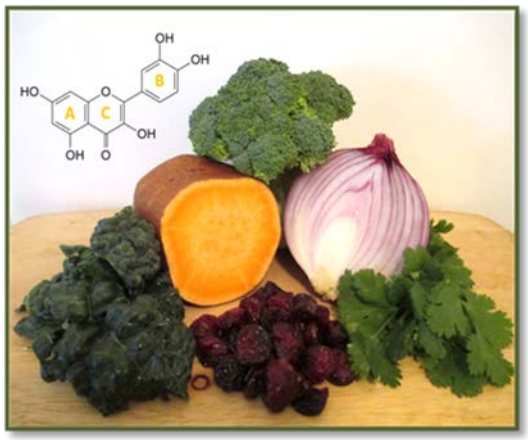
Quercetin



Quercetin (3,3',4',5,7-pentahydroxyflavone) is a flavonoid, or more specifically a subclass called flavonol, and is widely distributed in the plant kingdom. Its name is from the Latin *quercetum* (oak forest) after *quercus* (oak) from which quercetin was first isolated.

All flavonoids are secondary plant metabolites which share a structural similarity based on three-phenol ring basic structure with hydroxyl (OH) groups attached. They are found in leaves, flowers, roots, seeds, nuts, and barks and fulfill many biological functions including UV-protection, pigmentation and antimicrobial defense. Quercetin levels in plants positively correlated with exposure to UVB radiation and its accumulation has been considered a natural protection against UV induced damage[12].

Quercetin, an active ingredient of many medicinal plants such as St John's Wort, has been used in folk medicine for centuries. However, interest in this compound among Western scientists started with the discovery of both vitamin C and rutin (quercetin-3-O-rutinoside) by Albert Szent-Gyorgyi who received the Nobel Prize in 1937 for this research.

In its free form called aglycone and also in its glycosylated (sugar-bound) form, quercetin represents about 60-75% of human flavonoid intake[15]. It has been widely investigated and found to have numerous health benefits ranging from prevention to treatment of many diseases. Many, but definitely not all, of these effects can be attributed to its antioxidant properties.

At the cellular level quercetin is a potent anti-oxidative, anti-inflammatory, and anti-allergy agent. In addition, it has demonstrated anti-cancer, anti-diabetic and antiviral properties as well

as cardiovascular and neuroprotective effects. Moreover, quercetin can offer protection against stress, cataracts, osteoporosis, and heavy metal and kidney toxicity. Numerous studies have shown the ability of quercetin to enhance the efficacy of some types of chemotherapy and ameliorate its toxic side effects[117].

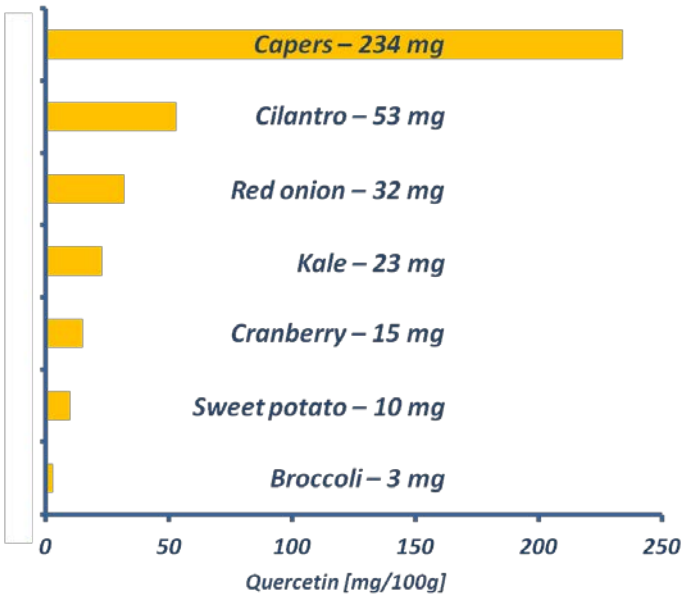


Fig.1. Quercetin content in selected foods

Quercetin's beneficial health effects are potentiated in synergy with vitamin C, resveratrol, curcumin, EGCG (epigallocatechin gallate), and many other nutraceuticals.

Food sources: Quercetin is found in many foods such as onions, cranberries, cilantro, sweet potatoes, broccoli, and kale, among others (see Fig.1.)[165, 166].

Bioavailability: Intestinal absorption and bioavailability of quercetin depends on several factors such as the form in which it is ingested (aglycone or glycoside), the presence of other dietary components, or differences in intestinal microflora[85]. Because in plants quercetin occurs mostly in the form bound to sugar molecules (glycosides), the first step after its oral ingestion is hydrolysis of sugar moiety. This can occur in the intestines on the surface of enterocytes (intestinal cells) by the action of the lactase enzyme, or after its transport inside the enterocytes by the action of cytosolic β-glucosidase[26, 85]. Glycosides that reach the colon are hydrolyzed and further degraded by the gut microflora/bacteria. All forms, either aglycone or glycoside, are absorbed in the stomach, small intestine and colon[102, 57]. It has been found that quercetin absorption can be further enhanced by Vitamin C[97], pectins and fat[102].

Metabolism: Quercetin is further metabolized in enterocytes and hepatocytes (liver cells) where it undergoes glucuronidation, sulfation, or O-metylation[33, 57] before entering the bloodstream to be transported to other tissues. The quercetin conjugates are carried in the blood and commonly distributed by albumins (transporting molecules) reaching virtually every

tissue, even brain tissue due to the ability to cross the blood-brain barrier. Animal studies have shown its presence in the colon, liver, kidneys, muscles, lungs and brain[34].

Quercetin and its metabolites are eliminated by the kidneys and excreted with urine[128]. Interestingly, quercetin has a long elimination half-life (time required to eliminate 50% of the total amount of the substance) of up to 28 hours, which promotes its accumulation in plasma with its continuous intake[40, 68].

Health Benefits

The health benefits of quercetin have been investigated in numerous *in vitro* and *in vivo* studies.

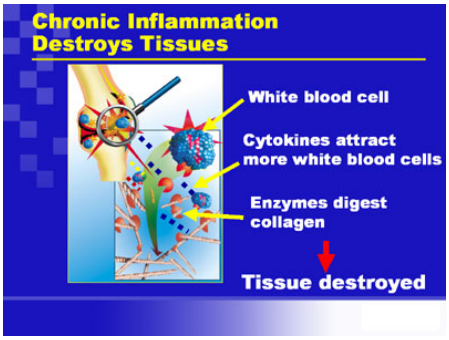
Antioxidant: The most characteristic feature of quercetin is its potent free radical scavenging capability[2]. Free radicals such as reactive oxygen species (ROS) are generated within the cells during metabolic processes and as well they come from environmental sources including tobacco smoke, air pollutants or radiation, among others. Elevated levels of ROS in the cells result in oxidative stress (see description box) which has been associated with etiology of various degenerative diseases such as atherosclerosis, cancer, diabetes, chronic inflammation, and Alzheimer's and Parkinson's disease.

