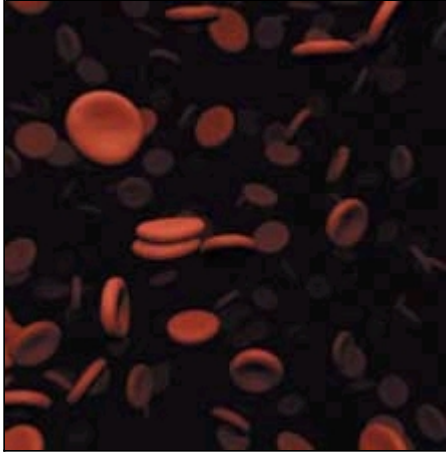


REPORT

The Quest for a Better Quercetin



Quercetin offers unique protection against age-related diseases, but is poorly absorbed into the bloodstream. For the first time, a bioavailable form of quercetin has been added to formulas already used by Life Extension members. This automatically enables members to obtain enhanced benefit without having to take additional pills.

program.

The American Thrombosis Association estimates that five million to 20 million cases of blood clot related diseases occur in the United States each year. An abnormal blood clot, or thrombus, can form in arteries, veins or the heart. Not only can a thrombus prevent blood and oxygen from reaching tissues and vital organs, but it can also break off and travel through the blood stream to the heart, brain, lung or a distant blood vessel. A traveling clot, called an embolism, can cause ischemia, heart attack, stroke or pulmonary embolism. For example, a thrombus in the large blood vessels of the leg, called deep venous thrombosis, will often break off to form an embolus that drifts through the bloodstream and cuts off circulation downstream from the spot where it eventually lodges.

A natural bioflavonoid called quercetin has proven in laboratory studies to have remarkable protective effects against the mechanisms involved in the development of degenerative disease. The problem has been that the oral bioavailability of quercetin supplements (quercetin dihydrate) is poor.

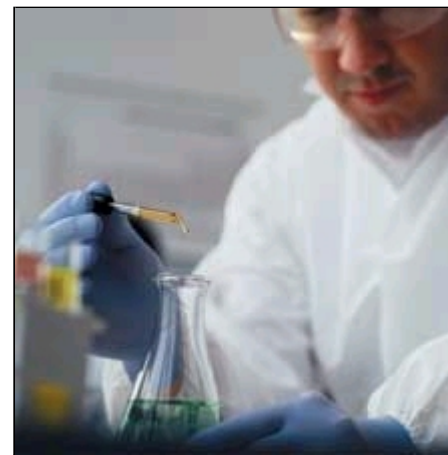
According to the Merck Index, "quercetin dihydrate is practically insoluble in water." This means that ingesting most quercetin supplements does not provide a meaningful quantity to the cells where it exerts its multiple beneficial effects.

Quercetin is soluble in alcohol, which helps explain the health-promoting effects of red wine. Red wine contains quercetin and other flavonoids that are made bioavailable to the body by the alcohol in the wine.

Quercetin became a popular dietary supplement based on evidence indicating it guards against a wide range of common disorders. Regrettably, the poor absorption rate means that people taking conventional quercetin supplements can't translate the impressive roster of research findings into reality. However, when quercetin is transformed into a water-soluble form, its absorption in the gastrointestinal tract and bioavailability are dramatically improved. Water-soluble quercetin delivers the benefits of quercetin-the predominant flavonoid in the human diet-at a lower dosage through improved absorption. Water-soluble quercetin is safe and non-mutagenic according to the standard Ames test for mutagenicity.

The good news is that water-soluble quercetin has been added to two popular supplements already used by Life Extension members. This article reveals quercetin's distinct mechanisms of action that make it a critical component of a disease prevention

Laboratory experiments suggest that a flavonoid called quercetin has the remarkable ability to prevent thrombus formation and to disperse thrombi that have already formed in blood vessels. A thrombus (the plural is "thrombi") is an aggregation of platelets, fibrin and other blood factors, frequently causing obstruction of a blood vessel. Researchers demonstrated that a low concentration of quercetin suppressed thrombus deposits on collagen bathed in a stream of blood. The researchers also tested quercetin in a model used to study interactions between platelets and the endothelium (inner blood vessel wall). When the blood flowing over a piece of rabbit aorta contained a low concentration of quercetin, platelet thrombi dissolved.



