid synthesis enzymes, (e.g., acetyl-CoA carboxylase), beta-oxidation enzymes (e.g., carnitine palmitoyltransferase), and peroxisome proliferator-activated receptors (PPARs) (99). Q supplementation in rats also improved the expression of SIRT1 (improves cellular ability to remove ROS and increase mitochondrial biogenesis) (104). Although most research is performed in animal models, Q increase may improve lipid metabolism and oxidation via the expression of AMPK via stimulating PI3K-PKB/AKT kinase activity (99). Current literature states that Q may serve as a lipid metabolism signaling modulator by accelerating lipolysis, fatty acid oxidation, and inhibiting lipid synthesis. Q may have promising effects inhibiting inflammation and oxidative stress by modulating the AMPK/SIRT1 pathway.

The benefits of Q have generally been ascribed to its combination of antioxidant and anti-inflammatory activity which may help increase exercise performance. It appears Q shows more of a health benefit (decreasing blood pressure, inflammation, and oxidative stress) in clinical populations (14, 45, 80, 101), but future research is warranted investigating its oxidative, anti-inflammatory, and recovery effects in exercise. Due to Q's ability to modulate antioxidative systems and inhibit the enzymes that produce inflammation, minimal information exists on how Q impacts sport performance and muscle-damaging bouts.

Muscle damage is often seen in eccentric muscle actions, characterized by the lengthening of skeletal muscle while producing force. However, mechanical shear stress produced by the muscle induces disruption of the contractile components and damage to the sarcolemma of muscle tissue followed by a subsequent inflammatory phase and release of free radicals that cause muscle damage (82). Further, muscle damage because of eccentric actions may be characterized by an impaired action potential propagation along the sarcolemma which is responsible for an immediate decrease in muscle function. This is a direct indicator of an impairment in the neuromuscular efficiency and peripheral function and causes eccentric EIMD.

However, since Q is purported to have potent antioxidant and anti-inflammatory properties, this molecule may seem reasonable to attenuate markers of EIMD. While literature is scarce on the impact of Q on anaerobic and muscle damage bouts, more information is known about the effect of Q on oxidative stress.

METHODS

All literature that investigated the effect of Q on aerobic and anaerobic adaptations and performance, muscle damage, and recovery were searched and obtained using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines, with a pre-determined search strategy (64). Articles were identified for inclusion via electronic database literature searches. An initial search was conducted using Google Scholar and PubMed on July 12th, 2021. Subsequent searches of Web of Science and PubMed were conducted, using identical search criteria, to capture the most recent publications available (1999–2021). The final search was conducted on December 1st, 2021 The full search strategy used for both databases by topic is as follows: ((quercetin) AND (aerobic/ endurance); (quercetin) AND (submaximal exercise); (quercetin) AND muscle damage; (quercetin) AND (muscle); (quercetin) AND (recovery); (quercetin) AND (resistance training); (quercetin) AND (oxidative stress) AND (inflammation) OR runner* OR cyclist* OR endurance* OR inflammation* OR *OR oxidative stress* OR athlete*). Asterisks denote truncation. The following exclusions were applied to the searches to narrow the scope of the article lists generated: animal studies, non-exercise specific, subjects with atherosclerosis, diabetes, or other health issues.

Study inclusion and exclusion criteria

Inclusion criteria included 1) the article was written or available in English, 2) peer-reviewed publication status, 3) clear information on the administration of Q, 4) Q supplementation was administered in the form of a capsule, powder, or a beverage with or without other ingredients, 5) the study was conducted on humans, 6) the study had at least two trials (or separate groups of subjects) in which Q was consumed in one trial (or group) and placebo in the other, 6) a test of performance (aerobic, anaerobic, strength, muscle damage or muscle soreness, and/or recovery outcomes. Studies were excluded for the following: 1) animal studies, 2) non-exercise specific, 3) subjects with coronary artery disease, metabolic syndrome, atherosclerosis, diabetes, or other health issues, 4) not published in peer-review journals, 5) if participants were older than 50 years, 6) articles published before 1999

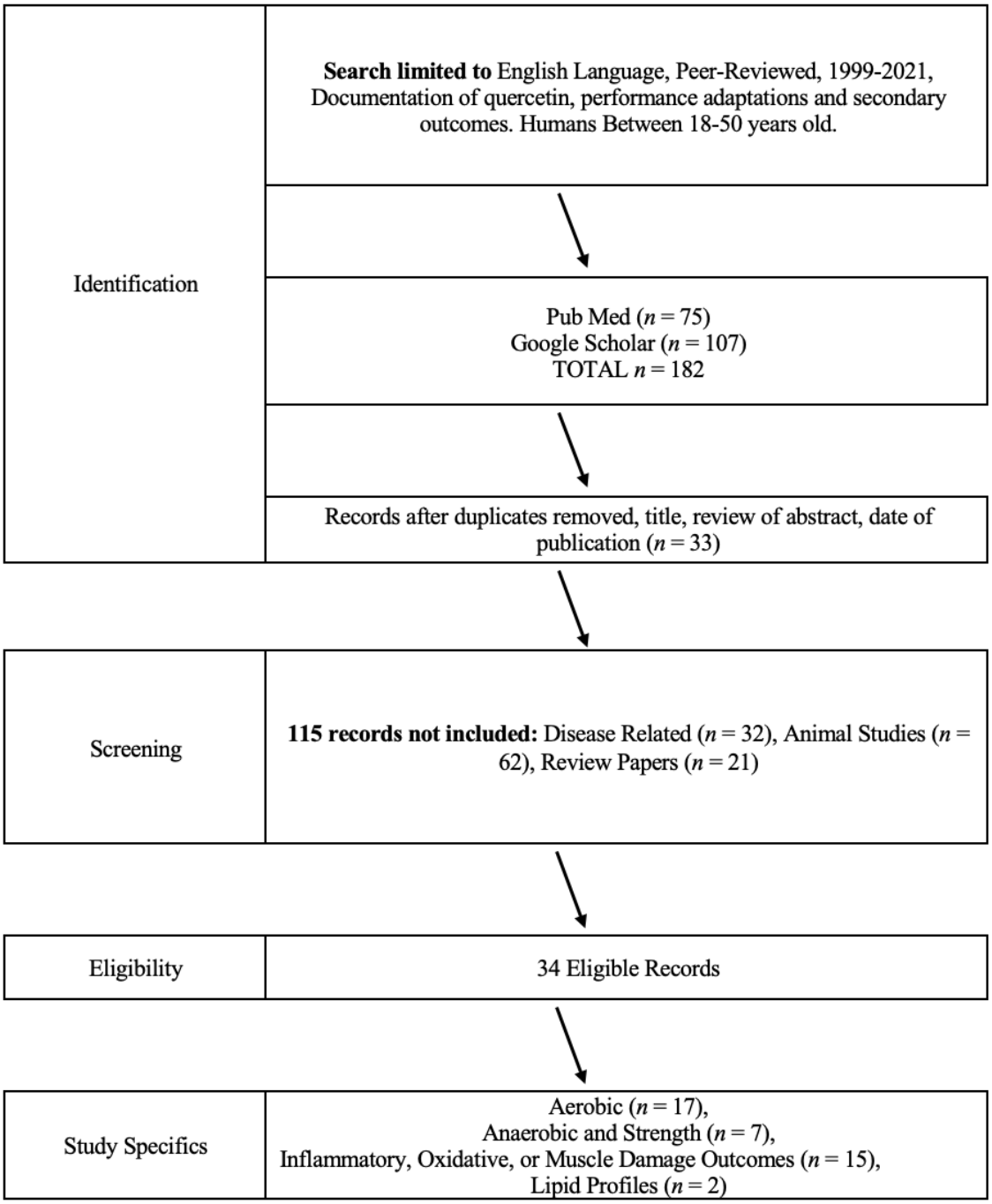
Selection of studies

Articles that met inclusion criteria from each database were compiled using Endnote software. Duplicates were removed, and abstracts were pre-screened for the source type. After identifying all eligible records data were extracted on the following variables: study design, sex, athlete type (i.e., sport, training level, age range), recruitment numbers, study length, training protocols, strength exercise bouts (e.g., eccentric, concentric, isometric) and running/ cycling

performance/secondary outcomes (e.g., LDH, CK, cytokines). Results were synthesized qualitatively.

RESULTS

In total, 182 publications were initially identified by the database searches and review of article reference lists. However, 33 publications were initially excluded based on title, review of the abstract, duplicate results obtained from the different databases, or on the above-mentioned inclusion indices (animal studies, n = 62; review studies, n = 21; human disease, n = 32). Data from the matrix are presented in Figure 1. Results were synthesized qualitatively. 34 publications were thoroughly evaluated. Among the 34 studies included in this review, sex and athlete type were inextricable variables. Among the examined studies, the type of subjects varied: six recruited trained runners (50, 61, 67, 83, 87, 96), five recruited trained cyclists (17, 27, 62, 68, 69), one recruited trained boxers (26), one recruited trained swimmers (22), five recruited recreationally active individuals (1, 8, 9, 19, 33, 36), seven recruited untrained to minimal training experience (16, 24, 28, 35, 60, 70, 72, 79). There were improvements in: aerobic outcomes (mitochondrial genes, $VO2_{max}$, TTE) (24, 70), strength (torque velocity) (8, 9, 79), redox markers (28), repeated sprint performance and oxygen extraction (36), lipid levels (26), lipid peroxidation (28, 61). Eighteen of the 34 studies examined athletes (4-6, 17, 21, 22, 26, 27, 50, 57, 61, 62, 67-69, 83, 87, 96). Of those athlete studies, 4 showed improvement in inflammatory or muscle damage markers (4-6, 69); two showed improvements in aerobic performance (21, 57); one showed improvements in lipid profiles (26) and lipid peroxidation (61). Two studies examined soldiers (11, 90). Seventeen of the studies examined aerobic parameters (e.g., $VO2_{peak}$, race times, TTE, oxidative capacity, etc) (4, 5, 16, 19, 21, 24, 27, 33, 35, 57, 67-70, 83, 87, 96). Seven of the studies measured anaerobic measures (e.g., strength, power, or repeated sprint performance) or muscle damage (1, 8, 9, 28, 36, 60, 72, 79). Fifteen of the 34 studies examined inflammatory, oxidative, or muscle damage outcomes (e.g., CK, LDH, myoglobin, cytokines, lipid peroxidation, etc) (4-6, 8, 9, 17, 28, 50, 60-62, 67, 69, 72, 87). Two athlete studies examined lipid profiles (6, 26) and showed mixed results.