Oxidative stress

Free radicals such as reactive oxygen species (ROS) are generated by the body in various biochemical reactions. Due to their high reactivity, ROS adversely alter lipids, proteins, and DNA triggering various diseases. Excessive production and/or inability to eliminate ROS lead to the condition known as oxidative stress

Quercetin's anti-oxidative properties result from its chemical structure that allows for direct neutralization of free radicals. Also, its plasma metabolites such as quercetin-3-O-β-D-glucuronide have radical scavenging properties inhibiting low density lipoprotein (LDL) oxidation as well as protecting erythrocytes (red blood cells) from damage caused by smoking[2, 12].

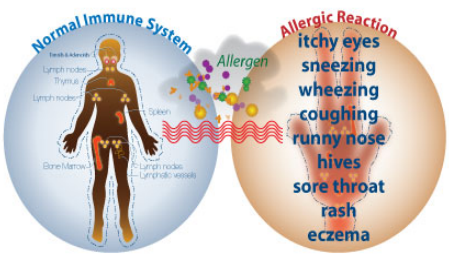
Detoxification: Quercetin can enhance both expression and activity of detoxifying and antioxidant enzymes such as glutamate cysteine ligase (GCL), which is needed for the synthesis of glutathione (GSH) which is the major antioxidant in our body. These enzymes play a key role in decreasing oxidative stress and its consequences[2]. Furthermore, quercetin can interact with reduced forms of transition metals, primarily copper (Cu II) and iron (Fe II, Fe III), which mediate free radical generation[113]. In this particular aspect the presence of multiple hydroxyl (OH) groups in the quercetin structure accounts for its metal chelating properties which was confirmed during lead (Pb) induced toxicity in rats[48]. In this case administration of quercetin markedly reduced both lead concentration and ROS level along with the restoration of antioxidant enzyme activity. Similar results were obtained in mice after cadmium (Cd) exposure[18]. Moreover, quercetin was found to make complexes with aluminum (Al), molybdenum (Mo), palladium (Pd), nickel (Ni), and cobalt (Co)[113]. The chelating properties of quercetin can result in reducing the bioavailability of metals and decreasing metal toxicity. Therefore its supplementation should be considered as a promising antidote for heavy metal poisoning.



Inflammation: Due to its antioxidant properties, quercetin can aid in fighting inflammatory problems because free radicals are involved in cellular mechanisms generating pro-inflammatory cytokines[12]. However, quercetin displays a more complex and diversifying anti-inflammatory mechanism of action providing relief in many inflammatory conditions such as in well-studied prostatitis[153]. Unlike classic non-steroidal anti-inflammatory drugs (NSAIDs) that reduce inflammation at the enzymatic level by blocking cyclooxygenase (COX) enzymes involved in the production of inflammatory mediators (e.g., prostaglandins), quercetin acts in a more sophisticated manner interfering with COX gene expression[175]. It also inhibits activity of the cellular protein complex called nuclear factor kappa B (NFkB) which, upon activation, translocates to the nucleus and initiates expression of many pro-inflammatory molecules such as tumor necrosis factor alpha (TNF-α) and COX enzymes[112].

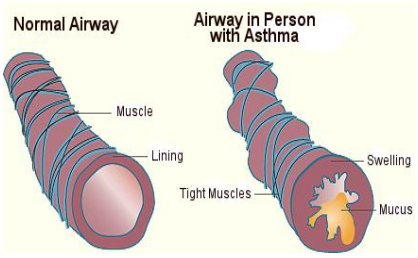
In addition, quercetin can directly inhibit another group of enzymes called lipoxygenases thereby reducing the production of leukotriens which play a critical role in asthma[110]. Furthermore, recent findings indicate that quercetin may enhance the secretion and production of anti-inflammatory substances by *Bifidobacteria sp.*, symbiotic gut bacteria[82, 83]. Since the importance of proper symbiotic microflora and gut condition on overall health has been increasingly understood, the interaction between quercetin and microbiota may provide additional health benefits especially for patients with inflammatory-related bowel disorders.

Allergy: In addition to its immuno-modulatory effect, quercetin's benefits have been well recognized in allergy relief. Sneezing, runny nose, watery eyes, and itchy eyes and skin are the results of histamine release from immune cells known as mast cells or basophiles (types of white blood cells)[9]. Quercetin has been shown to inhibit the release of histamine from these cells upon allergen stimulation[114]. Also, results from human studies have shown beneficial effects of quercetin supplementation on allergy symptoms due to pollen release[65, 90]. Another study demonstrated quercetin to be more effective than the drug cromolyn against contact dermatitis and photosensitivity which are types of skin allergy[169]. In the same study, researchers found that in order for cromolym to be effective it must be added at the same time as the trigger, while quercetin can be used prophylactically.



Food allergies: Prophylactic supplementation of quercetin may be especially beneficial in the control of food allergies. According to research data, quercetin was found to block intestinal allergic inflammation *in vitro*[103]. Very promising findings came from an animal study in which quercetin completely attenuated life-threatening anaphylactic response to peanuts in peanut-allergic rats[152]. Considering that peanut allergy in humans is one of the most frequent and dangerous food allergies, and that the anaphylactic reaction is often fatal, the authors propounded the use of quercetin as an alternative approach against immunoglobulin E-mediated food allergies.

Asthma: Asthma affects millions of people worldwide and results in a high mortality rate. In



experimental models of asthma, quercetin could counteract allergic reactions by significantly reducing both histamine levels and inflammation-mediated enzyme activity. It also decreased the number of leucocytes in the lungs and blood and it relaxed smooth muscle cells in airway passages[79, 118, 138]. In one of these studies quercetin was found to be as effective as conventional medications such as cromolyn and dexamethasome[118]. Therefore, quercetin has emerged as a useful natural candidate in controlling asthma symptoms.

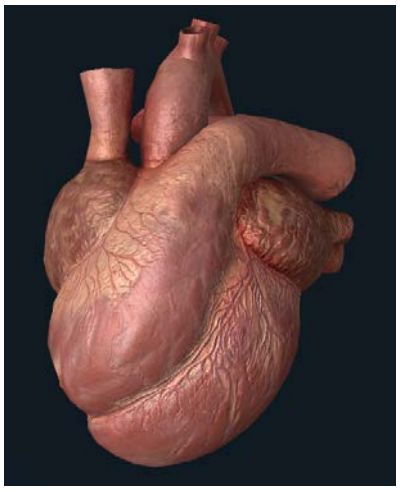
COPD: In another respiratory condition known as chronic obstructive pulmonary disease (COPD), quercetin administration markedly improved lung function. COPD is characterized by progressive degeneration of lung tissue. Oxidative stress, inflammationand an imbalance in tissue degrading enzymes are considered to be the main causes of this pathological condition. As expected, quercetin used in the animal model of COPD considerably decreased oxidative stress, reduced inflammation, and restored normal elasticity of lung tissue[51].

Sepsis: In the case of sepsis, proper control of the immune system is a matter of life or death. Because of extensive inflammatory cytokine production, sepsis is associated with multiple organ failure and a high lethality rate. However, due to its multifactorial activity quercetin has been found to profoundly alleviate inflammatory responses and attenuate these deadly or life-threatening reactions[21, 161]. These findings provide clues that quercetin may be a promising agent against sepsis and is definitely worthy of further investigation.

