Quercetin: A Scientific Journey of Discovery

Quercetin is a plant-derived substance, or phytochemical, known as a flavonoid. Flavonoids are compounds found in fruits and vegetables; to date, more than 4,000 have been identified. The flavonoids have generated scientific interest because of their potential beneficial effects on human health, including antioxidant, anti-inflammatory, antitumor, and antiviral activities. Quercetin, the major flavonoid in the human diet, is widely found in apple skins, onions, berries, grains, herbs, tea, and red wine.

There has been increasing interest in quercetin in the sports science and athletic communities because research has shown that its antioxidant, anti-inflammatory, psycho-stimulant and other properties are likely to improve mental and physical performance. Human clinical trials have confirmed that quercetin enhances endurance and performance. Also, emerging research suggests quercetin may reduce infection risk during intense physical exercise. In addition, quercetin has demonstrated the ability to stimulate mitochondrial biogenesis in vivo (mice). This is an exciting and important discovery as traditionally, exercise training has been the only practical way to increase the amount of mitochondria in cells, and in turn, increase aerobic capacity and endurance. This paper reviews the scientific evidence on quercetin, particularly with respect to its potential benefits for athletes and others seeking increased endurance, in order to clarify the current state of science on this exciting flavonoid.

Biological Properties of Quercetin

Herbs and botanicals have a long history of traditional medicinal use in many countries. However, Flavonoids themselves were not discovered until the 1930s. In recent years, these naturally occurring substances have been receiving increased attention by researchers and have been subject to many rigorous scientific and clinical studies. Quercetin in particular has shown great promise in a number of areas relevant to human health. Quercetin is a phenolic

antioxidant with a chemical structure that counteracts the damaging effects of oxidation caused by reactive oxygen species (ROS) or free radicals in the body's cells (Harwood 2007). Oxidation reactions occur as part of the body's normal metabolic processes and also occur following exposure to environmental factors such as toxins in pollution, cigarette smoke, and fried foods.

Quercetin's superior free radical scavenging capacity is believed to be one of the mechanisms by which quercetin enhances endurance and performance, particularly insofar as research demonstrates that radicals and other ROS are an underlying aetiology in exercise-induced physiological disturbances (Powers 2004, Reid 2008). Quercetin possesses other biological properties that are known to positively affect both physical and mental performance during intense aerobic exercise, including anti-inflammatory activity (Harwood 2007), positive psycho-stimulant effects (Alexander 2006), and, especially, mitochondrial biogenesis in the muscle and brain of mice (Davis 2009). There is much excitement about the recent evidence showing that quercetin is able to increase mitochondrial biogenesis in mice (Davis 2009), a finding that could have a major impact on exercise performance and health. Quercetin has also demonstrated other biological effects in preclinical testing, including anti-inflammatory, antiviral, and anticancer activity, as well as protective effects on the heart and nervous system (Alexander 2006, Ansari 2008, Harwood 2007, Utesch 2008).

The benefits of quercetin are largely dependent on its bioavailability – the extent to and rate at which the active substance enters the body's circulatory system – after oral administration. Bioavailability is determined by a substance's pharmacokinetics, or how well the substance is absorbed, distributed, retained in the body, and excreted. Initial reports on quercetin indicated that its bioavailability was limited; however, recent pharmacokinetic data show that quercetin can be detected in plasma within 20-30 minutes after ingesting a 250 or 500 mg chewable preparation, and reaches a peak concentration two to three hours after ingestion. Clinical studies have demonstrated that quercetin has a long half-life in human plasma, conservatively, approximately 16 - 17 hours (Olthof 2000). The half-life of a substance is the

time required for the body to eliminate one-half of the total amount of the substance consumed at a given time. Quercetin is fully eliminated within 24 hours, with plasma levels returning to baseline (Davis 2009; Egert 2008). In vivo (animal) studies have shown that quercetin reaches and accumulates in the colon, kidney, liver, lung, muscle, and brain (De Boer 2005).

Quercetin is safe for human consumption, and has not been found to cause adverse reactions in humans at doses of several grams per day. Long term animal toxicology studies on quercetin have further confirmed the safety of quercetin (Harwood 2007, Utesch 2008).

Can Quercetin Affect Exercise Performance?

Endurance Capacity & Performance

Quercetin has been shown to increase endurance and boost performance in clinical studies published in peer-reviewed scientific journals. In a randomized, double-blind, placebo-controlled, cross-over clinical trial published in the International Journal of Sport Nutrition and Exercise Metabolism, MacRae and Mefferd at Pepperdine University tested the effects of quercetin on endurance performance in highly-trained cyclists (MacRae 2006). In this study on eleven elite cyclists, the effects of an antioxidant formula containing 300 mg of quercetin (FRS), taken twice daily for six weeks, were measured against placebo (antioxidant formula without quercetin). Subjects consumed the active substance and then crossed over to the placebo for another six weeks of supplementation and testing. Subjects performed the time trial at baseline and at three and six week intervals.

