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QUERCETIN'S BIOACTIVE EFFECTS IN HUMAN ATHLETES

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ABSTRACT: ***Quercetin exerts strong anti-oxidative, anti-inflammatory, anti-pathogenic, and immune regulatory effects in vitro and in animal-based studies. Epidemiologic data indicate reduced rates of cardiovascular disease and various types of cancer in groups self-selecting diets high in quercetin. Several recent quercetin supplementation studies in human athletes have focused on potential influences as a countermeasure to post-exercise inflammation, oxidative stress, and immune dysfunction, in improving endurance performance, and in reducing illness rates following periods of physiologic stress. When quercetin supplementation is combined with other polyphenols and food components such as green tea extract, isoquercetin, and fish oil, a substantial reduction in exercise-induced inflammation and oxidative stress occurs in athletes, with chronic augmentation of innate immune function. Quercetin supplementation (1,000 mg/day for two to three weeks) also reduces illness rates in exercise-stressed athletes. Animal studies support a role for quercetin as an exercise mimetic for mitochondrial biogenesis, and recent data in untrained human subjects indicate modest enhancement in skeletal muscle mitochondrial density and endurance performance. Quercetin has multiple bioactive effects that support athletic endeavor, and research continues to better define optimal dosing regimens and adjuvants that amplify these influences.***

KEY WORDS: Exercise, flavonoids, immune function, inflammation, oxidative stress

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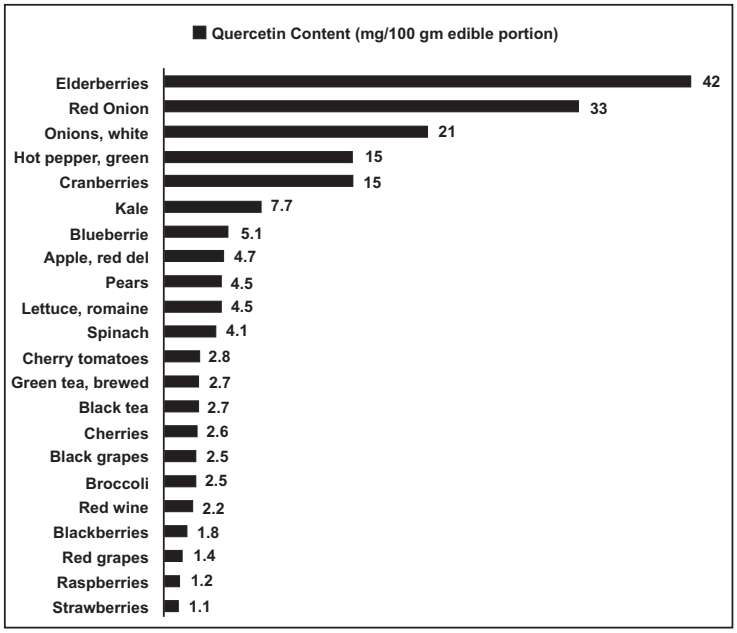
INTRODUCTION

Polyphenols are a large class of colorful, plant-based, phenolic organic compounds. Flavonoids, a polyphenolic subgroup, comprise several thousand compounds classified into five subgroups (USDA Nutrient Data Laboratory, 2007). One of these subgroups, the flavonols, includes quercetin, a widely distributed and investigated flavonoid.

Food sources for quercetin include tea, onions, apples, peppers, blueberries, and dark green vegetables (USDA Nutrient Data Laboratory, 2007; Chun et al., 2007) (Figure 1). Quercetin accumulates in the outer and aerial tissues (skin and leaves) because its biosynthesis is stimulated by light. Flavonol intake is only about 13 mg/day for U.S. adults, with quercetin representing three-fourths of this amount (Chun et al., 2007). Human subjects can absorb significant amounts of quercetin from food or supplements, and elimination is quite slow, with a reported half-life ranging from 11 to 28 h (Conquer et al., 1998; Edwards et al., 2007; Egert et al., 2008, 2009; Manach et al., 2005).

