The Influence of Short-term Quercetin Supplementation on Peak Oxygen Uptake during Simulated Altitude Exposure in Trained Cyclists

JUSTIN CARLSTROM[‡1], JAMIE M. VENER[‡2], JUSTIN L. MATTHEWS[‡3], and ASHLEIGH RAUB[*1]

[1]Castleton College, Castleton, VT, USA; [2]Southern Oregon University, Ashland, OR, USA; [3]California State University, Monterey Bay, Seaside, CA, USA

‡Denotes professional author, *Denotes undergraduate student author

ABSTRACT

International Journal of Exercise Science 8(4): 394-402, 2015. Endurance performance and peak oxygen uptake (VO_{2peak}) decline as altitude increases. Some data exist suggesting that quercetin supplementation improves aerobic capacity in trained and untrained individuals at sea-level (normobaric normoxic conditions). Few studies have examined the effects of quercetin on endurance performance during simulated altitude exposure (normobaric hypoxic conditions). The purpose of this study was to determine the effects of consuming 1000 mg·day^{-1} of quercetin for two weeks on cycling VO_{2peak} in healthy trained male cyclists performing under normobaric normoxic and hypoxic conditions (NP and HP, respectively). Fourteen age-matched healthy male subjects were randomized to either a placebo or quercetin group. Baseline and post supplementation VO_{2peak} values were quantified during incremental cycling under normobaric normoxic (FIO_2 = 20.9%) and normobaric hypoxic (FIO_2 = 13.6 $\pm$ 0.2%) conditions. Subjects consumed capsules twice daily with either 500 mg quercetin or placebo (Tang) for two weeks and were re-assessed. Test order was randomized and assessments were separated by 48-72 hours. At baseline, there were no significant differences between groups for VO_{2peak} normobaric normoxic trials ($NP_{baseline}$ Placebo vs. $NP_{baseline}$ Quercetin = 58.7$\pm$8.8 and 61.5$\pm$7.9 ml · kg^{-1} · min^{-1}, respectively, p = 0.541) and normobaric hypoxic trials ($HP_{baseline}$ Placebo vs. $HP_{baseline}$ Quercetin = 48.5$\pm$8.3 and 50.8$\pm$4.8 ml · kg^{-1} · min^{-1}, respectively, p = 0.534). No significant differences were found after treatment (Placebo: $NP_{baseline}$ vs. NP_{post} = 58.7$\pm$ 8.8 and 56.7$\pm$7.4 ml · kg^{-1} · min^{-1}, respectively, p = 0.10; $HP_{baseline}$ vs .HP_{post} = 48.5$\pm$8.3 and 47.1$\pm$8.3, respectively, p = 0.50; Quercetin: $NP_{baseline}$ vs. NP_{post} = 61.5$\pm$7.9 and 62.4$\pm$7.3 ml · kg^{-1} · min^{-1}, respectively, p = 0.558; $HP_{baseline}$ vs. HP_{post} = 50.8$\pm$4.8 and 51.2$\pm$3.8 ml · kg^{-1} · min^{-1}, respectively, p= 0.656. These data suggest that short-term quercetin supplementation at 1000 mg · day^{-1} does not affect VO_{2peak} elicited via incremental maximal cycle testing under normobaric normoxic and hypoxic conditions in trained male cyclists. Furthermore, quercetin supplementation did not attenuate the decline in VO_{2peak} that was evident in the normobaric hypoxic condition.

KEY WORDS: Hypoxia, VO_{2Peak}, cycling, endurance performance

INTRODUCTION

In recent years, much attention has been given to the role of dietary antioxidants in preventing disease and improving overall health. Quercetin, a polyphenolic flavonoid, is a naturally occurring substance that is found in a variety of food.