The study results indicated a statistically significant improvement in quercetin users overall time to complete the 30 km time trial, demonstrating peak sustained power output. The cyclists taking the quercetin-containing formula improved their time to complete the 30 km time trial by 3.1% over baseline time ($P \leq 0.01$). Their time during the critical last 5 km was improved by 2% ($P \leq 0.05$). Cyclists consuming the quercetin-containing formula generated greater power during their time trials, which resulted in faster speed. The difference between the time at trial

end and baseline in the quercetin group can be compared with the results of the men's 2004 Olympic 50 km road time trial. At the end of the race, the difference between 1st and 9th place was 3%.

The investigators in this study indicated that the improvement in time trial performance could be attributable to quercetin's inhibition of catechol-O-methyltransferase (COMT), an enzyme that degrades norepinephrine, and that adding quercetin to other antioxidants most likely produced a synergistic effect in defending against oxidative stress (MacRae 2006).

The performance-enhancing results of quercetin in trained cyclists found by MacRae and Mefferd were corroborated by investigators at Appalachian State University in a group of untrained men. In another randomized, double-blind, placebo-controlled, cross-over study conducted by researchers at Appalachian State University and published in Medicine & Science in Sports & Exercise, investigators studied the effects of quercetin in 26 untrained males who performed a 12-minute time trial on a graded treadmill following 60 minutes of moderate exercise. Quercetin was given in a dose of 1000 mg/day, mixed with a supplement beverage. The study subjects drank half of the beverage in the morning and half at 1:00 pm each day for two weeks before and after a two-week washout period, during which they did not drink any of the beverage to eliminate any remaining quercetin from the body. The results showed a statistically significant improvement of 2.9% in distance achieved during the 12-minute treadmill time performance in quercetin users compared to placebo (-1.2%) (P=0.038).

In another randomized, double-blind, placebo-controlled, crossover clinical study published in the International Journal of Sport Nutrition and Exercise Metabolism, Davis and researchers at the University of South Carolina examined the effects of seven days of quercetin supplementation in healthy, fit, but not highly trained men and women (Davis 2009). Twelve volunteers were assigned to receive either 500 mg of quercetin twice daily dissolved in vitamin-enriched Tang® or a similar-tasting placebo drink. The Tang beverage included niacin and vitamin C. Test measures included ride time to fatigue on a bicycle ergometer and maximal

oxygen uptake, or VO_{2max}. After seven days of quercetin treatment, ride time to fatigue and VO_{2max} were examined. The quercetin group saw statistically significant results in increased endurance and $VO_{2max.}$ Ride time to fatigue increased by 13.2% compared to placebo ($P < 0.05$) and VO_{2max} increased by 3.9% compared to placebo ($P < 0.05$).

In another study conducted by Nieman and researchers at Appalachian State University and published in Medicine & Science in Sports & Exercise, the effects of quercetin with and without additional flavonoids and other food components on highly trained cyclists were tested (Nieman, 2009). Using a study protocol designed to improve and extend quercetin's bioavailability and bioactive effect, 39 cyclists were randomized to receive either placebo; quercetin; or quercetin plus the flavonoid epigallocatechin 3-gallate (EGCG) found in green tea, isoquercetin (the glycosylated quercetin found in onions and other foods), N_3-polyunsaturated fatty acids (N_3-PUFA), vitamin C, and folate. Each cyclist was given two chews to take each morning and two chews to take each afternoon for two weeks before, three days during, and seven days after intense exercise. The quercetin chews contained 250 mg quercetin, 250 mg vitamin C, 10 mg niacin, and 200 mcg folic acid. The quercetin-EGCG chews contained these ingredients plus 30 mg EGCG from green tea extract, 100 mg isoquercetin, and 100 mg N_3-PUFA from fish oil.

While there were no effects of supplementation on cycling performance or on markers of mitochondrial biogenesis compared with the placebo group, the study results showed that quercetin combined with EGCG, isoquercetin, and N_3-PUFA was more effective than quercetin alone in partially countering exercise-induced inflammation. These data add support to the concept that quercetin's effects are amplified when it is co-ingested with other nutrients. It should be noted that in this study, the testing was conducted over and above the athlete's normal training, which was not controlled. This factor adds considerable variability to the individuals participating in the study and could mask any potential effect of treatment.

More recently, Cureton and colleagues at the University of Georgia measured the effects of quercetin on muscle oxidative capacity, and metabolic, perceptual, and neuromuscular determinants of performance in prolonged exercise and cycling performance in untrained men. Using a double-blind, pretest-posttest control group design, 30 active but untrained young men were randomly assigned to quercetin or placebo. Measurements were made before and after seven to 16 days of supplementation with 1000 mg/day of quercetin in a sports hydration beverage containing carbohydrate, sodium chloride, niacin, and vitamins B6 and B12, or a similar beverage with no quercetin. The authors of the study found no differences in any of the measures between the two groups. However, unlike other studies, this study did not use a crossover design, and some sports science researchers have questioned the sensitivity of the measures used by investigators to measure performance and muscle oxidative capacity.

