The Dietary Flavonoid Quercetin Increases VO$_{2\text{max}}$ and Endurance Capacity

J. Mark Davis, Catherine J. Carlstedt, Stephen Chen, Martin D. Carmichael, and E. Angela Murphy

Quercetin, a natural polyphenolic flavonoid substance present in a variety of food plants, has been shown in vitro and in animal studies to have widespread health and performance benefits resulting from a combination of biological properties, including antioxidant and anti-inflammatory activity, as well as the ability to increase mitochondrial biogenesis. Little is known about these effects in humans, however, especially with respect to exercise performance. The authors determined whether quercetin ingestion would enhance maximal aerobic capacity and delay fatigue during prolonged exercise in healthy but untrained participants. Twelve volunteers were randomly assigned to 1 of 2 treatments: (a) 500 mg of quercetin twice daily dissolved in vitamin-enriched Tang or (b) a nondistinguishable placebo (Tang). Baseline VO$_{2\text{max}}$ and bike-ride times to fatigue were established. Treatments were administered for a period of 7 days using a randomized, double-blind, placebo-controlled, crossover study design. After treatment both VO$_{2\text{max}}$ and ride time to fatigue were determined. Seven days of quercetin feedings were associated with a modest increase in VO$_{2\text{max}}$ (3.9% vs. placebo; $p < .05$) along with a substantial (13.2%) increase in ride time to fatigue ($p < .05$). These data suggest that as little as 7 days of quercetin supplementation can increase endurance without exercise training in untrained participants. These benefits of quercetin may have important implications for enhancement of athletic and military performance. This apparent increase in fitness without exercise training may have implications beyond that of performance enhancement to health promotion and disease prevention.

**Keywords:** fatigue, exercise performance, nutrition, human subjects

Quercetin is one of a broad group of natural polyphenolic flavonoid substances that are being investigated for their widespread benefits to health and performance. Quercetin, one of the most abundant natural flavonoids, is present in a wide variety of fruits, vegetables, and berries (Harwood et al., 2007). These compounds have been shown to possess multiple biological properties including antioxidant and anti-inflammatory activity (Hamalainen, Nieminen, Vuorela, Heinonen, & Moilanen, 2007; Harwood et al.; Justino et al., 2004; Lee, Kim, Park, The authors are with the Div. of Applied Physiology, Dept. of Exercise Science, Arnold School of Public Health, University of South Carolina, Columbia, SC 29208.
Davis et al. (2003) and, perhaps most exciting, the ability to increase mitochondrial biogenesis in both muscle and brain in mice (Davis, Murphy, Carmichael, & Davis, 2009). However, very little of this evidence comes from human studies, especially with respect to exercise performance.

An increase in muscle mitochondrial content is one of the most important factors responsible for increased endurance-exercise performance in response to exercise training. The typical doubling of muscle mitochondria that occurs during exercise training plays an important role in the increase in maximal O2 uptake (VO2max), shift in substrate utilization toward increased oxidation of fat relative to carbohydrate, increased lactate threshold, and fatigue resistance (Calvo et al., 2008; Holloszy & Coyle, 1984). Until recently there were no other practical behavioral means to increase mitochondrial biogenesis. However, evidence is accumulating rapidly to show that natural flavonoids, such as quercetin and resveratrol, and flavonoid derivatives (i.e., drugs) can increase mitochondrial biogenesis via intracellular signaling pathways involving peroxisome proliferator-activated receptor-γ coactivator (PGC-1α) and sirtuin 1 (SIRT1), which have been linked to improved endurance and health in mice (Lagouge et al., 2006; Narkar et al., 2008; Rasbach & Schnellmann, 2008). Of particular interest regarding the effects of quercetin on endurance is our recent study showing that short-term feedings of quercetin in mice increased mitochondrial biogenesis in muscle and brain, along with an increase in both maximal endurance capacity (forced treadmill running) and voluntary physical activity (24-hr voluntary wheel running; Davis et al., 2009). The potent antioxidant and possible psychostimulant effects of quercetin could also play a role in increasing endurance capacity (Alexander, 2006; Justino et al., 2004; Lee et al., 2003). Strenuous exercise increases free-radical content in skeletal muscle, which has been shown to promote fatigue in certain circumstances (Reid, 2008). However, the use of antioxidant nutrients, including quercetin, in conjunction with prolonged intense exercise has had limited success in reducing oxidative stress and fatigue (MacRae & Mefferd, 2006; McAnulty et al., 2008; Reid). Quercetin may also enhance endurance capacity via a caffeinlike psychostimulant effect. Quercetin, like caffeine, is an adenosine-A1-receptor antagonist, at least in vitro (Alexander), and the delay in fatigue that occurs with cafeine results at least in part from its ability to block adenosine receptors in the brain (Davis et al., 2003; Ferre, 2008).