Key Words: quercetin, endurance, anaerobic, aerobic, strength, muscle soreness, muscle damage, recovery, adaptations

Figure 1. Criteria Outline of articles for review.

Aerobic performance results

Eighteen of the 26 aerobic studies investigated athletes. Among the athlete studies, $VO2_{max}$, $VO2_{peak}$, TT, race times (n = 9), lipid metabolism, or oxidative capacity outcomes were mixed: two studies reported improvements in cycling TT performance with Q capsules (1000 mg/, 8 weeks) (21) or Q in a Q cocktail containing other vitamins and minerals (300 mg Q, 6 weeks) (57), eight reported no difference in performance measures (4, 5, 27, 67, 69, 83, 87, 96). Four athlete studies showed a decrease in LDH (500 mg Q with 200 mg vitamin C) (5, 6) and cytokine markers (Q mixture with antioxidants (EGCG and vitamin C) (4, 69), Q 1000 mg + 120 mg EGCG (69), 500 mg Q with 200 mg vitamin C. One study showed improvements in lipid profiles (500 mg Q, 15 minutes prior to exercise) (26) and one study showed improvements in lipid peroxidation. Young female-trained swimmers showed no improvement in aerobic performance (TTE, $VO2_{max}$, lactate, or body fat percentage) (22). Two of the studies had mixed aerobic measurements performed with soldiers had no improvements in performance (11, 90), Table 4. An improvement in mitochondrial biogenesis genes was found in untrained males (1000 mg Q in a beverage form, 2 weeks) (70). There was a reported modest increase in $VO2_{max}$ and ride time to exhaustion in untrained men and women (500 mg of Q twice daily dissolved in sugar-free vitamin-enriched Tang, 7 days) (24). Results are presented in Tables 1, 2, 4.

Table 1. Cycling studies to date and outcomes.

Study	*n*	Participants	Age (yrs.)	Supplementation Protocol	Exercise Protocol	Outcomes
Cheuvront et al. 2009	10	Healthy men	mean (range): age 23 (18–37)	Volunteers drank 30 ml/kg of fluid electrolyte beverage either P (Group P), caffeine (Group C; 9 mg/kg), or Q (Group Q; 2,000 mg) the night before each test	30-min of cycle ergometry at 50% Vo2peak followed by a 15-min performance time trial after receiving either placebo o, caffeine, or Q	Supplementation with caffeine and Q ↑ pre-exercise blood concentrations of caffeine and Q. No treatment effects were observed for any physiological or perceptual measure except for elevated rectal body temperatures. For Group C vs. Groups Q and P. Supplementation did not affect total work performed or the self-selected pacing strategy employed

Chou et al. 2012	13	Trained cyclists	30.1 ± 7.1 y	Supplementation for 28-days with either an antioxidant supplement containing vitamins and Q (Q-VIT: 1000mg Q, 820mg Vitamin C, 40mg Vitamin B3) or the same vitamin supplement without Q (VIT: 820mg Vitamin C, 40mg Vitamin B3)	Subjects completed a simulated time trial on a cycle ergometer	Q-VIT compared to VIT did not affect post-exercise plasma IL- 6, CRP, and IL-10. There was a trend that Q-VIT lowered plasma CRP compared to VIT
Cureton et al., 2009	30	Recreationally active, but not endurance-trained, young men		Q ingested a sports hydration beverage four times daily, with the morning, midday, and evening meals, and prior to sleep, containing carbohydrate (sucrose and maltodextrins), NaCl, vitamins (niacin, B6, B12), citric acid, a gel-forming additive, and Q (1,000 mg/day), whereas untreated participants in group P ingested the same beverage without Q. Participants remained on the treatment for 9–16 days, beginning immediately after the pretests and continuing until all the posttests were administered	Performance was measured on a 10-min cycling test in which participants performed as much work as possible, following 1 h of cycling at a moderate intensity	Pretreatment-to-posttreatment changes in phosphocreatine recovery time constant, $VO2_{peak}$, substrate utilization, and perception of effort during submaximal exercise, total work done during the 10-min maximal effort cycling trial, and voluntary and electrically evoked strength loss were not significantly different

Daneshvar et al. 2013	26	Male athlete badminton players	Q, *n* = 14 (17.5 ± 2.0); *P*, n = 12 (17 ± 1.5)	Q (1000 mg) or P (1000 mg dextrose) at two capsules per day for two months	At pre- and post-supplementation protocol, all participants performed a cycling graded exercise test (GTX) to determine $VO2_{peak}$ and TTE	Lactate concentration, body fat percentage, and $VO2_{max}$ did not show any significant difference after eight weeks of supplementation with placebo and Q between two groups and within one group. There was a significant ↑ in TTE after intervention in the Q group
Davis et al., 2009- In combination	12	7 men and 5 women untrained student volunteers	22.9 ± 2.4	500 mg of Q twice daily dissolved in sugar-free vitamin-enriched Tang or (b) a nondistinguishable placebo (Tang). Treatments were administered for 7 days	Baseline $VO2_{max}$ and bike-ride times to fatigue were established. After treatment, both $VO2_{max}$ and ride time to fatigue were determined	Seven days of Q feedings were associated with a modest ↑ in $VO2_{max}$ along with a substantial increase in ride time to fatigue
Dumke et al. 2009	40	Trained male cyclists	Q, (*n* = 20) 26.1±1.8; P, (*n* = 20) 29.1±2.4	3 weeks of Q (1000 mg/day–1) or P supplements prior to and during the 3-day period of intensified exercise	Subjects cycled for 3 hr at ~57% watts max each of these	No Q treatment effect was observed for any of the outcome measures in this study

MacRae & Mefferd, 2006 - In Combination	12	Elite male cyclists		6 wk of FRS (300 mg) versus FRS FRS-Q (300 mL, 2 × per day one drink in the morning with a meal, and one in the afternoon or evening with a meal). Each serving of FRS and FRS-Q contained green tea extract (300 mg), vitamin C (150 mg), vitamin E (50 mg), caffeine (45 mg), niacin (25 mg), taurine (9 mg), vitamin B-6 (2.5 mg), vitamin B-2 (2.1 mg), vitamin B-1 (1.9 mg), and vitamin B-12 (0.008 mg)	29.82 km cycling TT performance after 6 wks of a free radical scavenger cocktail containing Q (FRS) versus FRS minus Q (FRS-Q)	30 km TT was ↑ by 3.1% on an antioxidant supplement (FRS) compared to baseline. Absolute and relative (%HRmax) heart rates and percent $VO2_{max}$ were not different between trials, but average and relative power (% peak power) was higher on FRS
McAnulty et al., 2008	40	Male trained cyclists	Q (26.1 ± 1.8), *P* (29.1± 2.4)	3 weeks of Q (1000 mg/day–1) or P supplements prior to and during the 3-day period of intensified exercise	Subjects cycled for 3 hr at ~57% watts max each of these	Chronic Q ingestion did not affect inflammatory or oxidative stress markers in trained individuals
Nieman et al., 2007 b.	40	Male trained cyclists	26.1 ± 1.8 (Q, *n* = 20); 29.1 ± 2.4 (*P*, *n* = 20)	Subjects received Q (1000 mg/d) or P supplements for 3 wk before, during, and 2 wk after the 3-d period of intensified exercise	Subjects came to the lab for three consecutive days after the 3-wk Q or placebo supplementation period. Subjects cycled for 3 h at approximately ~57% Wmax or 57% of the maximal watts attained during graded maximal protocol	Q did not alter exercise-induced changes in several measures of immune function, but it significantly ↓URTI incidence in cyclists during the 2-wk period after intensified exercise

Nieman et al., 2009 c.	39	Trained male (n = 32) and female (n = 7) cyclists	26.3 ± 1.7 (*P*, *n* = 12); 26.8 ± 2.6 (Q, *n* = 13); 28.1 ± 2.8, (Q–EGCG, *n* = 14);	1000 mg of Q with or without 120 mg of EGCG, 400 mg of isoquercetin, and 400 mg of eicosapentaenoic acid and docosahexaenoic acid (Q–EGCG) on exercise performance. Trained cyclists were randomized to P, Q, or Q–EGCG and ingested supplements in a double-blinded fashion for 2 wk before, during, and 1 wk after a 3-d period	Subjects then came to the laboratory for three consecutive days and cycled from 3:00 to 6:00 p.m. at ~57% Wmax. During the test sessions, experimental subjects cycled using their bicycles on CompuTraineri Pro Model 8001 trainers (RacerMate) with the exercise load set at ~57% Wmax	↑ in plasma Q and Q–EGCG and GOBA in Q–EGCG. Immediately after the third exercise bout, significant ↓ for CRP, and plasma IL-6 and IL-10 were measured in Q–EGCG compared with P. GM-CSF and CRP were ↓ in Q–EGCG 14 h after exercise

↑ = improved performance, ↓ = decreased performance, CRP = c-reactive protein, Q = quercetin, P/PLA = placebo, mg/kg = milligram per kilogram, IL-8/IL-6/IL-10 = interleukin 8, 6, 10, TTE = time to exhaustion, Wmax = Watts per maximum, GTX = graded exercise test, TT = time trial, GOBA = granulocyte oxidative burst activity, GM-CSF = granulocyte-macrophage colony-stimulating factor, EGCG = epigallocatechin 3-gallate, FRS = free radical scavenger cocktail containing Q, FRS-Q = free radical scavenger cocktail minus Q

Table 2. Running studies to date and outcomes.