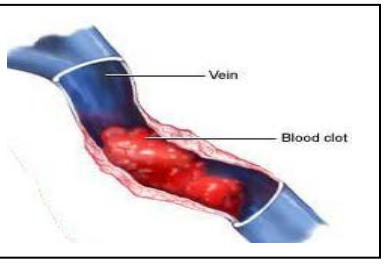
Cardiovascular health: According to epidemiological studies a diet high in quercetin, among other flavonoids, provides significant protection against cardiovascular diseases[102]. Quercetin has been shown to act on multiple biological pathways that synergistically benefit the cardiovascular system. As an antioxidant it scavenges free radicals and helps protect the endothelial cells (cells of the inner blood vessel wall), the extracellular collagen matrix (the structure or “glue” that binds cells together), and the plasma lipids (LDL and Lp(a)) from oxidation and consequently reduces the likelihood of atherosclerosis development[102]. Study

results from quercetin supplementation in humans show a significant reduction in total and LDL cholesterol, and an increase in beneficial HDL cholesterol[104, 159].

High blood pressure: Quercetin was found to decrease high blood pressure in animals and humans[102]. After 28 days of supplementation with quercetin, systolic (top number) and diastolic (bottom number) blood pressure were reduced by seven and five units (mmHg), respectively, without affecting normal blood pressure[39]. Two mechanisms behind quercetin's antihypertensive effect were identified. The first mechanism includes regulation of vasoconstriction (constriction of blood vessels). In this aspect, quercetin stimulates endothelial production of nitric oxide (NO), a well-known vasodilator (an agent that relaxes and widens blood vessels), and decreases the level of endothelin-1 (ET-1), a vasoconstriction agent. The second mechanism is related to the inhibition of angiotensin-converting enzyme (ACE) activity[102]. ACE is involved in the increase of blood pressure and, interestingly, quercetin inhibits its activity in a manner very similar to antihypertensive medications including captopril and imidapril[102]. Untreated hypertension may lead to heart overgrowth and eventually to its inability to effectively pump blood which can contribute to early death. In the animal model of cardiac hypertrophy (heart overgrowth) induced by pressure overload, quercetin could completely inhibit cardiac hypertrophy through beneficial alternations of cellular pathways in the heart tissue[60].

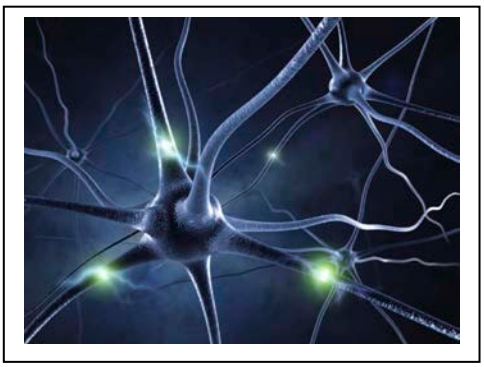


Blood clotting: Another cardiovascular protective effect of quercetin results from its ability to inhibit thrombocyte aggregation (clumping together of blood platelets). It has been shown that either 150 mg or 300 mg of a highly bioavailable form of quercetin ingested by human participants almost instantly (after 30 minutes) decreased platelet aggregation[73]. This may have profound health implications since excessive or inappropriate blood clotting may lead to vascular blood clot



formation resulting in a heart attack or stroke. Taking all into consideration, it is justified to say that quercetin is a potent natural promoter of cardiovascular health.

Neuroprotection: Various *in vitro* and *in vivo* studies strongly suggest that quercetin may cross the blood-brain barrier into the brain[43, 44, 80]. This opens new perspectives in research and clinical applications of quercetin. Several neurological disorders including Parkinson's disease, Alzheimer's disease, and depression have been associated with neurodegeneration induced by free radicals. Quercetin has been found to protect neurons (in cell cultures) against oxidative stress induced by toxins and peroxides[64, 142]. A study on astrocytes (star-shaped neurons) showed that quercetin can enhance resistance to oxidative stress by increasing the expression of the antioxidant enzyme, paraoxonase-2 (PON-2)[29]. Some studies reported that quercetin applied in supra-physiological levels may have neurotoxic effects on pure neuron cultures[75]. However, in experiments where neurons were co-cultured alongside glial cells (non-neuronal cells in the nervous system) to resemble physiological conditions, quercetin showed no signs of neurotoxicity even at much higher concentrations[170]. This is because glial cells, which are responsible for maintaining homeostasis and protection of neurons, may rapidly metabolize the surplus of quercetin.



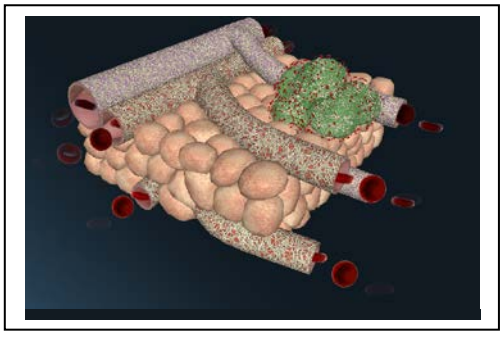
Parkinson's disease: In some conditions like Parkinson's disease, over-activation of glial cells can trigger the production of inflammatory cytokines and contribute to neuro-inflammation followed by death of dopaminergic (dopamine producing) neurons. It has been reported that quercetin can significantly decrease the levels of proinflammatory cytokines (e.g., TNF-α, IL-1α). It is anticipated that these cytokines mediate the apoptotic cell death of these dopaminergic neurons in Parkinson's disease[19].

Alzheimer's disease: Another neurodegenerative condition is Alzheimer's disease which is characterized by extracellular deposition of so called amyloid-β peptides that, under certain conditions, may inappropriately aggregate the forming oligomers which are thought to

contribute to the severity of this disease. Interestingly, it has been found that quercetin metabolite (quercetin-3-O-glucuronide) can markedly reduce the generation of amyloid-β peptides[67]. In addition, this compound was shown to interfere with the initial protein-protein interaction (aggregation) that is necessary for the formation of neurotoxic oligomers. Moreover, it has been reported that quercetin and quercetin-3-O-rutinoside (rutin) almost completely inhibited ROS, while rutin decreased the activity of β-secretase which is an enzyme involved in amyloid-β formation[77].

Depression: Another condition that could be affected positively by quercetin is depression. According to current knowledge, decreased levels of monoamine neurotransmitters such as serotonin, dopamine, and norepinephrine in the brain are a possible etiology of this disease[139]. Interestingly, many natural compounds with antidepressant properties, such as St. John's Wort, Ginkgo biloba, and onion powder, contain quercetin glycosides which would imply that quercetin may play an active role. It has been shown that the administration of onion powder to rats decreased serotonin and dopamine metabolism in the brain indicating the inhibition of monoamine metabolizing enzymes, which are the primary targets for drugs known as monoamine oxidase (MAO) inhibitors[141]. This was confirmed in *in vitro* studies, showing that quercetin can inhibit the activity of monoamine oxidase A[10, 24, 140, 177]. Furthermore, quercetin and its glycosides were shown to decrease plasma levels of stress hormones such as adrenocorticotropic hormone and cortisol[20, 86]. Since it is well known that prolonged exposure to cortisol damages neurons and impairs learning ability, and increases susceptibility for neurodegenerative disorders, quercetin might be a natural alternative for depression.