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The researchers concluded that quercetin exerts its anti-thrombotic effect by binding selectively to platelet thrombi on blood vessel walls, and by restoring normal synthesis of endothelium-derived relaxing factor and prostacyclin.¹ Prostacyclin inhibits platelet aggregation and is a powerful vasodilator. It is also an antagonist of thromboxane A₂, a proinflammatory mediator that causes platelet aggregation, vasoconstriction, and small muscle cell proliferation—all factors linked to cardiovascular disease—when it rises relative to prostacyclin. Several studies show that quercetin inhibits thromboxane A₂, which helps keep prostacyclin and thromboxane A₂ in a healthy balance.² Moreover, new research shows that mice deficient in prostacyclin develop ischemic kidney disorders—one more mechanism through which quercetin protects the kidneys (see "Quercetin and kidney disease" later in the article).³

Clotting begins when blood platelets clump together, a process called platelet aggregation. A common trigger of platelet aggregation is collagen exposed when a blood vessel wall is damaged, as for example by an arterial plaque. A recent study evaluated the effects of quercetin and catechin on collagen-induced platelet aggregation. The researchers found that both quercetin and catechin inhibited platelet aggregation, but quercetin was effective at a much lower concentration (about one-fifth that of catechin). Moreover, they discovered that when used together, these flavonoids synergistically inhibited platelet aggregation and the adhesion of platelets to collagen. The researchers found that quercetin and catechin inhibited the hydrogen peroxide burst that signals platelet aggregation.⁴

Quercetin and cardiovascular disease

Epidemiological studies have shown reduced long-term mortality from coronary heart disease in those who consume diets high in flavonoids— including quercetin, anthocyanins and catechins. In the Zutphen Elderly Study, for example, researchers evaluated the diets of 805 Danish men between the ages of 65 and 84. These men were then followed up for five years. It was found that the men who took in the most flavonoids were slightly less than half as likely to have suffered a heart attack during the course of the study.⁵

Moreover, intake of flavonoids, mainly quercetin, was inversely associated with stroke. Men with the lowest flavonoid intake (bottom quartile) were almost four times as likely to suffer a stroke as men with the highest intake (top quartile).⁶

Quercetin battles cardiovascular disease along multiple fronts. Its anti-thrombotic action helps prevent the proclotting state that sets the stage for cardiovascular disease and major cardiovascular events. We will now review five additional cardioprotective mechanisms of quercetin.

● Inhibition of smooth muscle cell proliferation and migration

During the formation of atherosclerotic lesions, the smooth muscle cells that line the coronary arteries multiply in number and begin to migrate into the interior of those vessels. When human aortic muscle cells are exposed to quercetin, this action is inhibited in a dose-dependent manner. Quercetin works by inhibiting the Mitogen-Activated Protein (MAP) kinase signaling pathway associated with smooth muscle cell migration. The researchers note that quercetin has been found to arrest the cell cycle in cancer cells, and observe that it appears to do the same in vascular smooth muscle cells, locking them into a quiescent state.⁷

In another study, Japanese researchers found that quercetin inhibited the vascular smooth muscle cell hypertrophy seen during the development of coronary artery disease. They hypothesize that quercetin works by inhibiting the activation of a key MAP kinase called JNK by the angiotensin II enzyme. This in turn inhibits the protein synthesis necessary for proliferation and hypertrophy of smooth muscle cells.⁸

● Anti-hypertensive effects

Spanish researchers evaluated the antihypertensive effects of quercetin in an animal model of essential hypertension.⁹ They discovered that 10 mg/kg of quercetin given orally to spontaneously hypertensive rats for five weeks reduced systolic blood pressure by 18%, diastolic blood pressure by 23%, and mean arterial blood pressure by 21%. Rats with normal blood pressure were also given quercetin, and it had no effect on their blood pressure measurements. Quercetin was also found to decrease cardiac and renal

hypertrophy, both of which follow hypertension and can lead to heart and kidney failure if left unchecked.