Study	*n*	Participants	Age (yrs.)	Supplementation Protocol	Exercise Protocol	Outcomes
Askari et al., 2012 - In Combination	56	Male athletes, but not involved in professional sports	21.0 ± 1.6	Subjects were randomly assigned to one of the four groups: 1) Q + vitamin C (500 mg/day Q + 200 mg/day vitamin C), 2) Q (500 mg/day Q + 200 mg/day P), 3) vitamin C (500 mg/day P + 200 mg/day vitamin C), and 4) P (500 mg/day P + 200 mg/day P). Q and its P were ingested after meals daily for 8 weeks before post-testing	Prior to and following the intervention, participants performed a continuous GXT using Bruce protocol to determine TTE. Plasma samples were obtained for the determination of plasma AST and creatine kinase concentrations	Supplementation with Q and vitamin C for 8 weeks did not improve exercise performance but reduced oxidative stress and reduced inflammatory biomarkers, including CRP and IL-,6 with little effect on E-selectin in healthy subjects
Askari et al., 2013 - In Combination	56	Male students having an athletic history of at least 3 years	0.93 ± 1.53, 21.50 ± 2.17, 21.21 ± 1.52, and 20.46 ± 1.18	The first to fourth groups received a 500 mg supplemental Q capsule plus a 250 mg vitamin C pill, a 500 mg supplemental Q capsule plus a 250 mg P vitamin C pill, a 500 mg P Q capsule plus a 250 mg vitamin C pill, and a 500 mg P Q capsule plus a 250 mg P vitamin C pill, daily for 8 weeks	An exercise test was performed for all participants using the Bruce protocol and HP cosmos treadmill to evaluate performance indices. VO2max and the distance covered were measured by a gas analyzer	Significant differences in LDH, $VO2_{max}$, TEE, TBW, and LBM among the Q and vitamin C groups. $VO2_{max}$ ↑ in the "Q" and "Q + vitamin C" groups following the intervention, non-significantly. No differences between "Q + vitamin C" and Q alone. LBM, total body water, BMR, and total energy expenditure ↑ significantly in the Q group after intervention

Askari et al., 2013 - In Combination	56	Male athletes, but not involved in professional sports	21.0 ± 1.6	Subjects were randomly assigned to one of the four groups: 1) Q + vitamin C (500 mg/day Q + 200 mg/day vitamin C) 2) Q (500 mg/day Q + 200 mg/day P) 3) vitamin C (500 mg/day vitamin C + 200 mg/day P) and 4) P (500 mg/day P + 200 mg/day P daily for 8 weeks	Intensive exercising (no specifics were mentioned)	LDL values ↓ significantly in the "Q + Vit C" group but decrease was not considerable in other groups before and after intervention and among groups
Freese et al., 2019	9	Recreationally active men	Q = 22.0 ± 3.2; *P* = 20.8 ± 0.8	Participants in the experimental group ingested four individually wrapped chews (weeks 4-11) (two with breakfast, two with dinner). Each chew contained 250 mg Q, Vitamin C, Vitamin B3, and folic acid for an 8-week treatment period. Total Q consumption for the experimental group was 1000 mg/day. During the first 3 and last 3 weeks, no Q supplementation was administered	Participants performed a graded treadmill running test to measure $VO2_{peak}$ each week (14-weeks, except for week 8)	$VO2_{peak}$ or physical work capacity did not change throughout the 14 weeks in non-endurance trained men and women

Ganio et al., 2010 - In combination	11 participants (5 males, 6 females)	Untrained, sedentary individuals	19.8 + 3.8	1000 mg/ day with Q for 5 days with a food bar with no Q added (P). Participants ingested two assigned bars after baseline testing (Day 1) and on the five subsequent mornings, Days 2–6 prior to a $VO2_{max}$ test	Participants repeated baseline $VO2_{max}$ testing on day 6, then completed a 22-day ''washout'' period (Days 7–28) prior to other supplement	5 days of Q supplementation did not influence $VO2_{max}$ or related variables (respiratory rate, blood lactate, RER, HR, RPE, tidal volume, respiratory rate, expired volume, rating of perceived muscle pain) in sedentary men and women
Konrad et al. 2011	20	20 runners	11 men, 9 women, age 38.4 ± 2.1 yr	Q-based chews or P 15 min were consumed before the runs. The 4 Q-chews provided 1,000 mg Q, 120 mg epigallocatechin 3-gallate, 400 mg isoquercetin, 400 mg each eicosapentaenoic acid and docosahexaenoic acid, 1,000 mg vitamin C, and 40 mg niacinamide	Subjects ran on treadmills at 70–75% $VO2_{max}$ for 2 hr post-ingestion	Plasma Q ↑ from immediately postexercise and 1 hr postexercise after ingestion of Q-chews, compared with no change in PL. Exercise caused significant ↑ in CRP, GM-CSF, IL-10, IL-1β, IL-2, IL-6, IL-8, TNFα, GR-PHAG, and MO-PHAG and ↓ GR-OBA and MO-OBA, but no differences in the pattern of change were measured between Q-chew and PL trials

McAnulty et al. 2013	14	Healthy trained males	26.7 + 5.2	Subjects were initially randomized to either resveratrol plus Q (120 mg resveratrol and 225 mg Q for 6 days and 240 mg resveratrol and 450 mg Q on day 7, just prior to exercise) or P	The exercise testing consisted of a 1-h run at a 3% grade and ~80% *V* $VO2_{max}$	The postexercise increase in F2-isoprostanes was more significant ↓ with resveratrol plus Q (68%) than with P (137%). Protein carbonyls, FRAP, ORAC, TEAC, IL-8, and CRP significantly increased after exercise but were not affected by treatment
Nieman et al., 2007 a.	63	Experienced male and female ultramarathoners from the 2006 160-km WSER	Q, *n* = 198 (44.2 ± 2.0); *P*, *n* = 21 (46.0 ± 2.3)	250 mg or Q or P, 4x/day; 1,000 mg/day total) or Q-free supplements 3 weeks before and during the 160-km WSER. On race day, participants ingested all four chews before the 5 a.m. start time	160-km WSER	↑ increased plasma Q levels but failed to attenuate muscle damage (DOMS), inflammation, increases in plasma cytokine and hormone levels, and alterations in leukocyte cytokine mRNA expression
Nieman et al. 2010	30	Young male adults	20.2 ± 0.4	2 wk of Q supplementation (1000 mg/d) compared with P before or after a 2-week wash-out period. Subjects consumed 16 oz of the supplement beverage at 8:00 a.m. and then again at 1:00 p.m. each day.	Subjects performed a 12-min time trial after a 60-min treadmill exercise preload at 60% V ̇O2max with a 10% treadmill grade	Small but significant ↑ in 12-min treadmill TT performance and modest but insignificant increases in the relative copy number of mitochondrial DNA and messenger RNA levels of four genes related to mitochondrial biogenesis

Quindry et al., 2008	63	Experienced male and female ultramarathoners from the 2006 160-km WSER	Q, *n* = 198 (44.2 ± 2.0); *P*, *n* = 21 (46.0 ± 2.3)	250 mg or P, 4x/day; 1,000 mg/day total) or Q-free supplements 3 weeks before and during the 160-km Western States Endurance Run. On race day, participants ingested all four chews before the 5 a.m. start time	160-km WSER	Q supplementation did not affect race performance nor blood plasma lipid or aqueous-phase antioxidant capacity, or oxidative damage
Scholten et al., 2013	8	Male long-distance runners	Q = 24.0 ± 5.4; *P* = 22.5 ± 3.0	Q (1000 mg/day) or P for 6-weeks prior to exercise	Treatment started after the completion of the first 10 km running TT and continued for 6 weeks through completion of the second $VO2_{peak}$ and 10 km TT	No notable differences in oxidative stress and antioxidant activity (SOD and TAC), protein carbonyl, RPE, heart rate, TT, or $VO2_{peak}$. There was a significant time × supplement interaction for MDA, an indicator of lipid peroxidation
Utter et al., 2009	63	Experienced male and female ultramarathoners from the 2006 160-km WSER	Q, *n* = 198 (44.2 ± 2.0); *P*, *n* = 21 (46.0 ± 2.3)	Q and P groups, and under double-blinded methods, ingested four supplements per day with or without 250 mg Q for 3 weeks before the WSER.	160-km WSER	The pattern of change in RPE over time was not significantly different between the Q and P groups. Race times were not different between the groups

↑ = improved performance, ↓ = decreased performance, CRP = c-reactive protein, Q = quercetin, P/PLA = placebo, mg/kg = milligram per kilogram, IL-2/IL-6/IL-8/IL-10/IL-1β = interleukin 2, 6, 8, 10, 1β, AST = aspartate transaminase TTE = time to exhaustion, LDH = lactate dehydrogenase, GTX = graded exercise test, TT = time trial, TNFα = tumor necrosis factor alpha, GM-CSF = granulocyte-macrophage colony-stimulating factor, GR-PHAG = granulocyte phagocytosis, MO-PHAG = monocyte phagocytosis, GR-OBA = granulocyte oxidative burst activity, FRAP = ferric-reducing ability of plasma, ORAC = oxygen radical absorptive capacity, TEAC = Trolox equivalent antioxidant capacity, LBM = lean body mass, BMR = basal metabolic rate, WSER = Western