FIGURE 1. Quercetin content per 100 mg of selected foods. Source: USDA Database for the Flavonoid Content of Selected Foods. (2007)



Quercetin supplementation in both animal and human studies does not cause adverse symptoms or harmful physiologic effects (Harwood et al., 2007; Knab et al., 2010; Utesch et al., 2008). Long term feeding of quercetin in rats leads to an accumulation in several organs including the lungs, testes, kidney, heart, liver, thymus, and muscle (de Boer et al., 2005). This finding, however, was not replicated in pigs, with quercetin found only in organs involved in its metabolism and excretion, including the liver, small intestine, and kidneys (Bieger et al., 2008). These data create some doubt about lung, heart, and muscle quercetin incorporation in humans, but biopsy or radiolabeled investigations have not yet been conducted.

QUERCETIN-RELATED BIOACTIVE EFFECTS

In vitro, animal, and epidemiologic studies support multiple quercetin-related physiologic and health effects (Williamson and Manach, 2005). Quercetin's effects are disparate and wide-ranging, and include anti-oxidative (Ciz et al., 2008; Dias et al., 2005; Najafzadeh et al., 2009), anti-inflammatory (Comalada et al., 2005, 2006; Nair et al., 2006), anti-pathogenic (Chen et al., 2006; Chiang et al., 2003; Cushnie and Lamb, 2005; Davis et al., 2008; Dimova et al., 2003; Vrijsen et al., 1988), immune regulatory (Akbay et al., 2003; Lin et al., 2009; Nair et al., 2002) anti-carcinogenic (Knekt et al., 2002; Neuhouser, 2004), cardioprotective (Erdman et al., 2005; Mink et al., 2007), and pro-mitochondrial biogenesis (Davis et al., 2009) influences.

Epidemiologic data, although not entirely consistent (Wang et al., 2009), provide evidence for multiple disease prevention benefits among those consuming diets high in quercetin. High compared to low quercetin intake has been linked in epidemiologic studies to a reduced risk of colorectal, kidney, pancreatic, prostate, and lung cancer (especially in smokers) (Bobe et al., 2008; Cui et al., 2008; Knekt et al., 2002; McCann, et al., 2005; Neuhouser, 2004; Nöthlings et al., 2007; Theodoratou et al., 2007; Wilson et al., 2009). Risk of cardiovascular disease and diabetes mellitus is also reduced among those self-selecting diets high in quercetin (Keli et al., 1996; Knekt et al., 2002). C-reactive protein is significantly lower among U.S. adults in the upper tertile of quercetin intake (Chun et al., 2008).

Inflammation and oxidative stress are key mechanisms in the pathogenesis of certain disease states, supporting the strategy of increased flavonoid and quercetin intake either through diet enrichment or supplementation for prevention of cancer, diabetes mellitus, and cardiovascular disease. Quercetin supplementation as a therapeutic strategy for reducing disease risk factors is supported with data from in vitro and animal studies (Boots et al., 2008a). For example, in rodents, quercetin supplementation lowered circulating plasma cytokines related to inflammation (Stewart et al., 2006), decreased serum total cholesterol and phospholipid levels (Odbayar et al., 2006), inhibited pro-inflammatory signals (Dias et al., 2005), countered oxidative stress (Gong et al., 2009), and decreased blood pressure (Duarte et al., 2001; Mackraj et al., 2008; Yamamoto and Oue, 2006).

Quercetin supplementation studies with human subjects are limited, but the most consistent finding when investigating disease risk factors is a modest reduction in blood pressure, with little or no effect on blood lipid profiles, or inflammatory and oxidative stress biomarkers (Edwards et al., 2007; Egert et al., 2008,2009; Knab et al., 2010; Loke et al., 2008a; Shanely et al., 2010). For example, although quercetin is a powerful in vitro antioxidant and free radical scavenger (Loke et al., 2008b; Najafzadeh et al., 2009), the majority of human studies indicate that supplementation with quercetin in aglycone form does not exert anti-oxidant effects even in daily doses up to 1,000 mg over 12 weeks (Boyle et al., 2000; Edwards et al., 2007; Egert et al., 2008; 2009; Shanely et al., 2010). Data on the effects of supplemental quercetin in lowering inflammation in human subjects also differs from in vitro and animal findings (Boots et al., 2008b; Egert et al., 2008, 2009; Knab et al., 2010). Egert et al. (2008, 2009) reported no effect of two weeks quercetin supplementation (50, 100, or 150 mg/day) on inflammatory markers in 35 healthy subjects, or in a subsequent crossover trial of 93 overweight subjects after six weeks of ingesting quercetin at a dose of 150 mg/day. A small decrease in IL-6 was reported following 12 weeks of 1,000 mg/day quercetin supplementation, but other inflammation biomarkers including C-reactive protein, tumor necrosis factor alpha (TNF-α), monocyte chemoattractant protein (MCP), and granulocyte colony stimulating factor (GCSF) were unaffected (Knab et al., 2010).