- Support of mitochondrial function in cardiac cells

When coronary blood flow is interrupted during a heart attack, cardiac cells downstream from the blockage are deprived of oxygen—a condition known as ischemia. When the flow of blood resumes, they are reperfused with blood and oxygen. New research finds that rats given oral low dose quercetin were significantly protected against the injury that normally occurs during ischemia and reperfusion.

The researchers found that quercetin preserved mitochondrial function in heart cells, and that mitochondrial function correlated with cardiac function. This enabled the mitochondria—the tiny cellular "engines" that metabolize carbohydrates and fats into energy using oxygen—to regenerate ATP (cellular energy) following ischemia-reperfusion injury.¹⁰

The dosage of quercetin used in this study corresponds (after adjusting for body weight) to the amount that would be consumed by the average adult male who drinks one to two glasses of red wine daily. Protection against ischemia-reperfusion injury persisted for 24 hours after the administration of the last dose of quercetin.¹⁰

- Inhibition of NF-kappa B

The inflammatory mediator nuclear factor-kappaB (NF-kB), has garnered considerable attention in research circles because of its role in heart disease, kidney disease and other age-related degenerative disorders. One eye-opening study in mice compared the expression of NF-kB in regions of the coronary arteries that are more prone and less prone to the development of atherosclerotic plaques. They found that the NF-kB pathway is primed for activation in the atherosclerosis-prone arterial regions. A high-cholesterol diet activated NF-kB in precisely those regions, and increased expression of genes regulated by NF-kB which are involved in plaque formation and pathology.¹¹



In the text *Markers in Cardiology*, the authors review current evidence that statins and aspirin reduce heart attack risk due to their anti-inflammatory effects on NF-kB and other inflammatory mediators. In their own research, they found that NF-kB activity is strongly elevated in patients with unstable angina, and that those with stable angina who experienced coronary plaque rupture within 24 hours of entering the study also had high NF-kB activity. In other words, NF-kB activity correlates closely with the likelihood and severity of a coronary event. As we shall see next, quercetin has been found to inhibit the activity of NF-kB and of the inflammatory cytokines its activity stimulates.

- Reducing cardiovascular inflammation

Secretions from mast cells play a central role in the development of inflammatory disorders, and recent research implicates them in cardiovascular inflammation, particularly following stress. Cardiovascular inflammation is now recognized as a key factor in coronary artery disease. Many studies have shown quercetin to inhibit mast cell secretion of inflammatory factors such as histamine, leukotrienes and prostaglandin D2.¹²

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Quercetin and kidney disease

Kidney disease leading to kidney failure is an under-recognized epidemic in the United States. As the population ages, the prevalence of kidney failure is expected to increase dramatically. In numerous experimental studies on both animals and humans, quercetin has been found to protect kidney tissues against age-related insult.

NF-kB activity in the kidneys increases with age and leads to increased oxidative stress. Caloric restriction, which is known to extend life span, has been found to reduce NF-kB activity in the kidneys of rats.¹³

Researchers tested the effect of quercetin on the activation of NF-kB in cultured rat kidney cells. The cells were proximal tubular cells (PTC's), which play a pivotal role in progressive kidney diseases by regulating the accumulation of macrophages.

They found that quercetin potently inhibited NF-kB activation in PTC.¹⁰ Since NF-kB regulates inflammatory signaling and adhesion molecules in PTC, these findings may explain earlier findings that preventive administration of quercetin inhibited tubular injury and the upregulation of inflammatory cytokines in the renal cortex.