Inflammation and Exercise

Exercise results in the increased production of reactive oxygen species (ROS) that can lead to fatigue, inflammation and muscle injury (Powers 2004, Reid 2008). Several nutritional supplements, including various antioxidants such as vitamins C and E have been studied for their potential to counteract the effects of intense exercise on inflammation and muscle damage (Nieman 2006). Quercetin, known to be a powerful antioxidant (Chen 2005), has been widely investigated to determine the exact cellular pathways by which it exerts its antioxidant and anti-inflammatory effects and what that knowledge would mean for athletes.

In one study of 40 trained cyclists, David Nieman and colleagues at Appalachian State University evaluated whether quercetin would have an effect on reducing the muscle inflammation that accompanies prolonged, intense exercise (Nieman 2007). Investigators measured the effect of quercetin supplementation on several plasma and muscle markers of inflammation and muscle damage before and after exercise. Study participants consumed 1,000 mg/day of pure quercetin powder dissolved in the noncarbonated drink Tang (two daily doses of

500 mg each) for 3 weeks before and during a three-day period of cycling for three hours per day. The total of nine hours of exercise over the three-day test period represented nearly a doubling of the athlete's normal training workload. The results showed that blood levels of the inflammation markers IL-8 and IL-10 mRNA were significantly reduced in cyclists taking quercetin compared with levels in those receiving the placebo. However, other markers of inflammation and muscle damage were similar in both groups.

In another study of 63 ultra-marathon runners randomized to receive either quercetin (1,000 mg/day) or placebo for three weeks before and on the morning of the 160 km Western States Endurance Run (Nieman 2007), the quercetin group showed no change in plasma levels of various markers of muscle damage and inflammation compared with those taking placebo. In this study, the quercetin subjects were given soft chews containing 250 mg quercetin, 250 mg vitamin C, and 20 mg niacin, and the placebo subjects received plain chews. The runners were instructed to consume two chews prior to breakfast and two chews prior to dinner, and to eat all four chews on the morning of the race, one hour before the 5:00 a.m. start time.

In this study, quercetin was given only until the morning of the race because the investigators hypothesized that plasma quercetin levels would remain high following the three weeks of supplementation and the pre-race dose. In fact, plasma levels of quercetin had dropped to pre-race placebo group levels when measured just after the grueling, 30-hour race and likely had been at those levels during a good part of the race as well. Whereas most runners were focused simply on finishing the race within the time limit, the race time for the quercetin group was about one hour shorter compared with the placebo group, but this difference did not reach statistical significance. Only 39 of the original 63 runners who entered the study finished the race and provided blood samples for testing.

Mitochondrial Biogenesis and Exercise

An emerging area of research in the field of sports medicine relates to the stimulation of mitochondrial biogenesis as a way to increase aerobic capacity and endurance and is perhaps the most exciting recent finding relating to quercetin's mechanism of action in supporting endurance and aerobic capacity.

Mitochondria are present in nearly all cells and contain enzymes that are responsible for energy production. With exercise training, the muscles adapt through an increase in mitochondrial content. This increases aerobic capacity, as measured by maximal oxygen update (or VO_{2max})**,** which is considered the best indicator of cardio-respiratory fitness. Mitochondrial increase also contributes to slower muscle glycogen and glucose utilization, a greater reliance on fat oxidation for energy, and a decrease in lactate production in the muscles (Holloszy 1984). All of these effects enhance the ability to perform prolonged strenuous exercise.

Other than exercise training, there have been no other means until recently to increase mitochondrial biogenesis. Evidence is building to show that natural flavonoids, such as quercetin, resveratrol, and their derivatives, can increase mitochondrial biogenesis via intracellular signaling pathways involving peroxisome proliferator-activated receptor-γ coactivator (PCG-1α) and sirtuin (SIRT1). These pathways have been linked to improved endurance and health in mice (Lagouge 2006, Rasbach 2008).

Davis and researchers from the University of South Carolina have demonstrated that quercetin stimulates mitochondrial biogenesis in mice (Davis 2009). In this study, investigators fed quercetin to sedentary mice for seven days, and then measured markers of mitochondrial biogenesis in the muscle and brain, as well as endurance exercise tolerance. Statistically significant increases in PCG-1α and SIRT1 gene expression, mitochondrial DNA, and cytochrome c concentration occurred. Moreover, researchers found these increases in mitochondrial biogenesis were associated with significant increases in endurance capacity

(treadmill running to fatigue), as well as voluntary wheel-running (willingness to be physically active) (Davis, 2009).

Human studies have been mixed with respect to mitochondrial biogenesis and some experts believed that highly trained athletes may have already reached capacity for muscle mitochondrial density as a result of their high level of aerobic training. However, in the above-referenced Nieman study on 26 untrained men, investigators did find consistent trends toward increases in several different markers of mitochondrial biogenesis in subjects consuming quercetin.