To date there has been only one study on the effects of quercetin on endurance performance in humans (MacRae & Mefferd, 2006). McRae and Mefferd reported a small (3%) improvement in bike time-trial performance after 6 weeks of quercetin supplementation (2 × 300 mg twice daily) in a commercial beverage (FRS, The FRS Co., Foster City, CA). However, the benefit of quercetin was found only with respect to an improvement over the initial baseline period, not when comparing time-trial performance after the quercetin and placebo treatments. In addition, the specific effects of quercetin could not be determined because quercetin was administered in combination with caffeine and tea catechins that might have interacted positively or negatively with it. Therefore, to further evaluate the possible benefits of quercetin supplementation on endurance capacity in humans, we tested the effects of 7-day feedings of quercetin on VO2max and fatigue resistance during prolonged cycling in healthy, untrained college students. Untrained participants were used instead of highly trained cyclists to avoid the possibility
that mitochondrial content and antioxidant capacity would have reached a physiological ceiling.

Participants and Methods

Participants

Twelve student volunteers (7 men and 5 women, mean age 22.9 ± 2.4 years, VO$_{2\max}$ 45.5 ± 1.3 ml/kg; Table 1) participated in this double-blind, placebo-controlled, crossover study (Figure 1). Testing for each participant was performed at the same time each day in a climate-controlled (approximately 22°C and 60% humidity) laboratory. All participants were involved in regular activity and considered fit but were not highly trained. They were recruited through flyers posted around the university campus. To be considered for inclusion, participants had to have a VO$_{2\max}$ value greater than 35 ml · kg$^{-1}$ · min$^{-1}$ and not be currently involved in an aerobic exercise-training program. They were asked not to alter their diet or over-the-counter medications during the course of the study, especially during the 24 hr before exercise testing.

Preliminary Session

Participants attended a preliminary session at which experimental procedures and participation requirements were explained, a health-history questionnaire was completed, and informed consent was obtained. The study’s experimental protocol was approved by the institutional review board of the University of South Carolina.

VO$_{2\max}$ Test

To determine VO$_{2\max}$, we had participants undergo a graded exercise test on a bike attached to a Computrainer Pro (RacerMate Inc., Seattle, WA). Testing was begun at 60 W for women, which was increased by 30 W every 3-min stage. Testing began at 70 W for men, increasing by 40 W every 3-min stage. If a participant performed past a fifth stage, wattage was increased every minute. Gas analysis was performed on a Moxus Modular VO$_2$ System (AEI Technologies, Inc., Naperville, IL), which was calibrated before each test. Metabolic measurements were

Table 1  Participant Characteristics

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Age</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>VO$_{2\max}$ (ml · kg$^{-1}$ · min$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>5</td>
<td>24.2</td>
<td>166.2 ± 2.1</td>
<td>56.2 ± 1.7</td>
<td>43.0 ± 2.3</td>
</tr>
<tr>
<td>Male</td>
<td>7</td>
<td>22.0</td>
<td>177.8 ± 2.3</td>
<td>72.5 ± 3.0</td>
<td>47.3 ± 1.1</td>
</tr>
<tr>
<td>M</td>
<td></td>
<td>22.9</td>
<td>173.0 ± 8.0</td>
<td>65.7 ± 3.0</td>
<td>45.5 ± 1.3</td>
</tr>
</tbody>
</table>