Thus the hypothesis that quercetin supplementation exerts anti-inflammatory and anti-oxidative effects in human subjects have been challenged recently because of the growing realization that quercetin is extensively transformed in the gastrointestinal tract and liver (Lotito and Frei, 2006). After ingestion, quercetin is metabolized into several glucuronides and/or sulfate conjugates with or without methylation and is not present in aglycone form (Loke et al., 2008c; Terao et al., 2008). Eventually, much of the conjugated quercetin passes into the bile through enterohepatic circulation, and reaches the colon where bacteria promote hydrolysis, ring cleavage and de-hydroxylation, forming lower molecular weight phenolics (Santos et al., 2008). After passing through the small intestine and liver, the majority of quercetin conjugates circulate in the human blood compartment in the plasma albumin fraction, and in comparison to quercetin aglycone, are more water soluble and have diminished anti-inflammatory and anti-oxidative effects (Loke et al., 2008c; Santos et al., 2008).

There is some evidence, however, that quercetin metabolites accumulate in the vascular tissue and there act as complementary antioxidants, with plasma albumin facilitating the translocation of quercetin metabolites to the vascular target (Terao et al., 2008). Activated macrophages at the site of inflamed arteries can take up quercetin conjugates where they are deconjugated into the more active aglycone and help suppress foam cell formation (Kawai et al., 2008). These data provide biologic plausibility to the impressive epidemiologic studies indicating a rather consistent disease prevention benefit when consuming diets rich in quercetin. Thus measurement of typical disease risk factors in humans using quercetin supplements or plant extracts high in quercetin may not be as revealing of health-related benefits when compared to histology-based experiments utilizing tissue taken from the

vasculature, small intestine, liver, and kidneys.

Long-term quercetin supplementation results in a highly variable plasma quercetin response, and little is known regarding factors that explain this variance. A 12-week study of 1,000 subjects randomized to placebo, 500 mg quercetin/day, and 1000 mg/day showed a wide range of plasma quercetin responses that was unrelated to gender, age, or body mass index (Jin et al., 2010). In a study of ileostomy subjects, a single 100 mg quercetin dose had a measured mean absorption rate of 24% with a large standard deviation (9%) and an accumulation in urine that varied more than 9-fold (Hollman et al., 1995). Egert et al. (2008) have speculated that the variation in plasma quercetin response to quercetin supplementation may be explained by differences in absorption rates due to polymorphisms for intestinal enzymes and transporters.

Prevention and treatment of upper respiratory tract infections (URTI) through supplementation with herbs, plant extracts, and isolated plant molecules is an active area of research, but clinical trials have led to mixed and confusing results (Linde et al., 2006; Predy et al., 2005; Schoop et al., 2006). Quercetin exerts strong antiviral activities when cultured with a wide variety of pathogens and target cells (Chen et al., 2006; Chiang et al., 2003). Quercetin also influences in vitro measures of immune function via upregulation of interferon gamma (IFN-γ), inhibition of NFκB signaling in macrophages, and augmentation of neutrophil chemotaxis and respiratory burst activity, macrophage phagocytosis, NK cell lytic activity, and mitogen-stimulated lymphocyte proliferation (Akbay et al., 2003; Exon et al., 1998; Lin et al., 2009; Nair et al., 2002; Yu et al., 2010). In mice, quercetin supplementation (12.5 mg/kg) for seven days prior to inoculation with an LD50 dose of A/Puerto Rico/8/34 (H1N1) influenza virus and a 3-day period of heavy exertion partially reduced the exercise-induced increase in morbidity and mortality (Davis et al., 2008).

The in vitro and animal data have created a strong interest in testing the efficacy of quercetin in reducing infectious illness rates in humans. A recent 12-week community trial showed a modest reduction in URTI among physically active subjects between the ages of 40-85 years consuming 1,000 mg quercetin per day, but not among younger adults (Heinz et al., 2010a). In a subgroup of these subjects, measures of innate immune function did not differ between quercetin and placebo groups (Heinz et al., 2010b). Research in this area continues, with an emphasis on quercetin-flavonoid mixtures that potentially amplify quercetin's bioactive effects.