Antioxidant and Other Biological Properties of Quercetin

As indicated, quercetin's powerful antioxidant activity is believed to contribute to its beneficial effect on exercise endurance (Davis 2009). Quercetin's chemical structure enables it to scavenge oxygen-centered free radicals, the reactive molecules in the body that participate in oxidative reactions that cause cell damage (Harwood 2007). Muscle fibers continually generate reactive oxygen species (ROS) as a byproduct of the normal metabolism of oxygen. During exercise, the body's oxygen metabolism and ROS production increase, which contributes to muscle fatigue especially during intense or prolonged training. Eventually, the body's reserve of antioxidants is diminished and the tissues become increasingly susceptible to oxidative damage (Reid 2008). Some studies have shown that antioxidant pretreatment can delay muscle fatigue in rodents (Reid 2008); in humans, the relationship between ROS production and endurance performance is less clear, and needs to be further defined before the protective effects of quercetin on exercise-induced oxidative stress can be fully described (Reid 2008, McAnulty 2008).

Quercetin's anti-inflammatory activity may also have a beneficial effect on the muscle damage experienced by athletes after intense exercise. Quercetin has demonstrated that it can inhibit nuclear factor-kappaB (NF-κB) (Harwood 2007), a chemical in the body which has been

shown to play a central role in regulating the immune response to inflammation. Cell culture studies and in vivo (animal) studies have provided evidence supporting quercetin's anti-inflammatory effects (Harwood 2007).

Another property of quercetin that may enhance physical and mental performance is its caffeine-like psycho-stimulant effect. Suggestions that caffeine can delay fatigue during endurance exercise through a primary effect on the brain, in part, by blocking the adenosine A_1 receptors, came from an earlier study (Davis 2003). Various flavonoids also show adenosine A_1 receptor antagonist activity in vitro (Alexander 2006). Studies of quercetin in mice provided further evidence of this effect by demonstrating an increase in gene expression of adenosine A_1 receptors in the brain following seven days of receiving quercetin. A recent study in humans comparing the psycho-stimulant effects of quercetin and caffeine reported no effect of quercetin on exercise performance during conditions of heat stress (temperature of 40 degrees C, relative humidity of 20%-30%) (Cheuvront 2009). However, there was also no beneficial effect seen with caffeine, which has been shown to enhance performance in other studies (Hogervorst, 2008), meaning that it is not certain to what degree heat stress played a role in overriding the psycho-stimulant effect.

Another mechanism by which quercetin is believed to enhance endurance is its inhibitory effect on the breakdown of catechol-O-methyltransferase (COMT), an enzyme that degrades norepinephrine (Nagai 2004, Van Duursen 2004). Experts in the field of sports medicine and performance believe this naturally extends the body's adrenaline, allowing for a more pronounced catecholamine effect during exercise and triggering the release of glucose from energy stores, as well as increasing skeletal muscle readiness (MacRae 2006).

Quercetin's Effects on Immunity and Infection

Studies have shown that exercise stress can decrease immune function and increase the risk for upper respiratory tract infection (URTI) in both animals and humans (Davis 2008, Nieman 2008). Various nutritional strategies to counteract these effects have been tested, but they have shown little success (Nieman 2008). Data from cell culture experiments provide strong evidence that quercetin may be effective as an anti-infective agent, reducing the infectivity and replication of a variety of respiratory viruses (Debiaggi 1990, Chiang 2003, Kaul 1985, Chen 2006). Although the exact mechanisms of quercetin's antiviral effects are still not clear, it is thought to block viral replication at an early stage of multiplication by suppressing enzymes that influence the virus's ability to cause disease, and by binding to the viral capsid protein that surrounds the virus core (Chen 2006, Chiang 2003, Cushnie 2005). Quercetin may also exert an antiviral effect through its action on interferon and other proteins involved in marshalling the body's immune response. It also may enhance the activity of several immune system components in fighting infection (Alvarez 2006, Nair 2002).

Animal and human data on the benefits of quercetin in infection are limited. In the initial group of cyclists studied by Nieman and colleagues at Appalacian State University, the investigators hypothesized that quercetin would lessen immune dysfunction and counter the risk of URTI following repeated and sustained exercise. In that study, 1,000 mg/day quercetin did reduce the incidence of URTI following three days of exhaustive cycling, although there were no accompanying effects of quercetin on several measures of immune function (Nieman 2007). And, in the study of ultramarathoners participating in the Western States Endurance Run, no benefits of quercetin on illness rates (i.e., self-reported illness symptoms) were reported (Henson 2008). In this study, immune changes were also similar between the quercetin and placebo groups following the race.