Common food sources of quercetin include tea, onions, apples, peppers, blueberries and dark green vegetables, with the average intake of U.S. adults at approximately 4 mg $\cdot$ day^{-1}. However, daily intakes may be as high as 200 – 500 mg in individuals consuming a diet high in fruits and vegetables (5). Although not entirely conclusive, epidemiologic studies provide evidence that self-selected diets high in quercetin may play a role in preventing various diseases. High quercetin intake has been linked to a reduced risk of colorectal, kidney, pancreatic, prostate, and lung cancer, as well as cardiovascular disease (10, 11, 29). *In vitro*, animal, and human studies have shown that quercetin possesses antioxidant, anti-carcinogenic, anti-inflammatory, and cardioprotective properties (3, 12, 14, 23, 26). In addition, there is evidence that quercetin may lower blood pressure through vasodilatory effects (14, 19). Based on these studies, quercetin appears to have significant health benefits.

Because of the purported health benefits of quercetin, investigators have begun to examine the efficacy of quercetin in improving athletic performance. Regular aerobic exercise can increase muscle mitochondrial density by 20% to 100%, depending on the workload (13). This increase in mitochondrial density contributes to improved fitness and performance by increasing the aerobic capacity of skeletal muscle. Limited data show that quercetin may have the ability to induce mitochondrial biogenesis and improve aerobic exercise performance. Human studies have shown that daily supplementation of quercetin (500 mg twice daily) improves aerobic capacity, time to exhaustion, time trial performance, and exercise tolerance (20, 21). Furthermore, recent evidence from both animal and human studies suggests that quercetin supplementation resulted in increased mitochondrial capacity, oxidative enzyme activity, and increased time to exhaustion (8, 9). Additional data show that quercetin may cause vasodilation, resulting in improved blood flow (5, 18, 22). An increase in blood flow to working muscle, coupled with an increase in mitochondrial density, could result in improved endurance performance by increasing an individual's aerobic capacity and fat utilization. Although these data support the use of quercetin to improve aerobic performance, other studies have shown that quercetin has no effect on aerobic capacity (1, 6). More work is needed in this area to better define the efficacy of quercetin in improving athletic performance under various conditions.

It is well established that altitude decreases VO$_{2peak}$ in humans and evidence suggests that oxidative stress increases at altitude (16, 27). Consequently, the use of nutritional interventions, such as antioxidant supplementation to enhance antioxidant capacity and prevent and/or treat symptoms of acute mountain sickness has gained attention. Although justification for their use is not based on scientific evidence, *Ginkgo Biloba* and *Hippophae rhamnoides* L. have been used for centuries in Chinese and Tibetan medicine to combat AMS (24). Data from Purushothama et al. (2008) show that *H. rhamnoides* exerted a protective effect in rats exposed to hypoxia (24). Quercetin is a major component of this supplement (30). However, there is very limited data regarding the efficacy of isolated quercetin in attenuating the effects

of hypoxia *in vivo*. Zhou et al. investigated the protective effect of quercetin in rats exposed to a chronic (23 h per day) hypobaric, hypoxic environment (31). Quercetin attenuated the decline in blood pH, PO_2, SpO_2, and PCO_2 that occurred in the control group. In addition, quercetin increased nitric oxide levels, a potent vasodilator (31). Based on this limited data, it is plausible that quercetin may exert protective effects in an individual exposed to a hypoxic environment.

Significant reductions in VO_{2peak} generally occur at an altitude of 1,500 to 1,600 m (5,000 ft). Beyond this altitude, VO_{2peak} decreases approximately 8% to 11% for every 1,000 m increase (or 3% for every 1,000 ft increase) (27). In addition, variables such as heart rate, ventilation, and perception of fatigue, at rest and during exercise, are increased at higher elevation. The lack of oxygen at altitude also affects substrate metabolism. At altitude, there is an increased reliance carbohydrate for fuel since this substrate can be metabolized anaerobically (4, 17). Therefore, aerobic exercise at altitude may be limited, in part, by glycogen depletion, as this is a very limited fuel supply. Due to the detrimental effect of altitude on athletic performance, many studies have investigated various nutritional strategies in an effort to offset the performance decrement typically seen in an individual performing in that environment. Recent studies have examined the efficacy of antioxidants and other nutritional supplements in 1) attenuating the decline in VO_{2max} and 2) enhancing fat utilization, thus sparing glycogen, in individuals exercising at altitude. However, there is very limited data regarding the efficacy of quercetin in

enhancing aerobic performance and fat utilization at altitude. The overall goal of this investigation is to examine the effect of quercetin on peak oxygen uptake (VO_{2peak}) in trained individuals exercising under normobaric normoxic and hypoxic conditions.