QUERCETIN AS A COUNTERMEASURE TO EXERCISE-INDUCED PHYSIOLOGIC STRESS AND INFECTION

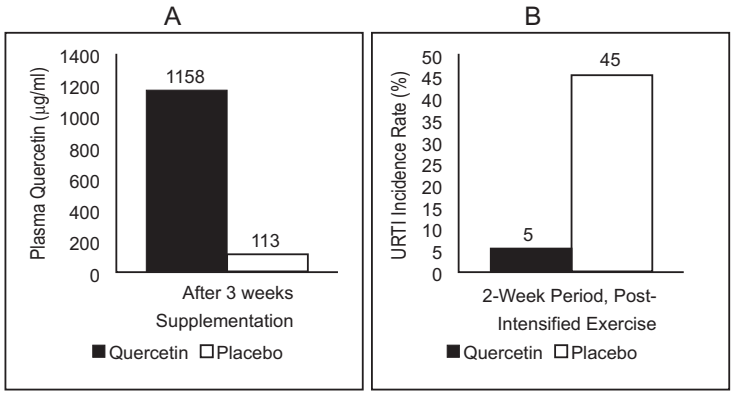
Physical activity influences immune function and risk of certain types of infection such as URTI. In contrast to moderate physical activity, prolonged and intensive exertion by endurance athletes causes heightened inflammation and oxidative stress, numerous changes in immunity in multiple body compartments, and an increased risk of URTI (Nieman, 2007, 2009). Elite endurance athletes must train intensively to compete at the highest levels and are prime candidates for immunonutrition support to bolster immune system function in the face of physiological stress (Nieman, 2008).

Various nutritional agents have been tested for their capacity to attenuate immune changes following intensive exercise and thus lower the magnitude of physiologic stress and URTI risk. This strategy is similar to the immunonutrition support provided to patients recovering from trauma and surgery, and to the frail elderly. Supplements studied thus far in human athletes include zinc, N-3 polyunsaturated fatty acids (N-3 PUFAs), plant sterols, antioxidants (e.g., vitamins C and E, beta-carotene, N-acetylcysteine, and butylated hydroxyanisole), glutamine, bovine colostrum, micronutrient mixtures, and carbohydrate. Except for carbohydrate, results have been disappointing, and focus has shifted to a new class of "advanced supplements" such as quercetin, isoquercetin, epigallocatechin 3-gallate (EGCG), β-glucan, other plant polyphenols, and N-3 polyunsaturated fatty acids (Nieman, 2008; Nieman et al., 2008; Nieman et al., 2009a,b).

Given quercetin's multiple and disparate in vitro effects, a series of human studies have been conducted to determine whether quercetin supplementation offsets exercise-induced inflammation, oxidative stress, immune dysfunction, and URTI risk, and influences exercise performance.

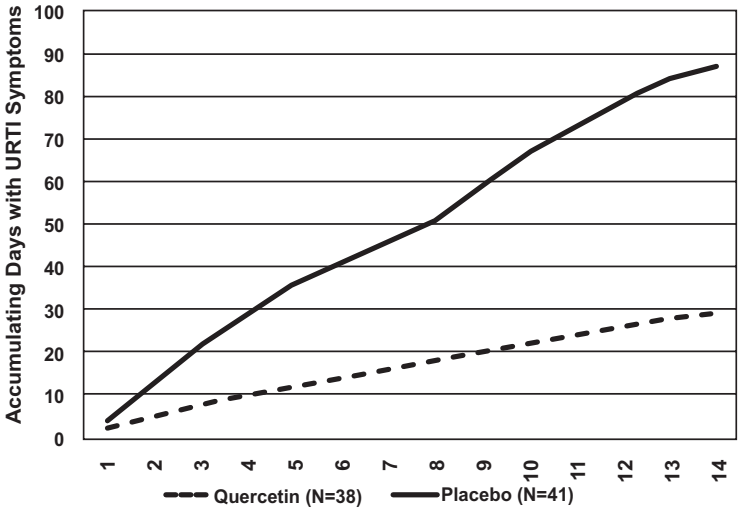
In the first study, cyclists were randomized to 1,000 mg/day quercetin or placebo for five weeks (McAnulty et al., 2008; Nieman et al., 2007b,c). After three weeks of normal training during the winter season, the athletes cycled for 3-h per day at 57% $Watts_{max}$, three days in a row. Multiple measures for inflammation, oxidative stress, and immune function were analyzed in parallel with incidence and severity of URTI. The results of this trial showed that quercetin supplementation significantly increased plasma quercetin levels and reduced incidence of URTI during the two-week period following the 3-day period of exhaustive exercise (Figure 2). Exercise induced immune dysfunction, inflammation, and oxidative stress, however, did not differ between quercetin and placebo groups.