In these human studies, many immune system parameters that are known to play a critical role in susceptibility to respiratory infection could not be measured. Because there are no standardized influenza virus preparations available for systematic study in humans, animal models are the only tool available to investigate the effects of nutrition on susceptibility to virus infection during intense exercise. Therefore, to study the effects of quercetin on susceptibility to infection following exercise stress in a controlled environment with controlled and accurate exposure to virus, Davis and colleagues conducted a study in which untrained mice were given seven days of quercetin feedings, then challenged them with a treadmill run for three days and inoculated them with a standardized dose of influenza virus. Mice that had been given the quercetin were significantly less susceptible to the influenza virus following stressful exercise ($P<0.05$) (Davis, 2008). Susceptibility was measured by time to sickness, symptom severity, and time to death. There was also a strong trend toward a decrease in susceptibility to infection in mice who were given quercetin but not exercise-stressed.

Quercetin in Chronic Diseases

Studies have shown that quercetin seems to mimic some of the effects of exercise training and regular physical activity via its antioxidant, anti-inflammatory, and psycho-stimulant activity, as well as its effect on mitochondrial biogenesis. Although additional research is necessary, these activities suggest that quercetin may also have benefits on certain chronic diseases such as diabetes, neurodegeneration, cardiovascular disease, and cancer. The hallmarks of these diseases include lack of physical activity, mitochondrial dysfunction, and/or oxidative stress and inflammation.

Diabetes is increasingly believed to develop, in part, as a result of mitochondrial dysfunction, inflammation, and reactive oxygen species. Several animal studies on quercetin have shown beneficial effects on blood glucose levels and lipid levels using doses ranging from

10 to 50 mg/kg^{-1} (Nuraliev 1992, Rivera 2008). A number of epidemiological studies in humans that have examined the relationship between dietary flavonoid intake and diabetes have yielded mixed results (Knekt 2002, Song 2005). These studies may be limited in their ability to detect a specific effect of quercetin on diabetes risk because of errors in measuring flavonoid intake, as well as difficulty in distinguishing quercetin from other flavonoids.

Neurodegeneration – the progressive loss of nervous system function that occurs in conditions such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, epilepsy, and stroke – is generally associated with aging. Because oxidative damage, inflammation, and mitochondrial dysfunction are recognized as playing a role in the aging process and are thought to bear some responsibility for the development of neurogenerative diseases, the effects of quercetin may prove to be of some benefit. Although no human epidemiological or experimental studies have been reported in this area, in vitro studies have shown a neuroprotective effect of quercetin, which is likely a function of its antioxidant and anti-inflammatory activity, as well as its beneficial effect on brain mitochondrial biogenesis. Moreover, there is evidence that consumption of foods rich in flavonoids such as quercetin holds the potential to limit neurodegeneration and to prevent or reverse age-dependent losses in cognitive performance (Vauzour 2008).

It is known that oxidative stress and inflammation play an essential role in cardiovascular disease; quercetin is being widely investigated for its potential as a safe alternative to antioxidant and anti-inflammatory drugs in this setting (Knekt 2002). Preclinical and clinical data suggest that quercetin can reduce several risk factors associated with cardiovascular disease, including hypertension (Edwards 2007) and elevated levels of C-reactive protein (Kaur 2007). Quercetin also has been shown to possess several cardioprotective effects against cell injury from oxidative stress (Angeloni 2007), as well as having potent vasodilatory effects in coronary blood vessels (Cogolludo 2007).

Numerous epidemiological studies suggest that individuals who consume diets rich in flavonoids including quercetin are less likely to suffer from heart disease. In vitro studies have clarified the mechanism by which modest amounts of quercetin, such as that found in two glasses of red wine, possess “clot-busting” activity (Booyse 2007). Despite the existing evidence of quercetin’s cardioprotective properties, its proper place in the prevention and treatment of heart disease still needs to be evaluated in Phase III clinical trials (Davis 2009).

The effects of quercetin on cancer have been tested mainly in cell culture models, where it has been shown to inhibit the development of cancer cells by its anti-mutagenic, antioxidant, and anti-inflammatory activity. Quercetin also appears to modulate signal transduction pathways such as apoptosis, cell cycle regulation, and angiogenesis, which are associated with the development of cancer (Davis 2009). Although these studies support a beneficial role of quercetin in cancer, the evidence in animal studies has been inconsistent and human data are limited. The inconsistencies observed in animal studies are likely caused by differences in the cancer model used, the dose of quercetin given, and the timing of quercetin administration in relation to the stage of cancer (Davis 2009). Human epidemiological data are also mixed, with some association found between a lower risk of disease and higher intake of quercetin (Knekt 2002).

Interpreting the Science

Clinical studies of quercetin have produced a range of results that may be subject to misinterpretation if not carefully examined and considered in their totality. Studies to date have been conducted using a variety of methodologies. Findings from one study may not be relevant to findings of other studies due to differences in subjects, test compounds, parameters measured, and limitations in trial design, including individual differences among participants and environmental factors that could account for variances between study outcomes.