States Endurance Run , TAC = total antioxidant capacity , DOMS = delayed onset muscle soreness, SOD = superoxide dismutase, MDA = serum malondialdehyde

Anaerobic performance results

No studies investigated were performed on athletes. Five studies reported an improvement in anaerobic measures: decrease in fatigue decrement (1000 mg Q in a beverage, 1 week) (1); improvement in strength and torque velocity (1000 mg Q 3 hr prior to resistance training bout) (79) (1000 mg Q in capsule form, 14 days) (8, 9); improvement in neuromuscular performance efficiency rate, total volume, and a decrease in maximal voluntary isometric contraction (MVIC) (1000 mg Q 3 hr prior to resistance training bout) (79); decrease in muscle fiber conduction velocity and a decrease in LDH and CK markers (1000 mg in capsule form, 14 days) (8, 9); improved redox status (1000 mg Q in capsule form, 14 days) (28); repeated sprint performance and oxygen extraction (Treatment A: 140 mg of Zynamite®, 140 mg of w, 147.7 mg of maltodextrin, and 420 mg of sunflower lecithin; Treatment B, 140 mg of Zynamite®, 140 mg of Q 1 hr prior to exercise) (36). There was one study that reported no effects on exercise-induced muscle damage or cytokine markers (72). There was one study with a mixture of aerobic performance (10 km) and anaerobic (vertical jump) showing a decrease in muscle pain over the 10-km race, myoglobin and alanine aminotransferase (men only), and accelerates the recovery of performance (loss of jump height and mechanical impulse) from a polyphenol-Q capsule mixture (70 mg of Zynamite® combined with 70 mg of Q, 1 hr prior to the start of the race and every 8 h after the race at lunch, dinner time and in the next morning before the vertical jump test, to a total of 420 mg of Zynamite® combined with 420 mg of Q) (60). Results are presented in Tables 3 and 4.

Table 3. Strength studies to date and outcomes.

Author	*n*	Participants	Age (yrs.)	Supplementation Protocol	Exercise Protocol	Outcomes
Eccentric Studies						
Bazzucchi et al., 2019	12	Young moderately active men	26.1 ± 3.1	Q (1000 mg/day) or P for 14 days in capsule form	A neuromuscular test isokinetic dynamometer was performed pre-post, 24 h, 48 h, 72 h, 96 h and 7 days after an intense eccentric exercise: "maximally during the whole ROM (from 40 to 140°). Each participant completed 10 bouts. The dynamometer was set to an angular velocity of 45 °/s, and participants were instructed to (separated by a 30 s-rest) of 10 maximal lengthening contractions of the elbow flexors. Each eccentric resist maximally during the whole ROM (from 40° to 140°). Each participant completed 10 bouts contraction lasted 2 s followed by 6-s rest. Blood samples were drawn at 48 h, 72 h, 96 h, 7 days during the recovery	Q supplementation significantly ↑ the isometric strength recorded during MVIC compared to baseline. The torque and MFCV decay were recorded during the eccentric exercise ↓ in Q compared to PLA. Immediately after the EIMD, isometric strength, the force-velocity relationship, and MFCV were significantly ↓ when participants were given P rather than Q. Q attenuated the increases in CK and LDH

Bazzuchhi et al., 2020	16	Healthy men	25.9 ± 3.3	Q (1000 mg/day) or P for 14 days in capsule form	A neuromuscular test isokinetic dynamometer was performed post–post, 24 h, 48 h, 72 h, 96 h and 7 days after an intense eccentric exercise: "maximally during the whole ROM (from 40 to 140°). Each participant completed 10 bouts. The dynamometer was set to an angular velocity of 45 °/s, and participants were instructed to (separated by a 30 s-rest) of 10 maximal lengthening contractions of the elbow flexors. Each eccentric resist maximally during the whole ROM (from 40° to 140°). Each participant completed 10 bouts contraction lasted 2 s followed by 6-s rest. Blood samples were drawn at 48 h, 72 h, 96 h, 7 days during the recovery	Q supplementation significantly ↓ the strength loss compared to PLA. The force-velocity relationship and MFCV persisted significantly less during the recovery when participants consumed PLA rather than Q, especially at the highest angular velocities. There was a higher MCFC decay in POST, 24 h, 72 h, 96 h, 7 d in PLA compared to Q. Greater ↑ in biomarkers of damage (CK and LDH) was also evident in PLA with respect to Q. Elbow angle was significantly ↓ both in Q and PLA. Q ↓ the time course of symptoms associated with the inflammatory response of the secondary damage and accelerates the recovery of neuromuscular function

Duranti et al., 2018	14	Healthy young men	25.5 ± 0.8	Q (1000 mg/day) or P for 14 days in capsule form	Subjects underwent eccentric protocol session 14-days after treatment (P or Q). The upper limb [right or left] was randomly assigned to EIMD, completing maximal lengthening contractions at the isokinetic dynamometer. The limb was reversed when the protocol was repeated with the other treatment. The dynamometer was set to an angular velocity of 45°/s, and participants were instructed to resist maximally during the whole ROM (from 50° to 140°). Each participant completed 6 to 10 sets of 10 maximal lengthening contractions of the elbow flexors; each set was separated by 30-seconds rest. Each eccentric contraction lasted 2 seconds and was followed by a 6-	Q significantly reduced erythrocytes lipid peroxidation levels and the susceptibility to hemolysis induced by the free radical generator AAPH, while no differences in antioxidant enzyme activities and glutathione homeostasis were found between the two groups. Q supplementation ↑ redox status as assessed by GSH/GSSG ratio analysis and ↓ TBARs levels both in erythrocytes and plasma

						seconds rest period in which the subject relaxed while the dynamometer arm returned automatically back to 50° of elbow flexion as previously described	
O'Fallon 2012	30	Healthy men and women	Q, *n* = 15 (M = 20.9 ± 1.8, W = 20.6 ± 1.1); *P*, *n* = 15 (M = 19.5 ± 1.1, F= 19.6 ± 1.3)	Subjects then ingested nutrition bars containing 1,000 mg/d Q or PLA for 7 d before and 5 d after the second exercise session, using the opposite arm	Subjects performed two bouts of 24 maximal eccentric contractions of the elbow flexors using a modified preacher-curl bench. Bout 1 was performed in Phase 1; Bout 2 was performed with the contralateral arm in Phase 3. Three isometric strength trials (3 s/trial) with 1-min rest between trials, 12 consecutive isokinetic contractions at 60°/s and 180°/s, muscle soreness, relaxed arm angle, and upper arm circumference were assessed daily	No significant main effects of group or phase on CK between PLA and Q. No significant group, phase, or time effects on these markers of systemic inflammation (IL-6, and Serum CRP) were observed. No effect of Q supplementation on the aforementioned markers of EIMD. Plasma Q ↑ after 7 d of supplementation and remained elevated during the 5-d postexercise recovery period. No differences between treatments were not detected in strength loss, muscle soreness, reduced arm angle, CK elevations, and arm swelling peak

Strength Studies						
Patrizio et al., 2018	10	Healthy trained non-smoker male volunteers	22.1 ± 1.8	Subjects consumed Q (1 g/day) or PLA in capsule form 3 h prior to a resistance training session and 5 days post-exercise	The resistance training session, which consisted of 3 sets of 8 repetitions at 80% of the (1RM) completed bilaterally for eight different resistance exercises	After a single dose of Q, the torque–velocity curve of knee extensors was ↑ and after the resistance exercise. Subjects showed a lower MVIC reduction with a greater rate of torque development and neuromuscular efficiency ratio. The total volume of the resistance exercises was significantly greater in Q compared to PLA. No significant differences were found in blood markers between treatments

↑ = improved performance, ↓ = decreased performance, CRP = c-reactive protein, Q = quercetin, P/PLA = placebo, mg/kg = milligram per kilogram, IL-6 = interleukin 6, PQ = acute paraquat, LDH = lactate dehydrogenase, CK = creatine kinase, MVIC = maximal voluntary isometric contraction, MFCV = mean fiber conduction velocity, EIMD = exercise induced muscle damage, 1RM = one repetition maximum, ROM = range of motion

Table 4. Mixed anaerobic and aerobic studies.

Author	*n*	Participants	Age (yrs.)	Supplementation Protocol	Exercise Protocol	Outcomes
Anaerobic Studies						
Abbey and Rankin 2011	15	Recreationally active, young adult men	23.3 ± 2.6	1 wk supplementation with a P, a 6% carbohydrate commercial sports drink, or that drink with 500 mg of Q-3-glucoside, consumed twice a day (1,000 mg/d)	2 RST, 12 × 30-m maximal-effort sprints, each after 1-week supplementation	Mean sprint time ↑ progressively and was significantly higher for both treatments; there were no significant differences between treatments. % FD for placebo was ↓ with Q. Changes in blood XO, IL-6 showed no difference by treatment. Repeated-sprint performance was not improved by Q supplementation and was worse than with placebo when expressed as %FD. Q showed no effect on indicators of XO activity or IL-6

Gelabert-Rebato et al. 2019	50	Physically active men (*n* = 26) and women (*n* = 24)	M: 23.1 ± 2.2, W: 23.5 ± 2.9	Treatment A, 140 mg of Zynamite®, 140 mg of w, 147.7 mg of maltodextrin, and 420 mg of sunflower lecithin; Treatment B, 140 mg of Zynamite®, 140 mg of Q, and 2126 mg of maltodextrin and Treatment C, 2548 mg of maltodextrin (P) 1 hr prior to exercise.	After a 4.5 min period of unloaded pedaling, they stopped pedaling, and the ergometer was switched to isokinetic mode. At the 5th minute, they performed a WanT (30 s all-out sprint in isokinetic mode at 80 rpm). This was followed by 3.5 min of unloaded pedaling and another 30 s period, during which they stopped pedaling, and the ergometer was switched to the isokinetic mode. At the 4th minute, a second 30 s WanT was performed, followed by another 3.5 min of unloaded pedaling and another 30 s period of rest. A third 30 s WanT was then performed.	↑ repeated-sprint performance and muscle O2 extraction and mitochondrial O2 consumption during ischemia