FIGURE 2. (a) Overnight fasted plasma quercetin levels in cyclists consuming quercetin or placebo for three weeks; (b) Upper respiratory tract infection (URTI) rates (%) in cyclists during the 2-week period following intensified exercise (three hours of cycling, three days in a row) in quercetin and placebo groups (N=20 each). Source: Nieman et al., 2007c.



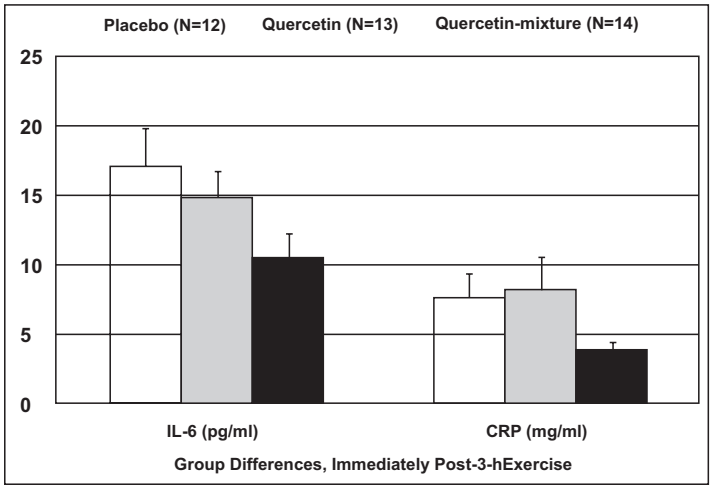
A second 5-week quercetin supplementation study with ultramarathon runners at the 160-km Western States Endurance Run (WSER) produced similar results to the laboratory-based study (Henson et al., 2008; Nieman et al., 2007a; Quindry et al., 2008). At the WSER, subjects ingested 1,000 mg quercetin or placebo supplements each day for three weeks and then just prior to the 160-km race (5:00 am), but did not ingest additional supplements until after post-race blood samples were acquired (an average of 27 h later). Plasma quercetin levels dropped to very low levels in the quercetin group and were not much different from the placebo group post-race. Quercetin supplementation had no influence on post-race inflammation, immune dysfunction, and oxidative stress when compared to placebo. URTI rates during the 2-week post-race period tended to be lower in the quercetin group, but statistical power was low given subject numbers and the time of the year (June-July). When URTI data were combined from the laboratory and field studies, a highly significant reduction in URTI rates was found following heavy exertion, with rates among athletes in the quercetin group two-thirds lower than among those in the placebo group (Figure 3).

FIGURE 3. Accumulating days of URTI per quercetin and placebo groups in endurance athletes (cyclists and ultramarathon runners, combined data) during the two week period following 3-days heavy exertion in the lab or after competing in the Western States Endurance Run. Sources: Henson et al., 2008; Nieman et al., 2007c.



The failure of quercetin supplementation to counter exercise-induced immune dysfunction, inflammation, and oxidative stress led to a reevaluation of the literature regarding the bioavailability and half-life of quercetin. One quercetin pharmacokinetics study suggests that the average terminal half-life of quercetin may be as low as 3.5 hours (Moon et al., 2008), but most other studies indicate a range of 11-28 hours (Manach et al., 2005). Additional literature indicates that isoquercetin (glycosylated quercetin) is more completely absorbed than is quercetin in aglycone form, and that the simultaneous ingestion of quercetin with vitamin C, folate, and additional flavonoids improves bioavailability (Harwood et al., 2007; Manach et al., 2005; Moon and Morris, 2007). The glucose molecule in isoquercetin may favor the use of the sodium-dependent glucose transport pathway of the intestinal brush border membrane, improving absorption rates when compared to the pure aglycone form of quercetin (Wolffram et al., 2002). Two or more flavonoids ingested together may increase bioavailability and decrease elimination via competitive inhibition of glucuronide and sulfate conjugation in both the intestine and liver, and by inhibiting efflux transporters such as P-glycoprotein, breast cancer resistance protein (BCRP), and multidrug resistance protein 2 (MRP2) (Chen et al., 2007;Kale et al., 2010; Moon and Morris, 2007; Shih et al., 2010).