In general, randomized, double-blind, placebo-controlled studies are considered the gold standard for research. In fact, an international group of researchers, methodologists, and medical journal editors have developed the CONSORT Statement (Consolidated Standards of Reporting Trials), which is an evidence-based, minimum set of recommendations for reporting randomized clinical trials. It offers a standard way for authors to prepare reports of trial findings, facilitating their complete and transparent reporting, and aiding their critical appraisal and interpretation. The CONSORT statement provides a checklist of items to help ensure complete reporting of trials (Moher 2001), and is endorsed by prominent general medical journals, many specialty medical journals, and leading editorial organizations.

Studies may be designed in a parallel, or cross-sectional design, in which participants are randomized to only one treatment under investigation, or in a crossover design, in which participants receive more than one of the treatments under investigation in a randomly determined sequence. In crossover studies, each subject serves as his or her own control, thereby eliminating variability when comparing treatment effects and reducing the sample size needed to detect a significant effect. In the quercetin clinical studies discussed, only three trials utilized a crossover study design (MacRae 2006, Nieman 2009, Davis 2009). These studies showed a significant endurance benefit of quercetin over placebo, while most of the other studies that used a parallel design yielded findings that were equivocal or difficult to interpret.

In addition to the trial design, differences in the study subjects between trials could account for the variances in results. The effect of athletic training may be an important independent variable that could affect the outcome of the mitochondrial biogenesis and performance findings. In addition, some studies used more stringent inclusion criteria than others when recruiting subjects, resulting in greater uniformity among subjects and less likelihood of confounding individual differences. The variability among subjects can be especially problematic in cross-sectional studies in which separate small groups are compared that may be different initially and may respond differently to the compounds tested.

Test conditions can also play a role in study outcomes. Several studies were conducted under controlled conditions in the laboratory, which helps to minimize the effect of individual variability on the results. In general, the inclusion of uncontrolled independent variables, such as temperature, humidity, wind, and distractions, lessens the likelihood of finding a statistically significant effect of the treatment due to the large variability between the tests, and even increases the likelihood of finding a false negative result. This is especially true for parallel or cross-sectional studies with small sample sizes. It is also important when designing studies to select measures that are sensitive enough to detect the treatment effect. For example, the most recent Nieman study of untrained cyclists used an indirect measure of mitochondrial function that may not have been sensitive enough to reliably detect increases in mitochondrial biogenesis, especially in the small sample cross-sectional study (Cureton 2010).

Finally, variations in pre-testing meals and instructions to the study subjects regarding the ingestion of nutrients can account for differences in results across studies. Furthermore, differences in the quercetin preparations used in the various studies likely have a profound influence on the findings. Quercetin appears to have greater bioavailability when combined with certain synergistic ingredients, such as vitamin C and niacin, as well as B vitamins. Some studies used quercetin mixed into a sports hydration beverage (Cureton 2010, Nieman 2009) that contained minimal amounts of niacin and no vitamin C. This may account for lower plasma levels of quercetin following consumption of the active compound, as compared with results of other studies that used quercetin mixed into Tang or as part of the FRS formula (Davis 2009, MacRae 2006); some of Nieman's studies which include adequate amounts of vitamin C and niacin). In addition, co-ingestion of quercetin with the flavonoid EGCG, vitamin C, and N_3-PUFA may augment quercetin's anti-inflammatory effects, and additional compounds may prove to be synergistic with quercetin as well. Recent studies on ellagitannins (polyphenols) derived from green tea and pomegranate have shown increased exercise performance and reduced inflammation and muscle soreness following exercise (Richards 2009, Trombold 2009).

Summary: The Balance of Evidence

Quercetin, a flavonoid found primarily in fruits and vegetables, has been shown to enhance endurance and exercise performance in randomized, double-blind, placebo-controlled studies of the type considered the gold standard for scientific research. There are many explanations for the differences in outcomes in the clinical studies that are unrelated to the efficacy of quercetin. Statistically significant improvements in endurance and performance were demonstrated by studies using a cross over design in which quercetin was consumed with synergistic ingredients such as EGCG and vitamin B3 (niacin), among other B vitamins, and vitamin C. While not all studies using quercetin have produced similar results, the weight of the evidence from endurance and exercise performance studies on quercetin demonstrates a benefit for both athletes and non-athletes.

Also, emerging research suggests quercetin may reduce the risk of upper respiratory tract infection during intense physical exercise, which is likely attributable to its antioxidant, anti-inflammatory and anti-pathogenic effects. In fact, quercetin has gained increased attention from the scientific community during recent years, spurring clinical studies, based on its broad spectrum bioactivity as demonstrated in animal and in vitro studies. Data on quercetin’s ability to significantly increase mitochondrial biogenesis in vivo represents an important research finding in the push to further elucidate quercetin's mechanism of action, particularly in the field of sports science.