Note. Student volunteers participated in this double-blind, placebo-controlled, crossover study. All participants were involved in regular activity and considered fit but were not trained. Inclusion criteria included a VO$_{2\max}$ value greater than 35 ml/kg.
Davis et al. calculated every 20 s throughout the duration of the test. Before beginning the test, participants were introduced to a rating of perceived exertion (RPE) scale and instructed on its proper use. Heart rate was recorded the last 15 s of each stage, and RPE was recorded at the beginning of the final minute of each 3-min stage. Criteria used by investigators to determine VO2max were as follows: VO2 values did not increase with a subsequent increase in workload, heart rate > 90% age-predicted maximal heart rate, respiratory-exchange ratio > 1.1, and RPE > 17. VO2max was determined when all four of the criteria were met.

**Endurance Ride**

Twenty-four hours after the VO2max test, participants performed a ride to fatigue on the same bike attached to a Computrainer that was used for their VO2max testing. The ride was performed at a power output that was 75% of that attained at VO2max. Wattage and pedal cadence were monitored to ensure that participants maintained the prescribed power, but these data were not collected throughout the bout for later analysis. Before beginning, the participants performed a 5-min warm-up. Water was provided at 15-min intervals (2.5 ml/kg) to ensure adequate hydration. Before beginning the ride, participants were encouraged to give a maximal effort and were instructed on the importance of this performance bout, but no encouragement of any kind was given during the ride. Fatigue was determined when participants felt they could no longer continue (RPE > 17) and could not maintain a cadence of 50 rpm for 30 s.

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**Figure 1** — Study design and timeline. A double-blind, placebo controlled, crossover study was used to examine the effects of 7 days of quercetin supplementation on maximal oxygen consumption (VO2max) and endurance capacity on healthy, fit but untrained participants.
Supplementation

Doses of 500 mg of food-grade quercetin powder (QU 995, Nutravail Technologies, Chantilly, VA) dissolved in enriched sugar-free Tang (Kraft Foods, Northfield, IL) or a nondistinguishable placebo (enriched Tang with yellow food coloring), consumed twice daily (in the morning before breakfast and in the evening before dinner), were randomly assigned to participants in a double-blind and counterbalanced fashion. Tang masks the taste, texture, and color of quercetin very well. Participants received treatments predissolved in squeeze bottles. The treatment bottles were opaque with identical tops to ensure that participants could not determine one treatment from the other. Prior testing in the laboratory had confirmed that taste and mouth feel of the treatments were indistinguishable from one another. Each participant received either quercetin or placebo for 1 week, followed by exercise tests on Days 7 and 8; they were then immediately crossed over to the other treatment for the next week, followed by the exercise tests. The 7-day feeding schedule was chosen based on a similar study in mice in which quercetin increased mitochondrial biogenesis and exercise tolerance (Davis et al., 2009). There was no washout period between treatments. This decision was based on well-documented plasma half-lives and biological effects of quercetin in vitro and in animal studies (Harwood et al., 2007), including a mouse study from our laboratory indicating that the effects of quercetin on mitochondria and performance are lost after 7 days without quercetin (unpublished data). At worst, if this were not the case in human participants, any residual effects from quercetin in the participants who received the placebo second might be an underrepresentation of the true benefit of quercetin. It would therefore only be a problem if the hypothesized benefit of quercetin were not supported. On the final day of supplementation (Day 7), 60 min after their last treatment, participants performed their VO$_{2\text{max}}$ test, followed 24 hr later by the ride-to-fatigue test. All data-collection procedures during these tests were identical to those during the preliminary session. On Day 9 participants began their second 7-day treatment ingestion followed by a final VO$_{2\text{max}}$ test on Day 15 and ride to fatigue on Day 16.