Anaerobic + Aerobic Studies						
Marcos Martin-Rincon 2020 - In Combination	48	24 women and 33 men, students	M: 23.1 ± 2.5, W: 23.3 ± 3.4	One hr before the start of the 10 km race, subjects ingested the treatment assigned. The P was delivered in the form of two capsules, each containing 364 mg of maltodextrin. The polyphenols were also provided in two capsules, each containing 70 mg of Zynamite® combined with 70 mg of Q in the form of 140 mg of Sophora japonica extract standardized to 50% Q, and 153 mg of maltodextrin. Three additional doses were ingested every 8 h after the race at lunch, dinner time, and in the next morning before the vertical jump test, to a total of 420 mg of Zynamite® combined with 420 mg of Q. Both treatments (polyphenols and placebo) were orally administered in opaque and non-distinguishable methylcellulose capsules ingested with 300 mL of water	To elicit EIMD, subjects participated in a 10 km running competition on the athletic track. At the end of the 10km running bout, they performed 100 drop jumps from a 59 cm step-in height, consisting of 5 sets of 20 repetitions with a 10-s interval between jumps and interspaced by a 2-min recovery period between sets to elicit EIMD	Competition times were similar, polyphenol supplementation attenuated the muscle pain felt after the competition and the loss of jumping performance and mechanical impulse 24 h later. The polyphenols attenuated the increase of serum myoglobin and alanine aminotransferase in men, but not in women. Polyphenol mixture attenuated muscle pain and damage and accelerated the recovery of muscle performance

Mixed Aerobic Studies

Bigeiman et al., 2010	58	Moderately trained men and women (recruited from Army and Air Force Reserve Officers' Training Corps (ROTC) programs)	Q: 22.0 ± 5.1; P: 20.3 ± 1.6	Each participant swallowed four individually wrapped chews daily (two with breakfast, two with dinner) during a 6-week treatment period. Each chew contained 250 mg Q (1000 mg total/day), 100 mg iso-Q, 100 mg omega-3 fatty acids (EPA and DHA]), 30 mg EGCG, a vitamin mixture, sucrose, and other ingredients in a carnauba wax and soy lecithin base	$VO2_{peak}$ during uphill treadmill running, performance on the APFT, BMPU (muscular endurance, WanT (power), and 36.6-m speed test were measured before and after 42-54 days of supplementation, with a minimum of 48 h between each physical test	Q supplementation did not have an ergogenic effect, as assessed using $VO2_{peak}$ and four physical performance measures: (APFT, BMPU, WanT, and a 36.6-m sprint

Sharp et al. 2012	16	Male trained soldiers	22 6 ±3	Soldiers consumed 2 energy bars, each containing 0 mg P or 500 mg of Q (1,000 mg/d) for 8.5 days. Beginning day 6 of supplementation, the soldiers performed the 3 exercise days	The subjects donned a 16-kg weighted vest and walked on a treadmill for 75 minutes. This load is similar to that carried while wearing protective body armor. Loaded treadmill walking was performed in three 25-minute bouts with a 5-minute break between each bout. After completing the treadmill exercise, the volunteers sat quietly for at least 10 minutes. After the rest, volunteers were given a 5-minute warm-up with the cycle ergometer set at 75 W in hyperbolic mode. The cycle ergometer was then placed in linear (pedal rate dependent) mode, and volunteers completed 200 kJ of work at	Significant ↑ in plasma Q after Q supplementation. No differences after P or Q supplementation compared with baseline in$VO2_{peak}$, TT trial, RER, RPE. During Q supplementation, muscle soreness was higher on day 2 compared with day 1, whereas no differences were seen over days for baseline or P testing

					maximal effort	
Other Aerobic Events						
Darvishi et al., 2013	26	Young, trained female swimmers	Q: 16.1 ± 2.5; P: 15.7 ± 1.5	Participants were randomly assigned to one of two groups: Q (1000 mg/day) or P (1000 mg dextrose/ day) for 8 weeks	Prior to and following the supplementation protocol, participants performed a GXT	No effect on $VO2_{max}$, TTE, lactate, or body fat %
Demirci et al., 2017	20	Junior male athletes	18.95 ± 1	Control and experimental group an exercise program of two hours applied to the athletes three times a week for one month	The participants were supplemented with 500 mg Q fifteen minutes before each workout in a one-month boxing training program	↓ in TC and LDL-C and an increase in HDL-C in EG while there was only significant ↑ in HDL-C of in controls

↑ = improved performance, ↓ = decreased performance, CRP = c-reactive protein, Q = quercetin, P/PLA = placebo, mg/kg = milligram per kilogram, IL-6/IL-8/IL-10 = interleukin, TT = time trial, TTE = time to exhaustion, %FD = percent fatigue decrement, XO = xanthine oxidase, EIMD = exercise induced muscle damage, APFT = army physical fitness test, BMPU = Baumgartner modified pull-up test, WanT = Wingate anaerobic test, EPA = eicosatetraenoic acid, DHA = docosahexaenoic acid, EGCG = epigallocatechin gallate, RER = respiratory exchange ratio, RPE = rate of perceived exertion, ROTC = Reserve Officers' Training Corps, RST = repeated-sprint test, TC = total cholesterol, LDL-C = low density lipoprotein cholesterol, HDL-C = high density lipoprotein cholesterol

DISCUSSION

The discussion will include details about studies that met the inclusion criteria for this review. Specifically, highlights of individual study methods, dosing, participants will be highlighted surrounding anaerobic, aerobic, and muscle-damaging exercise. Following, conclusions are highlighted and synthesize the research to date as it pertains to the aforementioned specific areas.

Quercetin and Aerobic Performance
Cycling

There is modest evidence to suggest Q improves cycling performance. Among 39 well-trained cyclists, supplementing 1000 mg of Q with or without 120 mg of epigallocatechin 3-gallate (EGCG) (flavonoid) for two weeks significantly enhanced Q concentrations, enhanced granulocyte oxidative burst activity, and resisted inflammatory markers (CRP, IL-6, and IL-10) in Q–EGCG after three days of heavy exercise (cycling for three hours at ~57% Wmax) (69). Q in combination with EGCG shows more of a promising effect in performance and inflammation, possibly due to improving the bioavailability of Q. However, 1000 mg of Q or placebo for 3 weeks prior to a 3-hr cycling bout did not alter improvements in exercise measures but it significantly decrease upper respiratory tract infections in trained cyclists (68). Since URTIs are common in heavy-trained endurance athletes (65), Q may lessen sickness and improve immunity. The comparison of caffeine to Q may shed insight into Q's effects on performance. Healthy men consumed caffeine (9 mg/kg), placebo, or Q (2,000 mg of Q) in a 30 ml/kg electrolyte the night before a 30-minute cycle ergometry at 50% Vo2peak followed by a 15-min performance time trial did not yield performance improvements (16). There is no effect of a 28-day consumption of Q vitamin (Q-VIT: 1000 mg Q, 820mg Vitamin C, 40mg Vitamin B3) on a time trial in trained cyclists (17). Q (1000 mg) ingested in a beverage form with other vitamins and carbohydrates, four times a day, revealed no performance improvements in $VO2_{peak}$, substrate utilization, perception of effort during submaximal exercise, total work done during the 10-min maximal effort cycling trial, and voluntary and electrically evoked strength (19). Further, Q (1000 mg, two times a day for 2 months) did not affect lactate concentrate, body fat percentage, or $VO2_{max}$ in male athlete badminton players (21). The ingestion of Q (500 mg) for 7 days in untrained individuals was associated with modest improvements in $VO2_{max.}$ Q (1000 mg) consumption for three weeks did not improve performance for 3 hr cycling bout or affect inflammatory or oxidative stress markers in trained cyclists (27, 62). With the little evidence that exists, it appears that Q does not improve cycling performance.

V02 peak/max in Cycling Performance

Ten healthy men consumed 30 ml/kg of fluid electrolyte beverage either placebo (Group P), caffeine (Group C; 9 mg/kg), or Q (Group Q; 2,000 mg) the night before a 30-min of cycle ergometry at 50% Vo2peak followed by a 15-min performance time trial (16). No treatment effects were observed for any physiological or perceptual measures except for elevated rectal body temperatures. For Group C vs. Groups Q and P. Supplementation did not affect total work performed or the self-selected pacing strategy employed (16).

Thirty recreationally active men consumed Q or a placebo in a sports hydration beverage four times daily, with the morning, midday, and evening meals, and prior to sleep (19). The drink contained carbohydrates and maltodextrins), NaCl, vitamins (niacin, B6, B12), citric acid, a gel-forming additive, and Q (1,000 mg/day), whereas untreated participants in group P ingested the same beverage without Q. Participants remained on the treatment for 9–16 days, beginning immediately after the pretests and continuing until all the posttests were administered. Pretreatment-to-posttreatment changes in phosphocreatine recovery time constant, $VO2_{peak}$, substrate utilization, and perception of effort during submaximal exercise, total work done

during the 10-min maximal effort cycling trial, and voluntary and electrically evoked strength loss were not significantly different between Q and placebo. Short duration, chronic dietary Q supplementation in untrained men did not improve muscle oxidative capacity; metabolic, neuromuscular, and perceptual determinants of performance in prolonged exercise; or cycling performance (19). Contrary, 12 untrained individuals (men and women) consumed 500 mg of Q twice daily dissolved in sugar-free vitamin-enriched Tang or a non-distinguishable placebo (Tang). Seven days of Q feedings were associated with a modest increase in biking $VO2_{max}$ along with a substantial (13.2%) increase in ride time to fatigue (24). There is not enough evidence to suggest Q supplementation improves $VO2_{peak/max}$ in cycling performance.