Quercetin’s findings to date provide the basis for further research to determine the full range of benefits of quercetin to human health and performance, and a clearer understanding of the compound’s mechanism of action.

References

Alexander SP. Flavonoids as antagonists at A1 adenosine receptors. Phytother Res. 2006;20:1009-1012.

Alvarez P, Alvarado C, Puerto M, et al. Improvement of leukocyte functions in pre maturely aging mice after five weeks of diet supplementation with polyphenol-rich cereals. Nutrition. 2006;22:913-921.

Angeloni C, Spencer JP, Leoncini E, et al. Role of quercetin and its in vivo metabolites in protecting H9c2 cells against oxidative stress. Biochimie. 2007;89:73-82.

Ansari MA, Abdul HM, Joshi G, et al. Protective effect of quercetin in primary neurons against Abeta (1-42): relevance to Alzheimer's disease. J Nutri Biochem 2008.

Chen JC, Ho FM, Pei-Dawn Lee Chao, et al. Inhibition of iNOS gene expression by quercetin is mediated by the inhibition of IkappaB kinase, nuclear factor-kappa B and STAT1, and depends on heme oxygenase-1 induction in mouse BV-2 microglia. Eur J Pharmacol. 2005 Oct 3;521(1-3):9-20. Epub 2005 Sep 19.

Chen L, Li J, Luo C, et al. Binding interaction of quercetin-3-beta-galactoside and its synthetic derivatives with SARS-CoV 3CL(pro): structure-activity relationship studies reveal salient pharmacophore features. Bioorganic Medicinal Chemistry. 2006;14:8295-8306.

Cheuvront SN, Ely BR, Kenefick RW, et al. No effect of nutritional adenosine receptor antagonists on exercise performance in the heat. Am J Physiol Regul Integr Comp Physiol. 2009;296:R394-401.

Chiang LC, Chiang W Liu MC, Lin CC. In vitro antiviral activities of Caesalpinia pulcherrima and its related flavonoids. J Antimicrob Chemther. 2003;52:194-198.

Cogolludo A, Frazziano G, Briones AM, et al. The dietary flavonoid quercetin activates BKCa currents in coronary arteries via production of H2O2. Role in vasodilatation. Cardiovasc Res. 2007;73:424-431.

Cureton KJ, Tomporowski PD, Singhal A, et al. Dietary quercetin supplementation is not ergogenic in untrained men. J Appl Physiol; In press.

Cushnie TP, Lamb AJ. Antimicrobial activity of flavonoids. Int J Antimicrob Agents. 2005;26:343-356.

Davis JM, Carlstedt CJ, Chen S, Carmichael, MD, Murphy EA. The dietary flavonoid quercetin increases VO_{2max} and endurance capacity. Epub Int J Sports Nutri.

Davis JM, Murphy EA, Carmichael MD. Effects of the dietary flavonoid quercetin upon performance and health. Curr Sports Med Rep. 2009;8.

Davis JM, Murphy EA, Carmichael JD, Davis B. Quercetin increases brain and muscle mitochondrial biogenesis and exercise tolerance. Am J Physiol Regul Integr Comp Physiol. 2009;296:R1071-1077.

Davis, JM, Murphy EA, McClellan JL, et al. Quercetin reduces susceptibility to influenza infection following stressful exercise. Amn J Physiol Regul Integr Comp Physiol. 2008;295:R505-509.

Davis JM, Zhao A, Stock HS, et al. Central nervous system effects of caffeine and adenosine on fatigue. Am J Physiol Regul Integr Comp Physiol. 2003;284:R399-404.

De Boer VC, Dihal AA, van der Woude H, et al. Tissue distribution of quercetin in rats and pigs. J Nutr. 2005;135:1718-1725.

Debiaggi M, Tateo F, Pagani L, et al. Effects of propolis flavonoids on virus infectivity and replication. Microbiologica. 1990;13:207-213.

Edwards RL, Lyon T, Litwin SE, et al. Quercetin reduces blood pressure in hypertensive subjects. J Nutr 2007;137:2405-2411.

Egert S, Wolffram S, Bosy-Westphal A, et al. Daily quercetin supplementation dose-dependently increases plasma quercetin concentrations in healthy humans. J Nutr. 2008;138:1615-1621.

Harwood M, Danielewska-Nikiel B, Borzelleca JF, et al. A critical review of the data related to the safety of quercetin and lack of evidence of in vivo toxicity, including lack of genotoxic/carcinogenic properties. Food Chem Toxicol. 2007;45:2179-2205.

Henson D, Nieman D, Davis JM, et al. Post-160-km race illness rates and decreases in granulocyte respiratory burst and salivary IgA output are not countered by quercetin ingestion. Int J Sports Med. 2008;29:856-863.

Kaul TN, Middleton E,m Ogra PL. Antiviral effect of flavonoids on human viruses. J Med Virol. 1985;15:71-79.

Kaur G, Rao LV, Agrawal A, Pendurthi UR. Effect of wine phenolics on cytokine-induced C-reactive protein expression. J Thromb Haemost. 2007;5:1309-1317.