Cancer: According to research data, quercetin exerts multifactorial anti-tumor activity reducing both the risk of cancer and the growth and spread of cancerous cells[42, 54, 101, 117, 163]. One of the anti-cancer mechanisms of quercetin can relate to its antioxidant properties and protection of cells from oxidative stress, inflammation, and DNA damage which all lead to carcinogenesis. In addition, a direct interaction of



quercetin with cellular components such as enzymes or transcription factors could provide beneficial biochemical responses keeping the cells in a "healthy" state. Interestingly, there is a growing body of evidence suggesting that quercetin may contribute to remodeling of chromatin (genetic material organization in the cell nucleus/complex of DNA, RNA and proteins) and thus interfere with unwanted epigenetic alternations (non-genetic influences on gene expression)[54].

Results from *in vitro* experiments demonstrated quercetin's efficacy in suppressing growth of many cancer cell lines. By affecting multiple cellular pathways, quercetin can block the cell cycle progression stopping the proliferation of cells and triggering apoptosis (cell death) of abnormal cells. These anti-cancer effects were observed in cancer cells originating from the human esophagus[178], breasts[76], lungs[176], prostate[122], and liver[120]. Scientists have documented the anti-cancer efficacy of quercetin in various animal studies. Quercetin administered simultaneously or prior to carcinogen (substance that triggers cancer) drastically reduced the occurrence, growth and metastasis (spread of cancer cells) in different types of cancers. It also decreased incidents of colon cancer in rats, and lung tumor burden in mice[87, 174]. Concomitant administration of quercetin and a cancer inducer resulted in a greater protection against liver cancer in rats[145]. In another study, four weekly injections of quercetin directly into breast tumor mass significantly reduced its volume[38].

In addition, human epidemiological studies show an inverse correlation between the intake of quercetin-rich food and risk of cancer. As such, a quercetin-rich diet reduced stomach cancer risk by 43%[42] and colon cancer by 32%[163]. Lung cancer risk could be decreased by 51% and even in the heavy smokers by 65%[101]. A Phase I clinical trial of intravenous quercetin administration in patients with different types of cancer demonstrated decreased activity of the enzyme tyrosine kinase in nine of 11 patients (this enzyme is required for tumor growth)[46].

There is a growing interest among scientists in exploring synergistic interactions of quercetin with standard chemotherapeutics. Both *in vitro* and *in vivo* studies have shown that quercetin can potentiate the efficacy of concomitant drugs by enhancing their bioavailability and accumulation and by sensitizing the cancer cells to these chemotherapeutics[117]. From a clinical

perspective this would allow reduction of the doses of toxic drugs thereby alleviating their severe side effects.

Obesity and diabetes: Obesity and diabetes are other conditions in which quercetin has demonstrated significant positive effects. Quercetin given to obese rats induced positive changes in many pathological parameters[137] such as reduction of elevated blood pressure, and lowering of high plasma cholesterol, triglycerides, and free fatty acids. These positive changes included better responses to insulin and the reduction of proinflammatory markers. These results have been replicated by others who also observed normalization in blood pressure, dyslipidemia and hyperinsulinemia, and the reduction in abdominal and liver fat accumulation[98, 129].

When untreated, obesity may lead to diabetes resulting in high plasma glucose levels. This has detrimental health effects due to the fact that excess glucose binds to the body's proteins in the process known as glycation, causing protein structure alteration which negatively affects their function. It has been shown in test tube experiments that in the presence of quercetin the glycation of hemoglobin, a red blood cell protein, can be reduced by 52%[6]. This effect was confirmed in various studies with animal models of diabetes mellitus[7, 93, 99, 172]. These studies further validated the reduction of plasma cholesterol, triglycerides, and glucose levels in animals supplemented with quercetin, and showed an increase of number of pancreatic islets and overall improvement in pancreatic and liver function. A separate study contributed to better understanding of one of the mechanisms behind quercetin's ability to lower postprandial blood glucose levels[78]. It has been shown that quercetin strongly inhibits α-glucosidases, intestinal enzymes involved in digestion of carbohydrate . Chemical inhibitors of α-glucosidase have been used as oral hypoglycemic medications prescribed to patients with type 2 diabetes mellitus to delay a spike in blood glucose after eating.

Another anti-hyperglycemic effect of quercetin involves skeletal muscle cells. Skeletal muscle is the most important glucose uptake tissue, responsible for more than 75% of insulin-mediated postprandial glucose disposal[36, 149]. Glucose enters skeletal muscle cells mainly by glucose

transporter, GLUT4. This transporter is stored inside the cells and is instantly translocated to the membrane upon insulin stimulation. However, in obese individuals this process becomes disturbed by an excess of fatty acids and over-secretion of TNF-α by abdominal fat [58]. Interestingly, recent *in vitro* studies have reported that quercetin can stimulate GLUT4 translocation markedly increasing glucose uptake[41, 84].

Over time diabetes, or inappropriately treated diabetes, may lead to undesirable complications. Some, such as painful neuropathy or cardiovascular, eye and kidney problems, are thought to be mediated by increased activity of the enzyme, aldose reductase. Interestingly, quercetin was found to be an inhibitor of this enzyme and delayed the onset of cataract formation in supplemented rats[171]. Additionally, quercetin has been demonstrated to protect kidney cells from oxidative stress and inflammation, to induce apoptosis, and to improve overall renal function in diabetic animals[55, 167].

These and other scientific and clinical results indicate that quercetin's antidiabetic effects should be further investigated as a potential naturally derived antidiabetic agent which could present a safe and effective alternative to hypoglycemic drugs with their undesirable side effects and reduced efficacy over time.

Immunity and infections: In addition to modulating immunity (see Allergy), quercetin can provide benefits in fighting viral and bacterial infections. This is especially important for people with a weakened immune system and patients with chronic lung diseases such as asthma, COPD, and cystic fibrosis, because respiratory viruses are responsible for 40-60% of exacerbation and accelerate progression of lung disease[95]. It has been shown that quercetin can block the replication of rhinovirus (responsible for the majority of common colds) and influenza A virus[27, 50]. Moreover, in one study quercetin was more effective against influenza A virus than the anti-flu drug Tamiflu[27]. Also, parainfluenza virus, respiratory syncytial virus and adenovirus, among others, were inhibited by quercetin[96, 111]. Results from animal and human studies show the efficacy of this natural compound in fighting infections and ameliorating their adverse symptoms. Mice supplemented with

quercetin and infected with influenza A virus displayed fewer serious flu symptoms along with decreased mortality[28]. Moreover, they had a 2000-time lower number of viruses in their lungs compared to the placebo-treated mice, and two-times lower than those that received Tamiflu.