Ischemia and reperfusion, discussed earlier in relation to cardiovascular disease, also damages the kidneys. Quercetin protects the kidneys during ischemia and reperfusion by preserving higher levels of the enzyme xanthine dehydrogenase relative to the injurious enzyme xanthine oxidase.¹⁴

Quercetin has recently been shown to protect against the kidney damage caused by a well-known nephrotoxic drug. Cyclosporine is a potent immune suppressant, the first-line therapy for solid organ transplant patients and autoimmune disease patients. It causes kidney damage in the form of fibrosis, arterial damage, and cyst formation, among other changes. Such extensive damage is thought to be due to a combination of factors, including increased free radical production, increases in renal nerve activity that cause constriction of renal arteries, blockade of the release of calcium from the mitochondria and a resultant rise in intracellular calcium. (If calcium concentrations rise too high, blood vessels become constricted.)

In a study of cyclosporine's effects on rat kidneys, a 20% to 30% reduction in glomerular filtration rate (the rate at which the kidneys filter wastes from the blood) and up to 40% reduction in renal blood flow were found. Rats given 2 mg/kg of quercetin suffered far less damage to their kidneys when given cyclosporine. Their urinary output increased and markers of free radical damage dropped.¹⁵

Quercetin's antioxidant effects and its enhancement of mitochondrial function-including improved intracellular/extracellular calcium balance -likely explain these protective effects. Protecting the kidneys is paramount, for once they are damaged, it becomes difficult, if not impossible to restore healthy function.

Quercetin as antioxidant

The voluminous literature on quercetin's antioxidant effects is beyond the scope of this article. We will focus here on quercetin's ability to quench hydrogen peroxide (H₂O₂), an oxidant that is pervasive in the body.⁴ We have already seen that quercetin reduces platelet aggregation and adhesion by reducing hydrogen peroxide production.

Hydrogen peroxide is normally present in the aqueous humor of the eye, and is thought to be a major oxidant in the formation of cataracts. In the laboratory, hydrogen peroxide causes lens opacification and a pattern of oxidative damage similar to that found in cataracts. Not surprisingly, hydrogen peroxide levels are very high in the aqueous humor of cataract patients.

Researchers studied the effect of quercetin in a model of cataract formation where a rat lens organ culture is exposed to hydrogen peroxide. They found that quercetin is methylated by an enzyme present in the lens, and that both quercetin and this methylated quercetin metabolite protected the lens from opacification and oxidative damage. Their results support the hypothesis that dietary

quercetin actively inhibits oxidative damage in the lens and could play an important role in the prevention of cataract.¹⁶

Hydrogen peroxide damages neurons by interfering with the cell's ability to regulate calcium levels, as occurs in many neurodegenerative diseases. In particular, hydrogen peroxide increases intracellular calcium levels, and if this condition is sustained too long, mitochondrial function is impaired and irreversible damage and/or cell death can result. Researchers tested the effect of quercetin and other flavonoids on calcium regulation in PC12 cells, commonly used in cellular models of the nervous system. They found that quercetin best protected cells against hydrogen peroxide-induced oxidative stress and calcium dysregulation. The researchers analyzed the chemical structural characteristics that confer these protective effects, and concluded that the quercetin molecule displays precisely the desired characteristics.¹⁷

How to obtain water-soluble quercetin

Quercetin, the predominant flavonoid in the human diet, has been unobtainable as a practical dietary supplement due to poor absorption. In fruits and vegetables, quercetin is bound to sugars that make it absorbable. Water-soluble quercetin concentrates the key flavonoid benefit of fruit and vegetable consumption into a convenient, absorbable form. Absorbability helps to bridge the hundreds of studies documenting the health-promoting effects of quercetin from the Petri dish to the vitamin shelf.



Starting in October 2002, Life Extension Super Carnosine and Chronoforte supplements were fortified with the amount of bioavailable quercetin that provides optimal potencies for most individuals. Most Life Extension members already take either Super Carnosine or Chronoforte to inhibit the glycation process.

Glycation is a pathologic mechanism that occurs when a glucose molecule inappropriately binds to a protein molecule. The result of glycation is the formation of non-functioning structures in the body known as advanced glycated end products (AGE).

Protein degradation caused by glycation is related to the development of numerous degenerative diseases. The next article describes how carnosine inhibits glycation and why it has become a popular supplement for those seeking to stave off the effects of aging.

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