Statistical Analysis

Twelve student volunteers participated in this double-blind, placebo-controlled, crossover study to examine the effects of quercetin on VO$_{2\text{max}}$ and ride time to fatigue. All 12 participants took part in the quercetin and placebo conditions, with an equal number participating in the quercetin ($n = 6$) and placebo ($n = 6$) treatments during Trial 1 and Trial 2. This was to control for the possibility of order effects. A Student’s $t$ test (paired samples) was used to determine the effect of 7 days of quercetin supplementation versus 7 days of placebo on VO$_{2\text{max}}$ and ride time to fatigue. All data were analyzed at a significance level of $p < .05$ (Systat Software, Inc., Chicago, IL) and are expressed as $M \pm SE$. 
Figure 2 — Short-term quercetin supplementation increased maximal oxygen consumption (VO$_{2\text{max}}$) in healthy, fit but untrained participants (*$p < .05$; Figure 2[A]). Quercetin supplementation (500 mg twice daily) for 7 days increased VO$_{2\text{max}}$ by approximately 3.9% relative to the placebo condition. Ten of the twelve participants had a higher VO$_{2\text{max}}$ after quercetin treatment than with placebo (Figure 2[B]).
Results

\[ \text{VO}_{2\text{max}} \]

Tests were conducted to determine the effect of quercetin, if any, on VO\(_{2\text{max}}\). Quercetin supplementation (500 mg twice daily for 7 consecutive days) was associated with a significantly higher VO\(_{2\text{max}}\) by about 3.9% relative to the placebo condition (47.7 ± 1.2 ml · kg\(^{-1}\) · min\(^{-1}\) [3.09 ± 0.14 L/min] vs. 45.9 ± 1.1 ml · kg\(^{-1}\) · min\(^{-1}\) [2.97 ± 0.13 L/min], respectively; \(p < .05\); Figure 2[A]). Body mass was not different between the quercetin and placebo trials (64.1 ± 2.3 and 63.8 ± 2.2, respectively; \(p > .05\)). Ten of the twelve participants had a higher VO\(_{2\text{max}}\) after quercetin treatment than with placebo (Figure 2[B]). VO\(_{2\text{max}}\) levels in the placebo and quercetin trials were approximately 1.4% and 5.2% greater than at baseline, respectively. This information is presented for general comparison purposes only. It is not appropriate to include the baseline data in the statistical analysis because they were collected before the random assignment of participants to experimental groups and the start of the crossover experiment. Baseline tests were performed to familiarize participants with the experimental protocols and to determine whether they met the inclusion criteria in terms of VO\(_{2\text{max}}\) and ability to complete the ride to fatigue at the appropriate power output. Even though an equal number of participants took part in the placebo and quercetin treatments during the first and second 7-day treatment periods in this crossover design, a post hoc analysis was performed to rule out a possible order effect. The analysis showed that there was no order effect for VO\(_{2\text{max}}\) when comparing baseline (45.5 ± 1.3 ml · kg\(^{-1}\) · min\(^{-1}\)), Trial 1 (46.8 ± 1.2 ml · kg\(^{-1}\) · min\(^{-1}\)), and Trial 2 (46.5 ± 1.0 ml · kg\(^{-1}\) · min\(^{-1}\); \(p > .05\)).

\[ \text{Ride Time to Fatigue} \]

Ride time to fatigue was 93.4 ± 6.6 min in the placebo condition and 105.7 ± 6.3 min in the quercetin condition, which represents approximately a 13.2% improvement in endurance capacity when participants consumed quercetin (\(p < .05\); Figure 3[A]). Eight of the twelve participants rode longer after quercetin treatment than with placebo treatment (Figure 3[B]), and 3 of the 4 participants who did not improve had similar ride times after both treatments. The differences in ride time to fatigue for baseline versus the placebo and quercetin treatments (approximately 12.9% and 26.2%, respectively) are larger than for VO\(_{2\text{max}}\), which is not unusual given the bigger influence that familiarization and learning have on time-to-fatigue tests. A post hoc analysis on a possible order effect was also done here. As expected, there was no effect of trial when comparing Trial 1 (99.4 ± 6.6 min) and Trial 2 (100.5 ± 7.0 min); however, ride times in Trial 1 and Trial 2 were both significantly better (\(p < .01\)) than at baseline (83.5 ± 6.1 min). This improvement in endurance capacity from baseline to Trials 1 and 2 is most likely attributable to a learning effect from being familiarized with the exercise protocol during the baseline measurement.
Figure 3 — Short-term quercetin supplementation increased ride time to fatigue during a prolonged endurance bout (*p < .05; Figure 3[A]). Quercetin supplementation (500 mg twice daily) for 7 days in healthy, fit but untrained participants increased ride time to fatigue by approximately 13.2%. Eight of the twelve participants rode longer after quercetin treatment than with placebo treatment (Figure 3[B]).
Discussion