Humans engaged in physical activity may also benefit from quercetin. Three weeks of quercetin supplementation (1000 mg/day) significantly reduced upper respiratory tract infection (URTI) incidents in male cyclists in training[126]. The same amount of quercetin taken for 12 weeks by physically fit middle-aged and older participants reduced the severity of URTI symptoms by 36% and the number of sick days by 31%[63].

Another finding identified quercetin as a potent suppressor of hepatitis C virus (HCV)[8]. Since hepatitis C is the major cause of liver failure and may lead to liver cancer, quercetin appears to be a natural non toxic anti-HCV alternative.

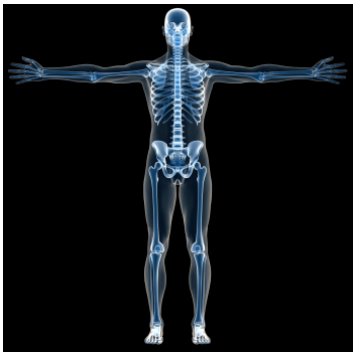
Quercetin also exhibits antibacterial activity. It was demonstrated in test tube experiments that it can inhibit the growth of methicillin-sensitive *Staphylococcus aureus* (MSSA) as well as methicillin-resistant *Staphylococcus aureus* (MRSA)[157]. MRSA is difficult to treat and is responsible for several serious human infectious diseases including life-threatening sepsis. *Helicobacter pylori*, a bacteria that causes stomach ulcers, is another candidate for quercetin treatment. Results from *in vivo* studies on guinea pigs and mice indicate that quercetin administration can reduce both the rate of bacterial infection (colonization) and inflammation of the stomach tissue[17, 56]. In the case of *Salmonella* infection quercetin also decreased inflammation, lowered bacterial count in the liver, prevented liver damage and prolonged survival in quercetin supplemented mice[158]. Due to the growing bacterial resistance to existing antibiotics, quercetin appears to warrant further research.

Athletic performance: Quercetin has been widely investigated by scientists interested in its potential to increase athletic performance and post-exercise recovery. Because excessive exercise can cause oxidative stress inducing muscle damage, quercetin appears to be beneficial as an antioxidant. In addition, muscle endurance

depends on mitochondrial content and function and quercetin is known to increase mitochondrial biogenesis so, again, quercetin supplementation should provide some advantages[31]. However, neither animal nor human studies have verified these assumptions[131]. Many results are difficult to compare and analyze due to experimental design differences. However, the majority of findings present different responses after quercetin treatment of those subjects in training and subjects who were not in training[117]. Generally, animals or human volunteers not in training had increased mitochondrial biogenesis and improved endurance performance, while those in endurance training displayed no significant differences[31, 124, 125, 131].

Longevity: Several studies have reported that animals supplemented with quercetin or those consuming food containing high amounts of quercetin live longer. As such, the life span of *Caenorhabditis elegans* was extended by 15% upon quercetin treatment [88]. Also, results from mice studies support positive age-related changes. However, the anti-aging effects seem to be attributed to quercetin antioxidant activity and all other beneficial properties that contribute to healthy aging and prolonged lifespan.

Bone health: Maintaining healthy bones is important because osteoporosis may severely affect the quality of life. This disease is triggered by numerous factors including, but not limited to, hormone imbalance (steroid use or menopause), diabetes or cirrhosis. Interestingly, quercetin is able to prevent and even reverse bone loss. It improved bone mineral density and bone volume when administered to ovariectomized mice (which is an animal model of menopause)[164]. Similar results were obtained in a rat model of diabetic osteopenia and also in rats with experimental biliary cirrhosis[37, 107]. These study results suggest quercetin as a vital ingredient for improving biomechanical quality and micro-architecture of the bone tissue.



Human Studies

Table 1 presents a short description of human studies involving quercetin supplementation.

Abbreviations used in Table 1:

BP - blood pressure
EMIQ - enzymatically modified isoquercitrin
HDL high density lipoprotein
IL-6 - interleukin 6
LDL - low density lipoprotein
Q - quercetin
T2DM - type 2 diabetes mellitus
TG - triglyceride
TNF-α - tumor necrosis factor alpha
VO_2max - maximum oxygen consumption

Table 1. Results from human studies involving quercetin supplementation.

OBJECTIVE	SUBJECTS	FORM & DOSE OF QUERCETIN	PRIMARY RESULTS AND CONCLUSIONS
[104] To determined if Q improves cardiometabolic risk components in healthy male smokers.	92 healthy male smokers.	Placebo or 100 mg of Q daily for 10 weeks.	Q reduced total cholesterol and LDL while it increased HDL. Q decreased both systolic and diastolic BP as well as glucose concentration, however no changes were observed in inflammatory markers.
[159] To evaluate effects of Q on blood lipid values in healthy persons with dyslipidemia.	400 hundred men and women.	Placebo or Q in the product Cardiofit for two months.	Q reduced total cholesterol and LDL while it increased HDL.
[39] To test the hypothesis that Q supplementation reduces BP.	Men and women with prehypertension (n=19) and stage 1 hypertension (n=20).	Placebo or 730 mg daily of Q for 28 days.	Q reduced BP in patients with stage 1 hypertension but not in patients with prehypertension.
[73] To investigate the relationship between the ingestion of Q and platelet function.	6 healthy people (3 men and 3 women).	Q (Q-4'-O-β-glucoside) 150 mg or 300 mg.	Q inhibited platelet aggregation 30 and 120 minutes after ingestion of both doses.
[178] To determine if Q improves cardiovascular risk factors and inflammatory biomarkers in women with T2DM.	72 women with T2DM.	Placebo or 500 mg of Q daily for 10 weeks.	Q decreased systolic BP but not diastolic BP. HDL was decreased in both groups. Total cholesterol, LDL, TG, and ratio TG/HDL, LDL/HDL were not changed. Q decreased TNF-α and IL-6.

[74] To evaluate the potential of Q to damp postprandial blood glucose level after maltose and glucose loading in patients with T2DM.	24 patients with T2DM.	Placebo or 400 mg of Q orally administrated 30 minutes before glucose or maltose intake.	Q decreased the magnitude of glucose spike after maltose intake. Q did not change the rate of postprandial hyperglycemia after glucose intake.
[32] To determine if Q enhances maximal aerobic capacity and delays fatigue during prolonged exercises in healthy but non-training participants.	Healthy non-trainingmen (n=7) and women (n=5).	Placebo or 500 mg of Q twice daily.	Q modestly increased VO_2 max and substantially the ride to fatigue.
[153] To confirm previous open-label study that Q improves nonbacterial chronic prostatitis and prostatodynia.	47 men with category IIIa and IIIb chronic pelvic pain syndrome. 2 from placebo group refused to complete the study because of worsening symptoms.	Placebo or 500 mg of Q or Prosta-O (supplement containing Q + bromelian + papain) twice daily for 1 month.	Improved chronic prostatitis symptoms by 25% in 67% of patients taking Q and in 82% of patients taking Prosta-O.
[66] To determine if Q is effective for relief of ocular symptoms caused by Japanese cedar pollinosis.	24 patients (19 men and 5 women).	Placebo or 50 mg of Q (EMIQ) twice daily for 8 weeks, starting 4 weeks prior to the onset of pollen release.	Q significantly lowered ocular symptom + medication score.
[89] To determine if Q is effective for interstitial cystitis.	22 patients (5 men and 17 women).	One capsule of Cysta-Q complex (500 mg of Q) twice daily for 4 weeks.	Q provided significant symptomatic improvement in patients with interstitial cystitis.