FIGURE 4. Plasma IL-6 and serum C-reactive protein in cyclists immediately following 3-days heavy exertion and 2-weeks supplementation with placebo, or quercetin with or without green tea extract, isoquercetin, and fish oil. Source: Nieman et al., 2009.



Quercetin's anti-inflammatory and anti-oxidative effects may be augmented by co-ingestion of N-3 polyunsaturated fatty acids (Camuesco et al., 2006), vitamin C, vitamin E (Mostafavi-Pour et al., 2008), and EGCG (Ivanov et al., 2008). For example, the concurrent administration of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), and quercetin resulted in a synergistic anti-inflammatory effect in rats with intestinal inflammatory disorders (Camuesco et al., 2006). In vitro data indicate that quercetin exhibits antiviral activity only when protected against oxidative degradation by ascorbate (Vrijsen et al., 1988). Another potential weakness of these early human studies was the supplementation regimen. Quercetin supplements were ingested 10-24 hours prior to the completion of exercise, a time period that may have been too long given the half-life of quercetin (Manach et al., 2005; Moon et al., 2008).

We tested the influence of 2-weeks ingestion of a supplement mixture containing 1000 mg quercetin (Q-alone) with or without 120 mg epigallocatechin 3-gallate (EGCG), 400 mg isoquercetin, and 400 mg EPA-DHA (Q-mixture) on changes in measures of immunity and inflammation in trained cyclists before and after a 3-day period of heavy exertion (Nieman et al., 2009b). The Q-mixture supplement was formulated to improve the bioavailability

and bioactive effects of quercetin, and the research design was changed to emphasize ingestion of half the daily dose one hour prior to heavy exertion. Subjects cycled for three hours per day at ~57% $Watts_{max}$ to induce physiologic stress, with blood samples before and after two weeks supplementation, and immediately and 14-h following the exercise bout on the third day. Two weeks supplementation with the Q-mixture resulted in significantly reduced post-exercise measures for both inflammation and oxidative stress, with a chronic augmentation of granulocyte oxidative burst activity (Figure 4). Thus in agreement with our hypothesis, the Q-mixture supplement produced more widespread effects on inflammation and oxidative stress than quercetin alone (in particular, reduced CRP and IL-6), and was related to the coingestion of quercetin with isoquercetin, EGCG, EPA, and DHA. The morning after the 3-day period of intensified exercise, plasma quercetin levels in the Q-mixture group were elevated 98% above placebo and 54% above Q-alone, thus supporting the concept of a more prolonged quercetin effect from ingestion of the quercetin cocktail supplement.

These data add to growing literature support for the concept that quercetin's anti-inflammatory and anti-oxidative effects are amplified when coingested with other flavonoids, food components, and micronutrients. We are currently involved in research projects to determine if the proportions and amounts used in this study (i.e., 1,000 mg aglycone quercetin, 400 mg isoquercetin, 120 mg EGCG, 400 mg N3-PUFAs) are optimal, and if additional food components might add to the effects measured in this study. The duration of supplementation used in this study (two weeks prior to intensified exercise) was based in part on quercetin pharmacokinetic data and findings from animal studies, but Q-mixture's countermeasure effects may benefit from a more prolonged supplementation period. We are also involved in research to determine if one large dose of Q-mixture can acutely lower exercise-induced inflammation and oxidative stress.