Time-to-exhaustion

Improving exercise time-to-exhaustion (TTE) is ideal to perform for longer durations and helps delay fatigue. In one study, badminton players (n = 26) consumed Q (1000 mg) or placebo (1000 mg dextrose) at two capsules per day for two months (21). Lactate concentration, body fat percentage, and $VO2_{max}$ did not show any significant difference after eight weeks of supplementation with placebo and Q between two groups and within one group. However, there was a significant increase in cycling TTE after intervention in the Q group (21).

Twelve elite male athletes consumed a free radical scavenger (FRS) cocktail containing Q (300 MG) versus FRS minus Q (FRS-Q). The total amount was 300 mL, 2 × per day, one drink in the morning with a meal, and one in the afternoon or evening with a meal for 6 weeks. Each serving of FRS and FRS-Q contained green tea extract (300 mg), vitamin C (150 mg), vitamin E (50 mg), caffeine (45 mg), niacin (25 mg), taurine (9 mg), vitamin B-6 (2.5 mg), vitamin B-2 (2.1 mg), vitamin B-1 (1.9 mg), and vitamin B-12 (0.008 mg). A cycling TT (30km) was improved by 3.1% on an antioxidant supplement containing essential vitamins plus Q (FRS) compared to baseline. Absolute and relative (%HRmax) heart rates and percent $VO2_{max}$ were not different between trials, but average and relative power (% peak power) were higher on FRS (57).

Among 39 well-trained cyclists, supplementing 1000 mg of Q with or without 120 mg of epigallocatechin 3-gallate (EGCG) (flavonoid) for two weeks significantly enhanced Q concentrations, enhanced granulocyte oxidative burst activity, and resisted inflammatory markers (CRP, IL-6, and IL-10) in Q–EGCG after three days of heavy exercise (cycling for three hours at ~57% Wmax) (69). Q in combination with EGCG shows more of a promising effect in performance and inflammation, possibly due to improving the bioavailability of Q.

Similarly, trained cyclists received Q (1000 mg/d) or placebo supplements for 3 weeks before, during, and 2 weeks after the 3-d period of intensified exercise (68). No significant differences were found between groups for age, body composition, training history, or maximal performance measures. Higher Q concentration levels (9.2 fold increase) were noted after the 3 wk intervention with a significantly lower incidence of URTI symptoms during the 2-wk period after intensified exercise (68). There was no beneficial effect of Q on any of the immune components measured, including natural killer cell lytic activity, polymorphonuclear

respiratory burst rate, or phytohemagglutinin-stimulated lymphocyte proliferation, despite the reduced incidence of URTI symptoms that were observed after Q feedings.

The same research group (70) investigated a 2-week of Q supplementation (1000 mg/d) compared with placebo (before or after a 2-wk wash-out period) ingestion on skeletal muscle mitochondrial biogenesis in untrained males. Q versus P for 2 wk in untrained males was associated with a small but significant improvement in 12-min treadmill time trial performance and modest but insignificant increases in the relative copy number of mitochondrial DNA and messenger RNA levels of four genes related to mitochondrial biogenesis (70). This modest increase is likely due to the untrained subjects having a lower mitochondrial biogenesis gene expression prior to exercise.

There was no effect of Q supplementation (1000 mg/day or placebo supplements prior to and during the 3 days of intensified exercise for 3 weeks) on cycling time trial performance, power output, $VO2_{max}$, HRmax in trained individuals (27). Further, there were no differences in investigating oxidative and inflammatory makers (F2-isoprostanes, ferric-reducing antioxidant potential, Trolox equivalent antioxidant capacity, C-reactive protein, plasma nitrite), in the Q treatment compared to placebo (62).

A co-ingestion of quercetin with other ingredients is suggested to improve TTE. Thirteen trained cyclists consumed either an antioxidant supplement containing vitamins and Q (Q-VIT: 1000mg Q, 820mg Vitamin C, 40mg Vitamin B3) or the same vitamin supplement without Q (VIT: 820mg Vitamin C, 40mg Vitamin B3) for 28 days prior to a maximal cycling bout (17). After supplementation, subjects completed a simulated time trial on a cycle ergometer. In endurance-trained athletes, chronic supplementation with Q did not influence plasma cytokine or exercise-induced cytokine response (IL-6, IL-10, CRP) (17). No performance improvements were detected. Limited evidence exists that suggests that Q improves TTE.

Swimming

With one study to date, it is not clear how Q may affect swimmers, especially younger trained individuals. Young female trained swimmers were randomly assigned to one of two groups: Q (1000 mg/day) or P (1000 mg dextrose per day) for 8 weeks (22). There was no aerobic performance (VO_{2max}, TTE, lactate, or body fat percentage) improvement with Q supplementation in young, trained female swimmers(22). Future research should investigate Q supplementation, especially in young, trained swimmers.

Boxing

Most Q research has focused on improving aerobic performance. Young male boxing athletes supplemented with 500 mg Q or P fifteen minutes before each workout in the one-month boxing training program [78]. The control and experimental group participated in an exercise program of two hours applied to the athletes three times a week for one month. There were significant

decreases in TC and LDL and an increase in HDL in the Q group, while there was only a significant increase in controls' HDL. Classic boxing training plus Q supplementation had a strong effect on lipid profile compared to controls (26). Q with exercise may serve as an antioxidant on free radicals and regulate lipid profiles in boxing.

Quercetin and Anaerobic Performance

There is minimal evidence on how Q impacts anaerobic performance. After a repeated-sprint exercise in 15 recreationally team sport trained athletes, 1-week supplementation of a placebo, a 6% carbohydrate commercial sports drink, or that drink with 500 mg of Q-3-glucoside, consumed twice a day (1,000 mg/d) did not affect the levels of the pro-inflammatory cytokine IL-6, uric acid, or xanthine oxidase. Mean sprint time was significantly higher in the sports drink and Q treatment, but the differences were not notable. Percent fatigue decrement for placebo (3.8% ± 2.3%) was significantly less than with Q (5.1% ± 2.7%). Repeated-sprint performance was not improved by Q (1). Fifty trained men and women were randomly assigned A, B or C Treatment: Treatment A, 140 mg of Zynamite®, 140 mg of w, 147.7 mg of maltodextrin, and 420 mg of sunflower lecithin; Treatment B, 140 mg of Zynamite®, 140 mg of Q, and 2126 mg of maltodextrin and Treatment C, 2548 mg of maltodextrin (P) 1 hr prior to exercise. Treatments A and B improved peak power output during the first three Wingates by 2.8% and 3.8%. Vastus Lateralis oxygenation (NIRS) was reduced, indicating higher O_2 extraction. Improved O_2 extraction was observed in the sprints after ischemia. Blood lactate concentration was 5.9% lower after the ingestion of Zynamite® with Q in men. There was a higher vastus lateralis O_2 extraction during 60 s ischemia with polyphenols, due to the greater muscle VO_2 in men (36). A single dose of Zynamite® combined with Q one hour before exercise improves repeated-sprint performance and muscle O_2 extraction and mitochondrial O_2 consumption during ischemia.

Anaerobic Performance Conclusions

There are inconsistent results with Q and anaerobic performance. Although only two studies were examined, both were performed in recreationally trained individuals with mixed outcomes. The majority of studies have reported Q supplementation by higher dosages (> 500 mg), administered during several days, but only one study to date has improved anaerobic performance (peak power) with the combination of Zynamite®. It is likely that the combined effect of Q with another polyphenol (mangiferin) improved peak power output and oxygen extraction during repeated maximal sprints. Each polyphenolic compound has unique chemical properties, determining its effect and specific actions in different cellular compartments (36). Although experimental evidence is lacking and inconsistent, a combination of polyphenols likely counteracts more efficiently the ROS produced during anaerobic exercise in different cellular compartments of the skeletal muscle fibers compared to single compounds. Although high levels of antioxidant capacity may limit force production and fatigue (81), Q, in combination with other polyphenols in smaller doses (< 200 mg), may provide an anaerobic performance benefit.

Mixed endurance

The consumption of Q was studied to improve functional performance tests in soldiers. Army and Air Force Reserve Officers' Training Corporation men and women (n = 58) swallowed four individually wrapped chews daily (two with breakfast, two with dinner) during a 6-week treatment period. Each chew contained 250 mg Q (1000 mg total/day), 100 mg iso-quercetin, 100 mg omega-3 fatty acids (eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]), 30 mg epigallocatechin gallate (EGCG), a vitamin mixture, sucrose, and other ingredients in carnauba wax and soy lecithin base. Dietary Q supplementation (1 g) by moderately trained men and women did not have an ergogenic effect, as assessed using $VO2_{peak}$ (uphill treadmill running) and four physical performance measures: army physical fitness test, Baumgartner Modified Pull-Up Test, Wingate Anaerobic Test, and a 36.6-m sprint after 54 days of supplementation (11).

Male soldiers (n = 16) consumed 2 energy bars, each containing 0 mg (placebo) or 500 mg of Q (1,000 mg/d) for 8.5 days. Beginning day 6 of supplementation, the soldiers performed the 3 exercise days (90). The subjects donned a 16-kg weighted vest and walked on a treadmill for 75 minutes. VO_2 during treadmill walking was maintained between 45 and 60% of $VO2_{peak}$. After 10 minutes of rest, volunteers were given a 5-minute warm-up with the cycle ergometer set at 75 W in hyperbolic mode. The cycle ergometer was then placed in linear (pedal rate dependent) mode, and volunteers completed 200 kJ of work at maximal effort performance and were assessed as the time required for completing 200-kJ work. There was a significant increase in plasma Q after Q supplementation. No differences after P or Q supplementation as compared with B in steady-state load carriage, metabolic responses, $VO2_{peak}$, TT trial, RER, or RPE. Though, Q supplementation muscle soreness was higher on day 2 compared with day 1, whereas no differences were seen over days for B or P testing (90). It is not certain that Q improves functional exercise modalities.