Synergy

All biochemical reactions and metabolic pathways in our body are interrelated and involve various compounds (e.g., substrates, cofactors), and as well as they are influenced by external factors (e.g., temperature, pH). Often the same results may be accomplished through alternative pathways. Therefore it is essential that optimal conditions and required compounds are present in the cells at the same time in order to avoid any missing links and achieve maximum biological effects.

Metabolism is based on biological synergy between substances that are directly involved in the same pathway or indirectly through alternative pathways that eventually result in the same physiochemical response. Synergistic interactions between different compounds can benefit various cellular processes, such as increasing absorption or bioavailability of molecules involved

in this process (i.e., helping them to get to the reaction place at the right moment, at the required amounts). Thus, micronutrients that are selected based on their synergy achieve better biological efficacy with lower doses of individual compounds than when nutrients are randomly compounded.

This principle of biological synergy was pioneered in Dr. Rath's research and applied in designing nutrient compositions in various aspects of health. Its advantage is better efficacy, the use of moderate micronutrient doses compared to application of a single compound, and maintaining cellular metabolic balance which is the basis of health.

Thus, synergy allows for using lower non-toxic micronutrient doses and results in better efficacy than that achieved by application of single nutrients in larger doses.

Quercetin has been found to work in synergy with other natural compounds as well as with existing drugs. Table 2 and Table 3 list examples of quercetin working in synergy with natural compounds and drugs, respectively.

Table 2. Quercetin synergy with select natural compounds.

Property	Natural compounds	Benefits of quercetin synergy
Antioxidant	Kaempferol, pterostilbene	↑antioxidant enzymes ↓Reactive oxygen species (ROS)[144]
	Glutathione	↓Oxidative stress [132]
	Resveratrol	↓ Membrane lipids oxidation (in vitro on human erythrocytes)[116]
Anti-inflammatory	Curcumin	↓Inflammatory markers, ↑anti-inflammatory enzyme (HO-1), ↓oxidative stress (rats study)[62]
	Yerba mate saponins	↓Pro-inflammatory enzymes, ↓pro-inflammatory cytokines (in vitro) [135]
	Resveratrol	↓ Inflammatory markers (mice study) [92]
Cardiovascular protection	Resveratrol	↓Stenosis [92]
	Resveratrol	↓ Vascular smooth muscle cell (VSMC) proliferation (in vitro)[92]
	Hyperoside	↓HMG-CoA reductase (in vitro)[72]
	Afzelin	↓Angiotensin converting enzyme activity (in vitro)[61]
Neuroprotection	Hyperforin	↓Depression (mice study)[109]
Chemoprevention/ Anti-cancer	Resveratrol, morin	↓Human prostate cancer cells[45]
	Epigallocatechin gallate	↓Human prostate cancer cells[168]

	Genistein	↓Human ovarian cancer cells [148]
Anti-obesity	Resveratrol	↓Adipose tissue triacylglycerol accumulation (rats study)[4]
	Fructooligosaccharide	↑Glucose tolerance, ↑Insulin sensitivity, ↓Total cholesterol [133]
	Resveratrol+Genistein	Adipogenesis ↓, Adipocyte apoptosis ↑ (in vitro on primary human adipocytes)[130]
Anti-diabetic	Quinic acid	↓Hyperglycaemia , ↓Hyperlipidemia, ↓Insulin resistance[5]
Antimicrobial	Gallic acid	↓*Staphylococcus aureus* [155]
	Kaempferol	↓Herpes simplex virus type 1 [3]
	Galangin	↓Herpes simplex virus type 1 [3]

Table 3. Quercetin synergy with select drugs.

Property	Drugs	Benefits of quercetin-drug synergy
Chemoprevention/ Anti-cancer	Adriamycin	↓MDR human leukemia cells[22]
	Menadione (vit. K3)	↓Human leukemia Jurkat T cells [11]
	Cisplatin	↓Human liver cancer cells [180]
	Daunorubicin	↓Human pancreatic cancer cells[14]
	Tiazofurin	↓Human ovarian cancer cells [147]
	5-Fluorouracil	↓Human colorectal cancer cells [13]
Antimicrobial	Fluconazole	↓*Candida tropicalis* [30]
	Minocycline	↓*Staphylococcus aureus* [100]
	Fusidic acid	↓*Staphylococcus aureus* [100]
	Rifampicin	↓*Staphylococcus aureus* [100]
	Amantadine	↓Influenza A and B viruses [95]

Safety

Based on animal and clinical studies quercetin is generally considered as safe (GRAS category). A recent study with mice concluded that a daily dose of 350 mg per kilogram of body weight for 12 weeks is safe without signs of liver and small intestine toxicity[35]. An earlier study in which rats were administered very high doses of quercetin daily for two years reported some kidney toxicity[127].

In humans typical oral doses used in clinical practice ranging from 500 mg to 1000 mg daily for the period of 12 weeks had no serious side effects[16, 146]. A Phase I clinical trial of intravenous quercetin administration in cancer patients resulted in recommendation of 1400 mg/m^2 (about 2.5 g for a 70 kg person) in weekly intervals, under professional supervision. Higher doses resulted in nephrotoxicity[46]. However, because of the prevalence of quercetin in the human diet, the level of supplementation should be established individually due variations in its absorption rate, possible interference with drug metabolism, and a long half-life that favors accumulation. Since quercetin can accumulate in plasma (two week supplementation of 150 mg/day of quercetin increased its plasma concentration by 570% [40]), periodic pauses in taking it are recommended.

Quercetin might decrease blood clotting, therefore people with bleeding disorders and those taking anticoagulant drugs or even NSAIDs, should consult with a doctor about adjusting drug doses. People taking drugs metabolized by the liver should consult with a doctor because quercetin can modulate drug detoxification pathways (cytochrome P450 enzyme system) in the body. As an estrogen agonist, quercetin might affect some hormone-sensitive conditions.

Taking into account the variety of quercetin supplements on the market, and the low absorption and bioavailability of this compound[115, 121], it is important to make right choices in selecting a product that delivers the best health benefits. Many products are claimed to be better than others without showing any valuable, scientifically proven data. Due to its lipophilic character, quercetin is practically insoluble in water[156] and can be absorbed via passive

(diffusion) uptake through the membrane of gastrointestinal epithelial cells. Therefore, many statements allege that aglycone absorption should be better than quercetin is in its glucoside form which requires preliminary hydrolysis. However, neither animal nor human studies support this view. Just the opposite. The evidence shows that isoquercetin (quercetin with glucose moiety such as is present in high amounts in onions) is absorbed rapidly and it has a 6-fold higher bioavailability compared to quercetin aglycone[52, 69, 70, 115, 119, 128, 150]. There are at least two mechanisms implied behind this phenomenon. First, the presence of the intestinal mucus layer provides a barrier for lipophilic substances, and can therefore hinder aglycone absorption. The second mechanism suggests the involvement of sodium-dependent glucose transporters (SGLTs) which facilitate transport of monoglucosides of quercetin into enterocytes[52]. However, isoquer**ce**tin or isoquer**ci**trin (the two molecules are very similar and differ only in glucose ring structure; isoquercetin has a glucopyranose ring structure whereas isoquercitrin has a glucofuranose ring structure) out perform aglycone in bioavailability by 6 times.