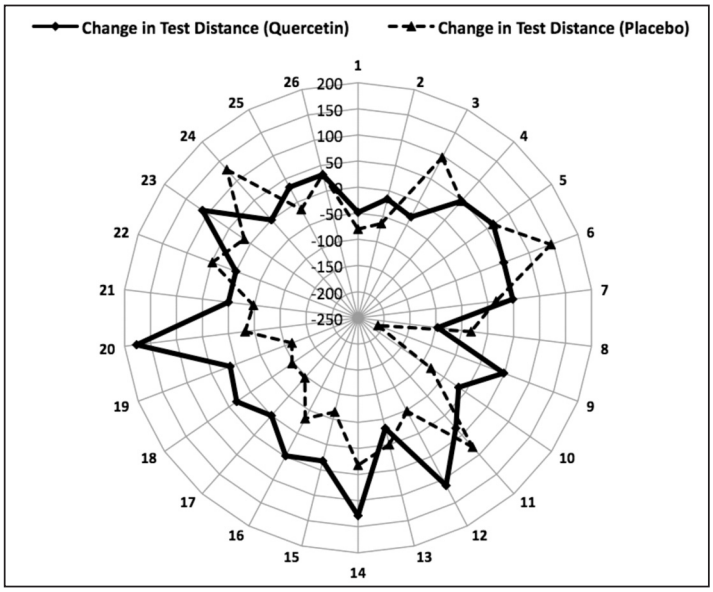
QUERCETIN'S INFLUENCE ON EXERCISE PERFORMANCE

Cardiorespiratory endurance exercise increases active skeletal muscle mitochondrial density by 20% to 100% depending on the exercise workload (Hoppeler and Fluck, 2003). This process is mediated by the increase in intracellular calcium levels during muscle contraction and involves the coordinated expression of mitochondrial and nuclear genes including the transcriptional coactivator peroxisome proliferator-activated receptor γ-coactivator-1 (PGC-1α) (Diaz and Moraes, 2008).

Investigators using animal models report that some of the adaptations in muscle phenotype elicited by exercise can be mimicked in part by energy restriction, genetic manipulation, drug treatment, and certain types of plant polyphenols including soy isoflavone derivatives, resveratrol, and epigallocatechin gallate (EGCG) (Civitarese et al., 2007; Lagouge et al., 2006; Murase et al., 2008; Narkar et al., 2008; Rasbach and Schnellmann, 2008).

Evidence indicates that quercetin supplementation also induces an increase in mitochondrial biogenesis and endurance performance in mice (Davis et al., 2009). This study with ICR male mice showed an increase in soleus muscle PGC-1α (~100%) and SIRT1 (~200%) mRNA, cytochrome C concentration (18-32%), and treadmill running time until fatigue (~37%) following a 7-day period of quercetin feeding at 12.5 mg/kg and 25 mg/kg. Mouse soleus muscle mitochondrial DNA (mtDNA) was approximately doubled after one week with the 25 mg/kg dose of quercetin but not with the 12.5 mg/kg dose. The mice were housed individually in regular cages and not trained through forced treadmill running. In a second experiment, mice fed quercetin and given access to running wheels increased running distance by 35% after six days compared to the placebo group (Davis et al., 2009).

FIGURE 5. Change in 12-minute time trial distance for each of 26 subjects following a 2-week period of quercetin or placebo supplementation (1,000 mg/day). Source: Nieman et al., 2010



A few recent studies have investigated quercetin's effects on endurance performance and mitochondrial biogenesis in human athletes. One study of 11 elite male cyclists reported a 1.7% 30-km time trial performance enhancement above placebo following six weeks of quercetin supplementation (mixed with green tea leaf extract and antioxidant vitamins) (MacRae and Mefferd, 2006). A study of 40 trained cyclists randomized to 1,000 mg/day quercetin or placebo for three weeks failed, however, to show any group differences in measures of cycling efficiency or skeletal muscle mRNA expression for PGC-1α or SIRT1 (Dumke et al., 2009). Another study of 39 trained cyclists also showed no effect of 1,000 mg quercetin a day compared to placebo on mRNA expression for mitochondrial biogenesis or cycling time trial performance when engaging in 5-km, 10-km, and 20-km time trials at the end of three 3-h cycling bouts (Nieman et al., 2009b).

The quercetin or flavonoid influence as an exercise mimetic in human mitochondrial biogenesis is probably modest. Thus quercetin supplementation may have a larger effect on mitochondrial biogenesis and endurance performance in untrained compared to exercise-trained subjects due to differences in pre-

study muscle mitochondrial density. Utilizing a randomized, crossover design with 26 untrained males, my research team measured a small but significant performance effect with 2-weeks quercetin (2.9%) compared to placebo (-1.2%) supplementation at the level of 1,000 mg/day (Figure 5) (Nieman et al., 2010). Most subjects experienced increases in mRNA expression of four genes related to skeletal muscle mitochondrial biogenesis (net range of 16 to 25% above placebo) and in mtDNA copy number (~10%) following quercetin supplementation, but P-values fell short of significance due to large inter-individual variation.