METHODS

Participants
Fourteen healthy male subjects (age: 38.9 $\pm$ 9.8 y, weight: 75.7 $\pm$ 7.9 kg) were recruited through flyers posted on the Castleton State College campus and throughout the Rutland community, and through solicitation of the Killington Pico Cycling Club. Prior to data collection, participants were advised of the possible risks, methods, and potential benefits of participation in the study. A health history questionnaire and informed consent (approved by the Castleton State College Institutional Review Board for research involving human subjects) was completed by each subject.

Protocol
Subjects were age-matched and randomized to either a placebo group (consumed one capsule twice daily with 500 mg Tang from the Kraft Foods Company, Northfield, IL) or quercetin supplementation group (consumed one capsule with 500 mg twice daily with quercetin from Jarrow Formulas, Los Angeles, CA) in a double-blind design. Subjects had no significant recent exposure to altitude training or racing and were asked to maintain their typical training and dietary routines for the duration of the study. Subjects were instructed to refrain from strenuous exercise and excessive alcohol for 24 hours prior to testing.

Subjects maintained a dietary record for 48 hours prior to initial testing and were asked to match it as closely as possible for each successive trial. All maximal trials were separated by 48-72 hours.

Metabolic data was collected using a ParvoMedics metabolic system (ParvoMedics, Salt Lake City, UT). All testing was conducted using an electronically-braked cycle ergometer designed to interface with the subject's personal cycle of choice (Velotron DynaFit Pro, Seattle, WA). Subjects completed a five minute warm-up at a workload of 50 watts at the start of each trial. Using a continuous incremental protocol, workload increased by 25 watts per minute until volitional exhaustion was achieved. All tests were terminated after subjects failed to maintain their final workload for 15 seconds and/or voluntarily identified that their maximal effort was achieved. VO_{2peak} was identified as the highest value recorded during the final workload achieved by each subject.

Subjects performed cycling trials under normobaric normoxic conditions (FIO_2 = 20.9%, 752 $\pm$ 4 mmHg) and hypoxic conditions (FIO_2 = 13.6 $\pm$ 0.2%, 754 $\pm$ 3 mmHg; simulated approximately 3600 meters above sea-level). Baseline and post treatment normoxic and hypoxic trials were randomized and subjects were not informed of the trial condition. Hypoxic conditions were produced using a hypoxic generator (Colorado Altitude Training, Louisville, CO) connected to two, 200 L Douglas bags that were used to create a reservoir of inspiratory gas for the subjects during hypoxic trials (Figure 1). In order to avoid subject bias, this method was also used during the normoxic trials with the Douglas bags filled with 20.9% O_2.

Figure 1. Experimental set up.

Statistical Analysis

A MANOVA examined oxygen level (normoxia/hypoxia), quercetin supplementation, and time as independent variables and VO_{2peak} and power (w) as dependent variables (Wilks' λ = .095, $F_{(9,4)}$ = 4.24, p = .09). Univariate ANOVAs examined differences in individual dependent variables. Thereafter, post-hoc t-tests were used to examine pair-wise differences. Using Bonferroni correction, a family-wise alpha of .05 was maintained for all post-hoc pair-wise comparisons.