By attaching glucose molecules to quercetin, scientists created a mixture of quercetin monoglucoside (mainly isoquercitrin) and its alpha-oligoglucosides known as enzymatically modified isoquercitrin (EMIQ)[115]. EMIQ is more water soluble and has been found to have superior bioavailability relative to quercetin aglycone and isoquercetin by 18-fold and 3-fold, respectively. This is consistent with the results from a recent human study in which the authors experimentally calculated that 166 mg of quercetin dihydrate (supplement) would be comparable to about 10 mg of quercetin aglycone equivalents from onion (quercetin glucosides)[150]. Thus, EMIQ supplementation dosesmay be proportionally lower than other forms of quercetin.

Another important aspect that increases the efficacy of quercetin is its synergy with other properly selected nutraceuticals. According to multiple studies, quercetin combined with other phytonutrients such as green tea catechins, resveratrol or turmeric shows enhanced potency through synergy and allows obtaining health benefits at a reduced intake level.

Mechanism of Action

According to thousands of *in vitro* and *in vivo* studies, quercetin can activate and inhibit numerous pathways and factors inside and outside of the cells.

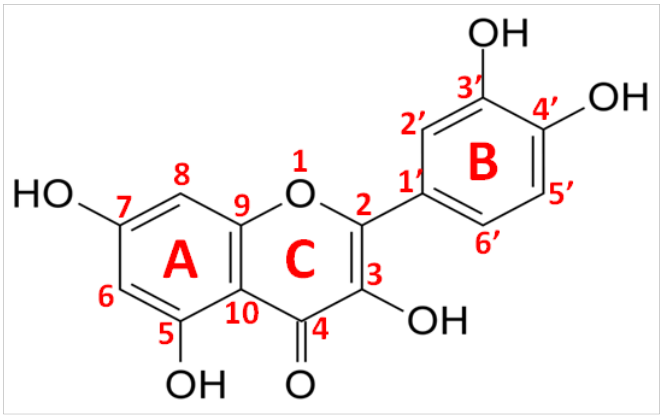


Fig.3. Chemical structure of quercetin

Antioxidant: Quercetin is a strong antioxidant due to its ability to scavenge free radicals and bind metal ions. It was found that flavonoids, which have catechol group (B ring) and 3-OH, are up to 10 times more potent towards peroxynitrite than ebselen which is a known RNS scavenger[59]. Quercetin antioxidant activity is attributed to its o-dihydroxy structure in the B-ring and the 3-hydroxy group and 2,3-double bond in the C ring[47]. Therefore glycosylated forms of quercetin have decreased antioxidant activity compared to aglycone[2].

Quercetin can also activate cellular antioxidant systems by increasing both transcriptional and post-transcriptional levels of Nrf-2, a transcription factor which induces expression of various antioxidant and phase II detoxifying enzymes including NAD(P)H quinone oxidoreductase 1 (Nqo1), glutamate cysteine ligase (GCL), heme oxygenase-1 (HO-1), and many others [2]. At the same time, quercetin reduces the level of Keap1 (that keeps Nrf-2 in cytoplasm and thus blocks its activity) through the modification of Keap1 protein rather than 26S proteasome degradation[162].

Quercetin was also found to decrease an ischemia-reperfusion injury by inhibiting the activity of iNOS[134]. However, at high concentrations quercetin may act as an oxidant and can induce double-strand DNA breaks leading to p53 activation and subsequently apoptosis[117].

Inflammation: Quercetin's anti-inflammatory effects involve numerous pathways[26]. Quercetin can suppress activity of cellular proteins involved in inflammatory response and inhibit NFκB transcription factor that controls the expression of proinflammatory molecules[26]. It can reduce the secretion of TNF-α, IL-6, IL-8, histamine and tryptase by human mast cells[91] by inhibiting intracellular calcium influx and PKC theta signaling.

Due to the fact that MMP-1 plays a key role in the rapid breakdown of collagen in human inflamed/UV-radiated skin, quercetin has been studied and found to strongly inhibit both the activity and expression of MMP-1, as well as activation of the transcription factor, activator protein-1 (AP-1)[108]. Furthermore, it suppressed activation of the extracellular signal-regulated protein kinase (ERK) and p38 mitogen-activated protein kinase (MAPK). In another study, quercetin was identified as a significant inhibitor of the nuclear enzyme, poly(ADP-ribose) polymerase-1 (PARP-1)[53]. PARP-1, which was initially known to be activated by oxidative stress-induced DNA strand breaks, has been found to be involved in the pathophysiology of acute and chronic inflammatory diseases. Quercetin reduced the PARP-1 activity, IL-8 production and preserved the cellular NAD(+) levels.

Allergy: The anti-allergy effects of quercetin can involve several mechanisms. One involves down-regulating the Fc epsilon RI expression, which is a high-affinity IgE receptor, followed by decrease in histamine release[151]. It was also found that quercetin can suppress the Fc epsilon RII mRNA expression and p38 MAPK activation in Caco-2 cells[105]. Another mechanism involves strong inhibition of CD63 and CD203c membrane expression in human basophils at a quercetin dose as low as 0.01 mcg/ml[25].

Vascular health: As an antihypertension agent, quercetin can regulate both vascular function (NO/ET-1) and renin-angiotensin-aldosterone system (RAAS). It was found that it can increase NO levels by quick phosphorylation of eNOS at serine 1179 via an Akt-independent cAMP/PKA-mediated pathway[106]. At the same time quercetin could decrease expression of ET-1, a potent vasoconstrictor[123]. In addition, quercetin can inhibit angiotensin converting enzyme (ACE) through its ability to chelate the Zn atom at the active site of the enzyme[102].

Neuroprotection: It has been shown that quercetin can interfere with amyloid β aggregation, which is characteristic for Alzheimer's disease[143]. It is thought that it can attack lysine residues at positions 16 and 28 of amyloid β, which are crucial to form an intermolecular β sheet[143]. Also activation of macroautophagy and proteasomal degradation pathways may be an additional explanation of how quercetin may prevent amyloid β aggregation[136].