Various nutritional strategies have been examined for their ability to delay fatigue during prolonged exercise, including carbohydrate and fluid replacement, which have proven successful (Coyle, Coggan, Hemmert, & Ivy, 1986). However, the vast majority of nutritional supplements with such claims have either not been studied or have been shown to be ineffective. Quercetin offers a unique combination of biological properties including antioxidant and anti-inflammatory activity, caffeinelike psychostimulant activity, and, more important, the ability to increase mitochondrial capacity in muscle and brain (Alexander, 2006; Davis et al., 2009; Harwood et al., 2007; Justino et al., 2004; Lee et al., 2003). In addition, evidence now shows that quercetin and other similar compounds can increase VO$_{2\text{max}}$, maximal endurance capacity, and voluntary physical activity in sedentary mice (Davis et al., 2009; Lagouge et al., 2006). However, with the exception of a single study involving highly trained cyclists that reported an approximately 3% increase in 30-km cycling time-trial performance after 6 weeks’ consumption of a cocktail containing quercetin (MacRae & Mefferd, 2006), these benefits of quercetin have not been examined in humans. The primary purpose of this study was to more specifically determine the effects of quercetin on VO$_{2\text{max}}$ and endurance capacity in healthy, fit but untrained participants. A simple ride-time-to-fatigue test at a constant power output elicited at 75% VO$_{2\text{max}}$ was used instead of a time-trial performance test to better determine the presumed benefit of quercetin on fatigue that would result from an increase in mitochondrial capacity. Time-trial performance tests may or may not be limited by metabolic factors. We also reasoned that untrained participants are more likely to benefit from quercetin than highly trained participants, who may have already reached a ceiling with respect to antioxidant and mitochondrial capacity (Brooks, Vasilaki, Larkin, McArdle, & Jackson, 2008; Hood et al., 2006). We show here for the first time that dietary supplementation with quercetin (500 mg twice daily for just 7 days) increased both VO$_{2\text{max}}$ and endurance capacity in healthy untrained participants. The relative benefits of quercetin on endurance performance in this study versus MacRae and Mefferd’s (increases of 13% vs. 3%) might be explained in part by their use of highly trained “elite” cyclists who may have reached a physiological ceiling for mitochondrial content and antioxidant capacity (Brooks et al.; Hood, Irrcher, Ljubicic, & Joseph, 2006).

Although this study was not designed to determine the biological mechanisms of the benefit of 7-day feedings of quercetin on VO$_{2\text{max}}$ and endurance capacity, the most likely explanation may involve an increase in mitochondrial biogenesis. This hypothesis is consistent with recent in vitro and in vivo evidence from rodent studies that have shown that natural flavonoids such as quercetin and resveratrol, along with their derivatives, have the ability to alter mitochondrial-membrane characteristics and energetic processes (Dorta et al., 2005; Rasbach & Schnellmann, 2008; Trumbeckaite et al., 2006) and to stimulate mitochondrial biogenesis (Davis et al., 2009; Lagouge et al., 2006). For example, short-term feedings (7 days) of quercetin in mice increased mitochondrial biogenesis in both muscle and brain tissue that was associated with increased PGC-1$\alpha$ and SIRT1 gene expression, which are responsible for mitochondrial biogenesis, and increased mitochondrial DNA and cytochrome c. An increase in both maximal
endurance capacity and voluntary wheel running also occurred in the mice fed quercetin. This increase in endurance capacity would be expected because increased mitochondrial capacity plays a primary role in the increase in oxygen utilization, shift in substrate utilization toward increased oxidation of fat relative to carbohydrate, and increased lactate threshold that are primary limiting factors to endurance performance (Calvo et al., 2008; Holloszy & Coyle, 1984). \( \text{VO}_2\text{max} \) is also influenced to a great extent by muscle mitochondrial oxidative capacity, but, relative to endurance capacity, it is limited to a greater extent by oxygen delivery by the cardiovascular system (Bassett & Howley, 2000). The fact that quercetin in this study affected endurance capacity more than \( \text{VO}_2\text{max} \) (approximately 13% vs. 4%, respectively) is consistent with this notion because there is no evidence that quercetin has important effects on cardiovascular dynamics during exercise.