Knekt P, Kumpulainen J, Jarvinen R, et al. Flavonoid intake and risk of chronic diseases. Am J Clin Nutr. 200276:560-568.

Lagouge M. Argmann C, Gerhart-Hines Z, et al. Resveratrol improves mitochondrial function and protects against metabolic disease by activating SIRT1 and PCG-1alpha. Cell. 2006;127:1109-1122.

MacRae HS, Mefferd KM. Dietary antioxidant supplementation combined with quercetin improves cycling time trial performance. Int J Sport Nutri Exerc Metab. 2006;16:405-419.

McAnulty SR, McAnulty SL, Nieman DC, et al. Chronic quercetin ingestion and exercise-induced oxidative damage and inflammation. Apppl Physiol Nutri Metab. 2008;33:254-262.

Moher D. Schulz KF, Altman D; for the CONSORT Group. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. JAMA. 2001;285:1987-1991.

Nagai, M, Conney, AH, and Zhu, BT. Strong inhibitory effects of common tea catechins and bioflavonoids on the O-methylation of catechol estrogens catalyzed by human liver cytosolic catchol-O-methyltransferase. Drug Metab Disp. 2004:32(5):497-504.

Nair MP, Kandaswami C, Mahajan S, et al. The flavonoid, quercetin, differentially regulates Th-1 (1FNgamma) and Th-2 (IL4) cytokine gene expression by normal peripheral blood mononuclear cells. Biochimica Biophysica Acta. 2002;1593:29-36.

Nieman DC. Immunonutrition support for athletes. Nutr Rev. 2008;66:310-320.

Nieman DC, Bishop NC. Nutritional strategies to counter stress to the immune system in athletes, with special reference to football. J Sports Sci. 2006 Jul;24(7):763-72.

Nieman DC, Henson DA, Davis JM, et al. Quercetin's influence on exercise-induced changes in plasma cytokines and muscle and leudocyte cytokine mRNA. J Appl Physiol 2007;103:1728-1735.

Nieman DC, Henson DA, Davis JM, et al. Quercetin ingestion does not alter cytokine changes in athletes competing in the Western States Endurance Run. J Interferon Cytokine Res. 2007;27:1003-1011.

Nieman DC, Henson DA, Maxwell KR, et al. Effects of quercetin and EGCG on mitochondrial biogenesis and immunity. Med Sci in Sports & Exercise. 2009;VOL:1467-1475.

Nuraliev lu N, Avezov GA. The efficacy of quercetin in alloxan diabetes. Eksp Klin Farmakol. 1992;55:42-44.

Powers SK, DeRuisseau KC, Quindry J, Hamilton KL. Dietary antioxidants and exercise. J Sports Sci. 2004;22:81-94.

Quindry JC, McAnulty SR, Hudson MB, et al. Oral quercetin supplementation and blood oxidative capacity in response to ultramarathon competition. Int J Sport Nutr Exerc Metab 2008;18:601-616.

Rasbach K. Schnellmann RG. Isoflavones promote mitochondrial biogenesis. J Pharmacol Exp Ther. 2008;325:536-543.

Reid MB. Free radicals and muscle fatigue: of ROS, canaries, and the IOC. Free Radic Biol Med. 2008;44:169-179.

Richards JC, Lonac MC, Johnson TK, Schweder MM, Bell C. Epigallocatechin-3-gallate Increases Maximal Oxygen Uptake in Adult Humans. Med Sci Sports Exerc. 2009 Nov 27. [Epub ahead of print]

Rivera L, Moron R, Sanchez M, et al. Quercetin ameliorates metabolic syndrome and improves the inflammatory status in obese Zucker rats. Obesity. 2008;1:2081-2017.

Song Y, Manson JE, Buring JE, et al. Associations of dietary flavonoids with risk of type 2 diabetes, and markers of insulin resistance and systemic inflammation in women: a prospective study and cross-sectional analysis. J Am Coll Nutr. 2005;24:376-384.

Trombold JR, Barnes JN, Critchley L, Coyle EF. Ellagitannin consumption improves strength recovery 2-3 days after eccentric exercise. Med Sci Sports Exerc. 2009 Nov 23. [Epub ahead of print]

Utesch D, Feige K, Dasenbrock J, et al. Evaluation of the potential in vivo genotoxicity of quercetin. Mutat Res. 2008;654:38-44.

Van Duursen, M et al., Phytochemicals Inhibit Catechol-O-Methyltransferase Activity in Cytosolic Fractions from Healthy Human Mammary Tissues: Implications for Catechol Estrogen-Induced DNA Damage, Toxicological Sciences. 2004: 81: 316-324.

Vauzour D, Vafeiadou K, Rodriguez-Mateos A, et al. The neuroprotective potential of flavonoids: a multiplicity of effects. Genes Nutr. 2008;3:115-126.