Running Performance
Endurance Run

A great deal of research has been focused on supplements to improve running times. Q's antioxidant functions may help decrease ROS, delay cognitive fatigue, and improve running performance times. In one study, 63 experienced male and female ultramarathoners from the 2006-160-km Western State Endurance Run were recruited to measure the effects of Q or placebo (250 mg Q 4x/day 1,000 mg/day total) for 3 weeks before the Western States Endurance Run (WSER)) on ratings of perceived exertion (96). On race day, participants ingested all four chews before the 5 a.m. start time. RPE was assessed at aid stations located at 40, 90, 125, 150, and 160 km (finish line) and did not show any improvement in perceived exertion or race times (96). Q supplementation did not affect race performance nor blood plasma lipid or aqueous-phase antioxidant capacity, or oxidative damage during an ultramarathon challenge (83). There was no reported benefit on illness rates following the run (83). Plasma Q levels were increased but failed to attenuate muscle damage (DOMS), inflammatory markers (IL-1R α, IL-6, IL-8, IL-10, G-

CSF, MCP-1, MIP-1, TNF-α, MIF-1), plasma cytokine and hormone levels, and alterations in leukocyte cytokine mRNA expression (67). With only a few studies to reference, we cannot say for certain that Q will improve race performance.

VO2 peak/max

The structure and function of Q may help improve oxygen consumption and utilization. For example, male and female runners ingested Q-based chews (Q-chew) or placebo chews 15 min before a 2-hr run at 70–75% $VO2_{max}$ (50). The 4 Q-chews provided 1,000 mg Q, 120 mg epigallocatechin 3-gallate, 400 mg isoquercetin, 400 mg each eicosapentaenoic acid and docosahexaenoic acid, 1,000 mg vitamin C, and 40 mg niacinamide. Plasma Q increased from 80.0 ± 26.0 µg/L to 6,337 ± 414 µg/L immediately after postexercise and 4,324 ± 310 µg/L 1 hr postexercise after ingestion of Q-chews, compared with no change in PL. Exercise caused significant increases in c-reactive protein, granulocyte, and monocyte phagocytosis and oxidative burst activity, inflammatory markers, and decreases in granulocyte and monocyte oxidative burst activity, but no differences in the pattern of change were measured between Q-chew and PL trials. After 15 min before heavy exertion, acute ingestion of Q-chews caused a strong increase in plasma Q levels but did not counter postexercise inflammation or immune changes relative to placebo (50). Similarly, 11 untrained sedentary individuals (men and women) consumed 1000 mg/ day of Q for days with a food bar or no Q added (placebo) for 6 days prior to a running $VO2_{max}$ test. Five days of Q supplementation did not influence $VO2_{max}$ or related variables (respiratory rate, blood lactate, RER, HR, RPE, etc.) in sedentary men and women (35).

Male long-distance runners consumed Q (1000 mg/day) or placebo while maintaining their current training schedules for 6 weeks while maintaining their current training schedules (87). Treatment started after the completion of the first 10 km running TT and continued for 6 weeks through completion of the second VO_{2peak} and 10 km TT. There were no notable differences in oxidative stress and antioxidant activity (SOD and total antioxidant capacity (TAC)), protein carbonyl, RPE, heart rate, TT, or VO_{2peak}. There was a significant time × supplement interaction for serum malondialdehyde (MDA), an indicator of lipid peroxidation (87).

Trained runners were initially randomized to either resveratrol plus Q (120 mg resveratrol and 225 mg Q for 6 days and 240 mg resveratrol and 450 mg Q on day 7, just prior to exercise) (61). Protein carbonyls, FRAP = ferric-reducing ability of plasma, ORAC = oxygen radical absorptive capacity, TEAC = Trolox equivalent antioxidant capacity, interleukin-8, and CRP significantly increased after exercise but were not affected by treatment (61). In addition, 1 week with an acute dose of resveratrol and Q administered in the hour prior to exercise resulted in a significant reduction in the immediate postexercise increase in F_2- isoprostanes (a marker of oxidative damage), compared with placebo.

In nine recreationally active men, ingested four individually wrapped chews (weeks 4-11) (two with breakfast, two with dinner) (33). Each chew contained 250 mg Q, Vitamin C, Vitamin B3,

and folic acid for and 8-weeks treatment period. Total Q consumption for the experimental group was 1000 mg/day. During the first 3 and last 3 weeks, no Q supplementation was administered. $VO2_{peak}$ or physical work capacity did not change throughout the 14 weeks in non-endurance trained men and women (33).

Three studies (4-6) performed by the same research group investigated Q in male trained students but not professionally involved in a sport. Subjects were randomly assigned to one of the four groups: 1) Q + vitamin C (500 mg/day Q + 200 mg/day vitamin C), 2) Q (500 mg/day Q + 200 mg/day placebo), 3) vitamin C (500 mg/day placebo + 200 mg/day vitamin C), and 4) placebo (500 mg/day placebo + 200 mg/day placebo). Q and its placebo were ingested after meals for 8 weeks. Supplementation with Q and vitamin C for 8 weeks did not improve exercise performance but reduced oxidative stress and inflammatory biomarkers, including CRP and IL-6, with little effect on E-selectin in healthy subjects (4). Q in combination with vitamin C revealed significant differences in LDH, $VO2_{max}$, TEE, TBW, and LBM among the Q and vitamin C groups (5). To evaluate performance indices, an exercise test was performed for all participants using the Bruce protocol and HP cosmos treadmill. $VO2_{max}$ and the distance covered were measured by a gas analyzer. After eliminating the confounding effects of initial variables, only $VO2_{max}$ changes remained significant. Lean body mass, total body water, basal metabolic rate, and total energy expenditure increased significantly in the Q group after intervention (5). a

The co-ingestion of Q and vitamin C were assessed on lipid profile and muscle damage (6). There were no significant changes that occurred in high-density lipoprotein levels within or between groups in the four groups before and after supplementation. LDH values decreased significantly in the "Q + Vit C" group, but it was not considered in other treatments and between groups (6). It appears that Q may be promising in minimizing muscle damage and improving body composition in trained individuals. However, exercise regimens were not monitored or incorporated in these studies. There is not enough evidence to suggest Q improves $VO2_{peak/max}$. It appears that Q may play more of a role in decreasing oxidative stress.

Aerobic Conclusions

As seen in previous literature, Q provides a small but trivial benefit in human endurance exercise, specifically cycling (VO_{2max}, TTE). Possible reasons for the inconsistent findings among these studies may include the range of subject fitness levels (i.e., untrained subjects compared to trained subjects), study design or protocol implemented, and/or differences in Q supplementation protocol/supplement types (beverage, capsule, chew, bar). The likely mechanism involved is Q's ability to improve mitochondrial biogenesis (via PGC-1α), which in turn would increase oxidative capacity and subsequently endurance exercise performance (51). It is unknown whether Q can enhance mitochondrial biogenesis or density in humans. It is also proposed that Q may act similarly to caffeine blocking the adenosine receptors via the central nervous system (CNS) (16). The effect of Q in the CNS needs to be further explored. There is still inadequate knowledge of the possible underlying mechanisms in humans. It appears that chronic supplementation (> 2 weeks) may provide a performance benefit from Q

supplementation compared to the short term. The benefits may be due to improved Q bioavailability in combination with other ingredients, such as vitamin C, resveratrol, or other antioxidants. More dose-response data (> 1000mg/d) is needed to understand the potential effects of Q on aerobic performance.

Strength

Resistance training is important to increase muscular strength and power. It is shown that an increased ROS can reduce strength force-generating capacity (12). Q, an anti-inflammatory nutrient, may reduce the inflammatory markers in the blood, thereby decreasing post-exercise muscular damage. Healthy trained non-smoker male individuals (n = 10) consumed Q (1 g/day) or placebo (PLA) 3 h prior to a resistance training session (79). After a single dose of Q, the torque–velocity curve of knee extensors was enhanced, and after the resistance exercise, subjects showed a lower MVIC reduction (Q: 0.91 ± 6.10%, PLA: 8.66 ± 5.08%) with a greater rate of torque development (+ 10.6%, $p < 0.005$) and neuromuscular efficiency ratio (+ 28.2%, $p < 0.005$). The total volume of the resistance exercises was significantly greater in Q compared to PLA. No significant differences were found in biomarkers between treatments (79). It is unknown whether Q will improve strength in trained individuals.

Quercetin and Muscle Damage

An associated inflammatory response is associated with muscle damage, seen especially in eccentric actions. Sarcomere length nonuniformities (overstretching) and myofibrillar disruption are thought to be the cause of muscle injury and damage from eccentrically contracting muscles (47). Q is proposed to attenuate the severity of muscle weakness caused by eccentric actions.