Quercetin’s powerful antioxidant activity may have also contributed to its beneficial effect on fatigue in this study. Although the generation of some reactive oxygen species (ROSs) is likely necessary for normal muscle adaptation, increased production may be counterproductive and can cause fatigue in some circumstances. ROSs have been shown to alter Ca\(^{2+}\) dynamics in numerous studies by reducing Ca\(^{2+}\) sensitivity, stimulating Ca\(^{2+}\) release channels, and reducing Ca\(^{2+}\) reuptake (Reid, 2008). The relationship between ROS production and exercise performance in humans has been demonstrated in interventional studies that used antioxidant treatments before exercise to enhance performance (Reid). However, unlike the well-characterized benefits of increased mitochondria on endurance performance and \( \text{VO}_2\text{max} \), the evidence for a specific benefit of antioxidant nutrients, including quercetin, on fatigue is limited (McAnulty et al., 2008; Reid).

Another potential explanation of the benefit of quercetin on fatigue may be its caffeinelike psychostimulant effect. Numerous studies have shown that psychostimulants can delay fatigue during exercise, at least in part because of their ability to block adenosine receptors in the brain and the resulting increase in dopamine activity (Davis et al., 2003; Ferre, 2008; Graham & Spriet, 1995). Recently, various flavonoids have been reported to possess adenosine-A\(_1\)-receptor antagonist activity similar to that of caffeine in vitro (Alexander, 2006). Of the flavonoids tested, quercetin was shown to have the highest affinity for this receptor (Alexander). Further evidence for this effect in mice comes from data from our laboratory that showed increased expression of adenosine A\(_1\) receptors in the brain after 7 days of quercetin feedings, which was associated with an increase in voluntary wheel-running activity (unpublished). In contrast, a recent study in humans reported no effect of an acute large dose of quercetin (2 g) on exercise performance in the heat (Cheuvront et al., 2009). However, it is not certain to what extent the thermal stress may have diminished the possible benefits of quercetin, because the typical ergogenic benefit of caffeine was also not found under these conditions. In this experiment, it is possible that the acute effect of quercetin contributed to the increase in \( \text{VO}_2\text{max} \) because the last dose of quercetin was consumed 60 min before the start of the test. However, the criteria for attaining \( \text{VO}_2\text{max} \) are largely not influenced by central nervous system effects like arousal or motivation. This is not an issue with respect to endurance capacity because it was performed 24 hr after the consumption of the last quercetin supplement, and the plasma half-life of quercetin is 6–12 hr (Egert et al., 2008). We did not specifically
measure plasma quercetin levels in this study, but analysis in our laboratory using the same dose resulted in maximal plasma concentrations of more than 1,500 µg/L, with peak levels from 2–3 hr (Davis, Murphy, & Carmichael, in press).

In summary, short-term feedings of relatively low doses of the naturally occurring dietary flavonoid quercetin were associated with a modestly higher maximal oxygen consumption, along with a substantially higher endurance capacity in healthy, fit but untrained participants. Quercetin supplementation at these doses is safe (Harwood et al., 2007; Utesch et al., 2008) and accumulates quickly in the blood after ingestion, with peak concentration occurring in 1–3 hr and a half-life of 6–12 hr (Davis et al., in press; Egert et al., 2008). If the findings of this study and hypothesized biological mechanisms are confirmed in more rigorous human clinical trials, the implications of this novel nutritional strategy go far beyond improvements in endurance capacity to possible prevention and treatment of metabolic (e.g., diabetes, obesity), cardiovascular, and various degenerative diseases of aging in which mitochondrial dysfunction and physical inactivity are hallmarks (Taivassalo & Haller, 2005; Tarnopolsky & Raha, 2005).

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References