The magnitude of quercetin-induced changes in muscle PGC-1α and SIRT1 mRNA, and endurance performance in mice (Davis et al., 2009) was much higher than found in the untrained human subjects (Nieman et al., 2010). There are several potential reasons, including the applicability of findings from the mouse model to humans in quercetin and flavonoid-related research. For example, quercetin exerts antioxidant effects in the mouse (Singh et al., 2003) but thus far this effect has not been shown in humans except when combined with other flavonoids such as EGCG (Nieman et al., 2009b). Other considerations relate to supplementation issues such as the length of time quercetin was ingested, the type and amount of quercetin used.

We chose a 2-week period for both quercetin supplementation and washout, and this was based on previous human and animal studies, and quercetin's relatively short half-life. Given the metabolic and lifespan differences of mice and humans, future research is needed to determine if a longer supplementation period (e.g., 4-6 weeks) is preferable in humans to measure potential quercetin effects on mitochondrial biogenesis. For example, although data are lacking, mice and humans may differ in the extent of metabolic transformation that occurs during first-pass conjugation of quercetin in the liver. Species differences in quercetin conjugate profiles, disappearance rates, and tissue incorporation may influence the process of mitochondrial biogenesis.

Another potential issue is the quercetin dose, set in this study at 1,000 mg/day. Human subjects may require a higher quercetin dose to more consistently induce mitochondrial biogenesis. The aglycone form of quercetin was used in this study, and future research may determine that the more bioavailable isoquercetin, as found naturally in onions and apples, has greater bioactive effects, especially when combined with other flavonoids and food components. Additionally, the synergistic effect of intensive exercise training with quercetin supplementation by untrained subjects should be tested, as modeled by Narkar et al. (2008).

One other study showed no influence of quercetin supplementation on exercise performance in lightly trained males (Cureton et al., 2009). The research design, however, was not optimal to capture what appears to be a small but significant influence of quercetin supplementation on endurance performance in untrained subjects. Subjects (N=30) were randomized to quercetin (1,000 mg/day) or placebo (in a sugar-based PowerAde beverage) groups, with ingestion maintained for a variable period of 9 to 16 days. Performance cycling tests and indirect measures of muscle oxidative capacity were administered pre- and post-study. Each group only had 15 subjects, the study did not utilize a cross-over design, and the mode of exercise testing was novel to the study participants. Future quercetin-performance studies should use longer supplementation periods with quercetin consumed in combination with other flavonoids and nutrients. Multiple performance measures should also be utilized, and these should be selected to appropriately measure the desired outcome.

CONCLUSIONS

Epidemiologic studies support multiple disease prevention benefits for those consuming foods rich in quercetin such as apples, onions, berries, peppers, and dark green vegetables. In vitro and animal studies indicate that quercetin is a strong anti-oxidant and anti-inflammatory agent, and exerts anti-pathogenic and immune regulatory influences. Quercetin supplementation studies in community-dwelling humans do not reflect these positive benefits, but research is ongoing to determine the proper outcome measures, dosing regimen, and adjuvants that may amplify quercetin's in vivo bioactive effects.

Quercetin supplementation studies in athletes have focused on potential influences on endurance performance, illness rates following periods of physiologic stress, and post-exercise inflammation, oxidative stress, and immune dysfunction. Results thus far have been negative for quercetin's countermeasure effects on post-exercise physiologic stress indicators, but supportive for a positive effect of quercetin in reducing illness rates in exercise-stressed athletes, and in improving endurance performance, especially in untrained subjects. However, when quercetin supplementation is combined with other polyphenols and food components such as green tea extract, isoquercetin, and fish oil, a substantial reduction in exercise-induced inflammation and oxidative stress occurs in athletes, with chronic augmentation of innate immune function.

The quercetin-related effects on performance and mitochondrial biogenesis in untrained humans are modest and far below those reported in mice (Davis et al., 2009). Future research should emphasize multiple types of performance measures, longer supplementation periods in humans, and combined ingestion with adjuvants including EGCG, luteolin, tiliroside, and isoquercetin that may augment quercetin's bioactive effects on mitochondrial biogenesis and post-exercise inflammation and oxidative stress. The potential synergism between initiation of exercise training and quercetin supplementation should be studied to determine if untrained subjects achieve amplified performance outcomes. In general, quercetin's bioactive effects support athletic endeavor, but additional research is needed to better define the optimal dosing regimen and adjuvants that optimize benefits during heavy training and competition.

CONFLICT OF INTEREST STATEMENT: David C. Nieman is a member of the scientific advisory board for Quercegen Pharma.

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