Eccentric Studies

The effect of Q supplementation may help decrease eccentric-work muscle damage. Thirty young, healthy, recreationally active, but not endurance-trained consumed Q (1000 mg/day) or PLA for 14 days (in capsule form) prior to eccentric exercise. Participants completed a comprehensive neuromuscular evaluation (NM) (maximal voluntary isometric contraction (MVIC)), before, during, and after an eccentric protocol able to induce severe muscle damage (10 sets of 10 maximal lengthening contractions, each eccentric resist maximally during the whole ROM from 40 to 140°). Q supplementation significantly increased the isometric strength recorded during a NM MVIC test compared to baseline. Moreover, the torque and muscle fiber conduction velocity (MFCV) decay recorded during the eccentric exercise was significantly lower in Q compared to PLA (9).
Q supplementation significantly decreased the strength loss compared to placebo in 16 healthy men (8). During the recovery force-velocity relationship and mean fibers, conduction velocity persisted significantly less when participants consumed PLA rather than Q, especially at the highest angular velocities ($p < 0.02$). There was a higher MFCV decay in POST, 24 h, 72 h, 96 h,

7 d in PLA compared to Q. Greater increase in biomarkers of damage (CK and LDH) was also evident in placebo compared to Q. Elbow angle was significantly decreased both in Q and placebo. Q may ameliorate the time course of symptoms associated with the inflammatory response of the secondary damage and accelerate the recovery of neuromuscular function (8).

In a double cross-over protocol (exercise limb and treatment), healthy men consumed 1000 mg/day or PLA for 14 days (in capsule form) prior to completing maximal lengthening contractions on an isokinetic dynamometer (28). Each participant completed 6 to 10 sets of 10 maximal lengthening contractions of the elbow flexors; each set was separated by 30-seconds rest. Q supplementation improved redox status as assessed by GSH/GSSG ratio analysis and reduced thiobarbituric acid reactive substances (TBARS) levels both in erythrocytes and plasma. After a single bout of eccentric exercise, Q supplementation improved redox status as assessed by reduced/oxidized glutathione ratio analysis and reduced TBARs levels in both erythrocytes and plasma. Q supplementation has antioxidant potential prior to and after a strenuous eccentric exercise, thus making the erythrocytes better able to cope with an oxidative insult (28).

Q in a bar-form yielded no significant improvements in muscle strength or muscle soreness. Healthy subjects (n = 30) ingested nutrition bars containing 1,000 mg/d Q or PL for 7 d before and 5 d after two bouts of 24 maximal eccentric contractions of the elbow flexors, using the opposite arm (72). There were no significant main effects of group or phase on CK between PLA and Q. In addition, no significant group, phase, or time effects on these markers of systemic inflammation (PQ, IL-6, and Serum CRP) were observed. There was no effect of Q supplementation on the aforementioned markers of EIMD. Plasma Q increased after 7 d of supplementation and remained elevated during the 5-d postexercise recovery period. Differences between treatments were not detected in strength loss, muscle soreness, reduced arm angle, CK elevations, and arm swelling peak (72). Q may be a promising supplement to mitigate exercise-induced muscle damage and improve redox balance following eccentric exercises.

Aerobic and EIMD mixed

Q consumed in a capsule form may be more promising especially in mixed events. Forty-eight student subjects ingested a Q or placebo treatment assigned one hour before a 10 km race (60). The placebo was delivered in the form of two capsules, each containing 364 mg of maltodextrin. The polyphenols were also provided in two capsules, each containing 70 mg of Zynamite® (Mangifera indica leaf extract, standardized to 60% mangiferin) combined with 70 mg of Q in the form of 140 mg of Sophora japonica extract standardized to 50% Q, and 153 mg of maltodextrin. Three additional doses were ingested every 8 h after the race at lunch, dinner time, and in the next morning before the vertical jump test, to a total of 420 mg of Zynamite® combined with 420 mg of Q. Although competition times were similar, polyphenol supplementation attenuated the muscle pain felt after the competition and the loss of jumping performance and mechanical impulse 24 h later. In addition, the polyphenols attenuated the increase of serum myoglobin and alanine aminotransferase in men, but not in women. A single

dose of 140 mg Zynamite®, combined with 140 mg of Q, administered one hour before the competition, followed by three additional doses every eight hours, attenuates muscle pain and damage, and accelerates the recovery of muscle performance (60). Although limited studies exist, research is necessary to investigate the effects of Q on oxidative stress, inflammation, and recovery following various damaging bouts of exercise.

Muscle Damage Conclusions

Eccentric-induced muscle damage causes myofibrillar and Z-disk disruption and sarcolemma action potential propagation impairment (9). Although the exact mechanism is unknown, Q can serve as a lipophilic compound and may be able to cross membranes easily and promote membrane stability, preserving the excitation-contraction coupling in myocytes (9).

Quercetin and the Central Nervous System

Q which may enhance mental and physical performance is its caffeine-like psychostimulant effect. Psychostimulants, like caffeine, can delay fatigue during endurance exercise because of their ability to block adenosine receptors in the brain, which increases dopamine activity (25). Q may have a blocking effect on the adenosine receptors at a central level. This may also be involved in neurotransmitter uptake's energetics and may influence motor unit recruitment capacity (8, 9, 53). A psychostimulant effect of Q has also been reported *in vitro* (3) similarly, but this effect was not found in human subjects (53). Although only performed in one study, Q supplementation, prior to and after a strenuous eccentric exercise, makes erythrocytes more able to cope with oxidative insult and could ensure efficient oxygen delivery to the working muscles. The anti-inflammatory and antioxidant properties of Q may reduce exercise-induced muscle damage (8, 9). Q may serve to improve neuromuscular improvement and strength, possibly by blocking adenosine receptors, improving RBC redox potential, augmenting Ca^{2+} availability, and thereby improving contraction rates. However, research is needed to elucidate these exact mechanisms.

The majority of the currently available literature supports that Q may serve as an anti-inflammatory agent and antioxidant without much mention of exercise; however, this literature has primarily been conducted in animal models and little is known about Q's effects in humans in exercise conditions. This is the first review to examine the impact and application of Q supplementation on aerobic or anaerobic performance and muscle damage in humans. Some studies reported improved exercise performance in humans after Q ingestion, whereas most other studies failed to find significance. It seems that the most notable effect of Q is related to a possible benefit is in endurance performance, possibly enhancing mitochondrial biogenesis, but only one study supports this (70). Much of the research to date comes from in vitro and rodent studies that show Q stimulates mitochondrial biogenesis, including proliferator-activated receptor-γ coactivator-1α (PGC-1α) and sirtuin-1(SIRT-1) gene expression, mitochondrial DNA and cytochrome c enzyme concentration in both the brain and soleus muscle of rats (53). Possible reasons for the inconsistent findings among these studies may include the range of subject

fitness levels, differences in plasma Q concentration and bioavailability obtained via the various sources, supplementation protocol, co-ingestion with other ingredients, and differences in research design (e.g., ingestion period, subjects, training history).

Dosage conclusion

- 500 mg - 1000 mg/day of Q given as a chronic dose (> 2 weeks) has been more effective in trained individuals. However, short term doses (< 2 weeks) may be more effective in untrained individuals
    - Normal dietary intake of Q needs to be taken into consideration prior to Q supplementation especially in trained individuals
    - The absorption rate and bioavailability show high interindividual variability
    - Little evidence documents high vs low Q responders
- Higher doses (> 1000 mg) may not make significant differences in sports performance if quercetin is already adequately consumed via normal dietary intake
- Q (< 200 mg) in combination with other antioxidant ingredients (vitamins and minerals) show more promising results relative to Q as a single ingredient
    - Polyphenolic compounds have unique chemical properties which determine specific actions in cellular compartments and could exhibit different antioxidant effects
- It is recommended to consume Q 1-3 h prior to exercise for peak bioavailability and chronically to avoid Q returning to baseline levels

Training status of individuals

- The population that would most benefit from this supplement remains unclear, given the range of subjects (trained, untrained, males, and females) and duration of consumption
    - It appears that athletes may benefit more from Q's effects but may take longer to see a performance increase possibly due to higher starting nutrient levels
    - Q consumption (~1000 mg/day) in untrained individuals may be more effective to improve exercise performance (i.e., cycling)
- It is important to consider the impact of type, level, and duration of training, genetics, recovery strategy, and sex of athletes compared to untrained individuals moderating the influence of Q consumption on performance outcomes

Quercetin and Performance

- There is mixed research that Q improves endurance and anaerobic performance and expedites the recovery of DOMS or markers of muscle damage
- Chronic Q ingestion (> 14 days in athletes) shows more promising results in reducing muscle damage and aerobic events, likely conferring to its role in neuromuscular and mitochondrial function. This longer timeframe is likely because of athletes having a higher starting concentration of Q; It may take longer to see a difference in the athletic population. It remains to be determined whether Q can enhance mitochondrial biogenesis in humans

- Lower doses of Q (< 200 mg) in combination with other ingredients (e.g., EGCG, tang, other vitamins (e.g., vitamin C), and minerals) likely improve Q's bioavailability and can elicit greater performance benefits
- The physiological mechanism that Q targets during exercise in skeletal muscle is warranted. The mechanisms that explain how Q affects exercise performance and the appropriate doses and sources for specific performance outcomes are unclear. While more research is continually developed regarding the effects of Q in sports and exercise, the consensus of these outcomes is unclear regarding's Q's role in aerobic and anaerobic performance, muscle damage, and recovery. Future research is needed to evaluate this novel dietary supplement further

Future Research

Previous research showed improvements in elbow isometric strength (maximal voluntary isometric contraction) and reduced muscle fatigue after consuming 1g of quercetin for 14 days prior to performing an elbow eccentric exercise compared to placebo in young recreationally trained men (9). Similarly, healthy subjects ingested 1000mg/day (or 1 gram per day) or placebo for 7 days and 5 days after an eccentric bout of elbow flexor exercise. Differences between treatments were not detected in inflammatory markers (IL-6 or CRP) or markers of muscle damage (creatine kinase) (72). To our knowledge, three studies exist investigating 1000 mg of quercetin for 14 days prior to eccentric elbow flexor exercise bout (using Biodex dynamometer) (8, 9, 28). However, research is necessary to investigate quercetin supplementation prior to lower-body eccentric muscle damaging protocols.

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