RESULTS

VO_{2peak} was not different between groups at baseline for normobaric normoxic trials (placebo vs. quercetin group = 58.7$\pm$8.8 and 61.5$\pm$7.9 ml $\cdot$ kg^{-1} $\cdot$ min^{-1}, respectively, $t(12)$ = -.63, p = 0.54) (Table 1) and hypoxic trials (placebo vs. quercetin group = 48.5$\pm$8.3 and 50.8 $\pm$ 4.8 ml $\cdot$ kg^{-1} $\cdot$ min^{-1}, respectively, $t(12)$ = -.64, p = 0.53) (Table 2). There was no statistically significant difference found in VO_{2peak} during normoxic trials for the placebo group when comparing baseline values to post placebo supplementation values (58.7 $\pm$ 8.8 and 56.7 $\pm$ 7.4 ml $\cdot$ kg^{-1} $\cdot$ min^{-1}, respectively, $t(6)$ = 1.95, p = 0.10 (Table 1). There was no statistically

significant difference found in VO_{2peak} during hypoxic trials for the placebo group when comparing baseline values to post placebo supplementation values (48.5 ± 8.3 and 47.1 ± 8.3 ml · kg^{-1}· min^{-1}1, respectively, $t(6) = .72$, $p = 0.50$ (Table 2). There was no statistically significant difference found in VO_{2peak} during normoxic trials for the quercetin supplementation group when comparing baseline values to post supplementation values (61.5 ± 7.9 and 62.4 ± 7.3 ml · kg^{-1}· min^{-1}, respectively, t(6) = -.62, $p = 0.56$) (Table 1). There was no statistically significant difference found in VO_{2peak} during hypoxic trials for the quercetin supplementation group when comparing baseline values to post supplementation values (50.8 ± 4.8 and 51.2 ± 3.8 ml · kg^{-1}· min^{-1}, respectively, $t(6) = -.47$, $p = 0.66$) (Table 2). As expected, VO_{2peak} for all hypoxic trials was significantly ($p < 0.05$) reduced when compared with normoxic trials (baseline normoxia vs. baseline hypoxia and post normoxia vs. post hypoxia) trails for all groups (range = -16.9% to -17.9% of baseline VO_{2peak}) (Table 3). These data suggest that short-term quercetin supplementation for 2 weeks at 1000 mg · day^{-1} does not improve VO_{2peak} in healthy trained male cyclists performing under normobaric normooxic and hypoxic laboratory conditions.

Table 1. Mean ($\pm$ SD) results for VO_{2peak} during normoxic trials for placebo and quercetin supplementation groups.

Normoxic Trials	Peak VO$_2$ (ml · kg^{-1} · min^{-1})
Placebo baseline	58.7 ± 8.8*
Placebo post	56.7 ± 7.4*
Quercetin baseline	61.5 ± 7.9*
Quercetin post	62.4 ± 7.3*

Table 2. Mean ($\pm$ SD) results for VO_{2peak} during hypoxic trials for placebo and quercetin supplementation groups.

Hypoxic Trials	Peak VO$_2$ (ml · kg^{-1} · min^{-1})
Placebo baseline	48.5 ± 8.3**
Placebo post	47.1 ± 8.3**
Quercetin baseline	50.8 ± 4.8 **
Quercetin post	51.2 ± 3.8 **

Table 3. Mean ($\pm$ SD) results for VO_{2peak} comparing normoxic and hypoxic trials for placebo and quercetin supplementation groups.

Normoxic vs. Hypoxic Trials Peak VO$_2$ (ml · kg^{-1} · min^{-1})	Normoxic	Hypoxic	% Decline
Placebo baseline	58.7 ± 8.8	48.5 ± 8.3	17.4†
Placebo post	56.7 ± 7.4	47.1 ± 8.3	16.9†
Quercetin baseline	61.5 ± 7.9	50.8 ± 4.8	17.4†
Quercetin post	62.4 ± 7.3	51.2 ± 3.8	17.9†

†p < 0.0125 (pair-wise)

DISCUSSION

The primary purpose of this investigation was to evaluate the effects of quercetin supplementation on VO_{2peak} during incremental cycle ergometry under normobaric hypoxic conditions that simulated approximately 3600 meters of elevation above sea-level. In addition, the effect of quercetin supplementation on VO_{2peak} during normobaric normoxic/sea-level conditions was investigated. We report no beneficial effects of 1000 mg · day^{-1} of quercetin supplementation for two weeks on VO_{2peak} under both hypoxic and normoxic conditions. While VO_{2peak} responses to normobaric hypoxia after quercetin supplementation have not been studied, our findings are consistent with others who have reported no beneficial effects to endurance performance and aerobic capacity after short-term (i.e., 2 - 4

weeks) quercetin supplementation (3, 4). Our findings are contrary to those who reported that quercetin supplementation improved cycling efficiency, aerobic capacity, fat utilization, and time trial performance in both trained and untrained individuals (7, 8, 9, 21).

Due to controversial findings related to the effects of quercetin supplementation on factors related to endurance performance in humans and animals, researchers have addressed the methodological variability of several of these studies. Jin and colleagues (2010) have questioned the bioavailability of extracted/processed verses natural forms of quercetin, suggesting that natural forms may be superior to processed forms. We chose a processed form for this investigation as dosage was easily controlled. Dosage has also varied from study to study. The 1000 mg $\cdot$ day^{-1} used here is among the higher doses studied, although even higher doses may be needed to yield beneficial effects (15). It is possible that longer duration supplementation (i.e., > 4 weeks) and/or higher doses may be necessary to induce structural and functional biological changes that could enhance endurance performance or VO_{2peak} under hypoxic conditions.

To our knowledge, the influence of quercetin supplementation on VO_{2peak} during simulated altitude using normobaric hypoxia has not been investigated. Subudhi et al. (25) studied the effects of a combination of antioxidants on ventilatory threshold at altitude and reported that 30 days of supplementation improved acute ventilatory kinetics associated with adaptive responses to hypobaric hypoxia (4300meters), but there appeared to be no

long term benefits associated with the supplement. These researchers reported a 28% reduction in VO_{2peak} at 4300 meters in both the control and treatment groups. Similarly, we found that VO_{2peak} decreased by approximately 17% in both the placebo and quercetin supplementation group under normobaric hypoxic condition studied here (approximately 3600m simulated altitude), however there were no significant differences in VO_{2peak} associated with quercetin supplementation.

Given that some studies have documented increased mitochondrial RNA, increased muscle blood flow and decreased blood pressure in response to quercetin supplementation, we felt that quercetin supplementation could be particularly beneficial to endurance athletes exercising at altitude. Our findings indicate no beneficial effects of short-term quercetin supplementation on VO_{2peak} during maximal cycle ergometry testing at a simulated altitude of approximately 3600 meters. The dose used in this investigation was determined based on evidence from previous research reporting enhanced endurance performance after 1-4 weeks of quercetin supplementation at similar doses to those used here (20, 21). Human studies have shown that daily supplementation of quercetin (500 mg twice daily) improves aerobic capacity (VO_{2max}), time to exhaustion, time trial performance, and exercise tolerance (20, 21). Furthermore, recent evidence from both animal and human studies suggests that quercetin supplementation resulted in increased mitochondrial capacity, oxidative enzyme activity, and increased time to exhaustion (8, 9). Additional data show that quercetin may cause vasodilation, resulting in

improved blood flow (18, 21, 22). An increase in blood flow to working muscle, coupled with an increase in mitochondrial density, could result in improved endurance performance by increasing an individual's aerobic capacity and fat utilization. Although these data support the use of quercetin to improve aerobic performance, our findings support those of others who have shown that quercetin has no effect on aerobic capacity as indicated by VO_{2peak} (1,6).

In conclusion, potential beneficial effects of quercetin supplementation that may be particularly relevant to endurance performance at altitude may involve structural changes at the muscle cell and vascular level (i.e., increased mitochondrial density, improved vasodilatory responses), therefore, longer durations of supplementation should be studied. Further, bioavailability of various forms of quercetin should be considered and natural forms of quercetin supplementation should be evaluated. Another area for study is the effects of quercetin supplementation and dose-response kinetics on untrained individual performing at altitude as these individuals may benefit more significantly from potential upregulation of structural components supporting VO_{2peak} and endurance performance at altitude.

ACKNOWLEDGEMENTS

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