Cancer: Quercetin exerts multifactorial effects with regard to chemoprevention. One of the mechanisms relates to chromatin remodeling by chemical modifications of DNA and histones. In this aspect, Quercetin was found to demethylate the p16INK4a gene promoter, whose hypermethylation is present in human colon cancer cells[160]. In prostate cancer cells, quercetin could activate histone deacetylase leading to decrease in histone H3 acetylation resulting in sensitization to TRAIL-induced apoptosis[94]. Another important anti-cancer effect of quercetin is its ability to regulate the cell cycle by modulating several molecular targets including cyclin B, p21, p27, cyclin-dependent kinases (CDKs), and topoisomerase II (see Fig. 4)[54]. It can block the cell cycle at G1/S or at G2/M transition, depending on cell type and tumor origin. For example, quercetin caused cancer cell-specific (not in normal cells) G1/S arrest in breast cancer cells[76]. The study revealed that a low dose of quercetin induced mild DNA damage which activated ataxia telangiectasia mutated (ATM). Consequently, ATM phosphorylated checkpoint kinase 2 (Chk2). Then Chk2 up-regulated p21 (cyclin-dependent kinase inhibitor) and that subsequently inhibited activity of cyclin-CDK (cyclin-dependent kinase) complexes which is required for the phosphorylation of retinoblastoma protein (pRb).

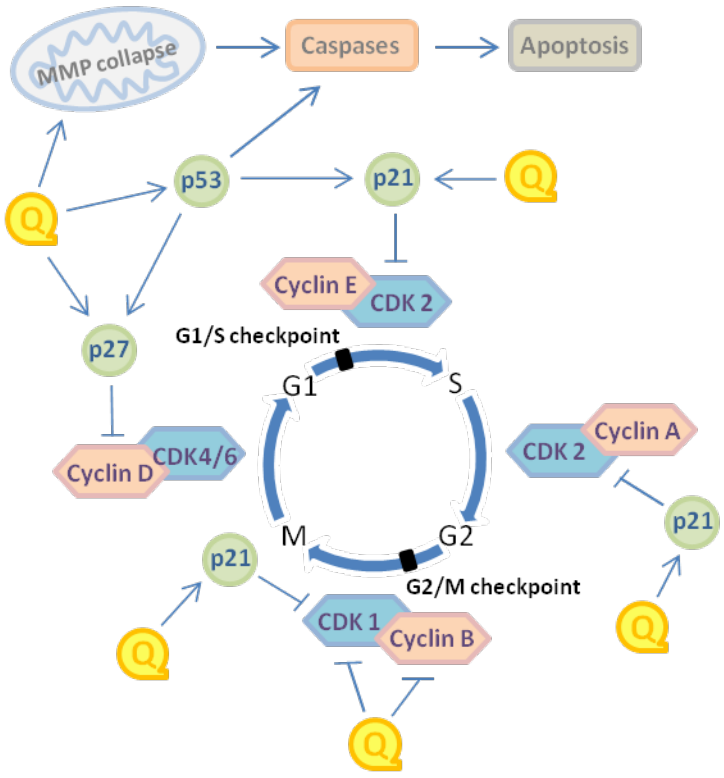


Fig.4. Effects of quercetin on cell cycle [54, modified]

Hypophosphorylated pRb binds to, and traps, the E2F1 transcription factor which is essential for the expression of cell proliferation-related genes, resulting in cell cycle arrest at the G1 phase. In the same study quercetin down-regulated cyclin B1 which is essential in CDK1 activity, and thus blocked the progression to the G2/M cell cycle (again, this did not occur in normal cells). The synthesis of cyclin B1 was inhibited at the transcriptional level by the repression of binding transcription factor NF-Y on/to the cyclin B1 gene promoter.

In another study, quercetin induced apoptosis via the mitochondrial pathway. It increased cytosolic Ca^{2+} levels and reduced the mitochondrial membrane potential (MMP) leading to the activation of caspase-3, -8 and -9[23]. Quercetin also up-regulated the pro-apoptotic protein Bax and down-regulated the anti-apoptotic protein Bcl-2.

Collectively, the anti-cancer effects of quercetin derive from its activity on multiple anti-tumor pathways that were described in more detail in a review article by Gibellini L. and colleges[54].

Obesity and Diabetes: Anti-obesity and anti-diabetic effects of quercetin are illustrated in the following diagrams based on the article by Aguirre L. and colleges[1].

Abbreviations:

ACC - acetyl-CoA carboxylase
FAS - fatty acid synthase
LPL - lipoprotein lipase
PDE - phosphodiesterase
PPARγ - peroxisome proliferator-activated receptor γ
SREBP-1 - sterol regulatory element-binding protein 1

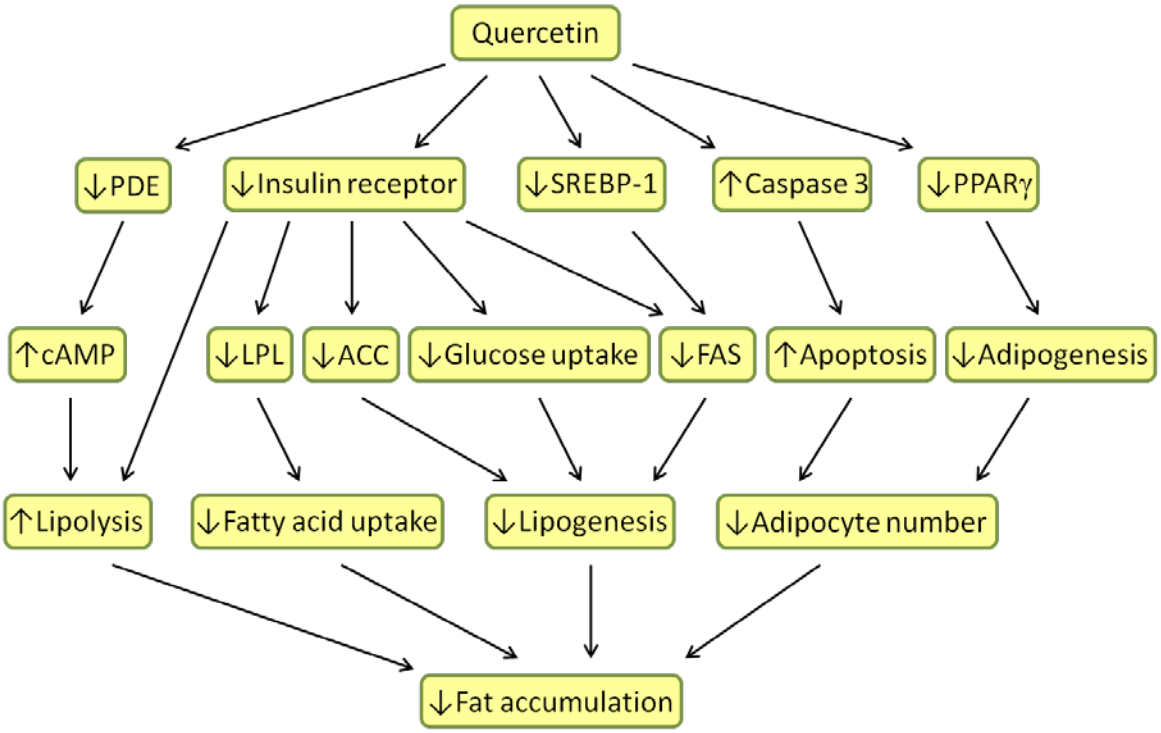


Fig. 5. Proposed mechanisms for body-fat lowering effects of quercetin in adipose tissue [1, modified].

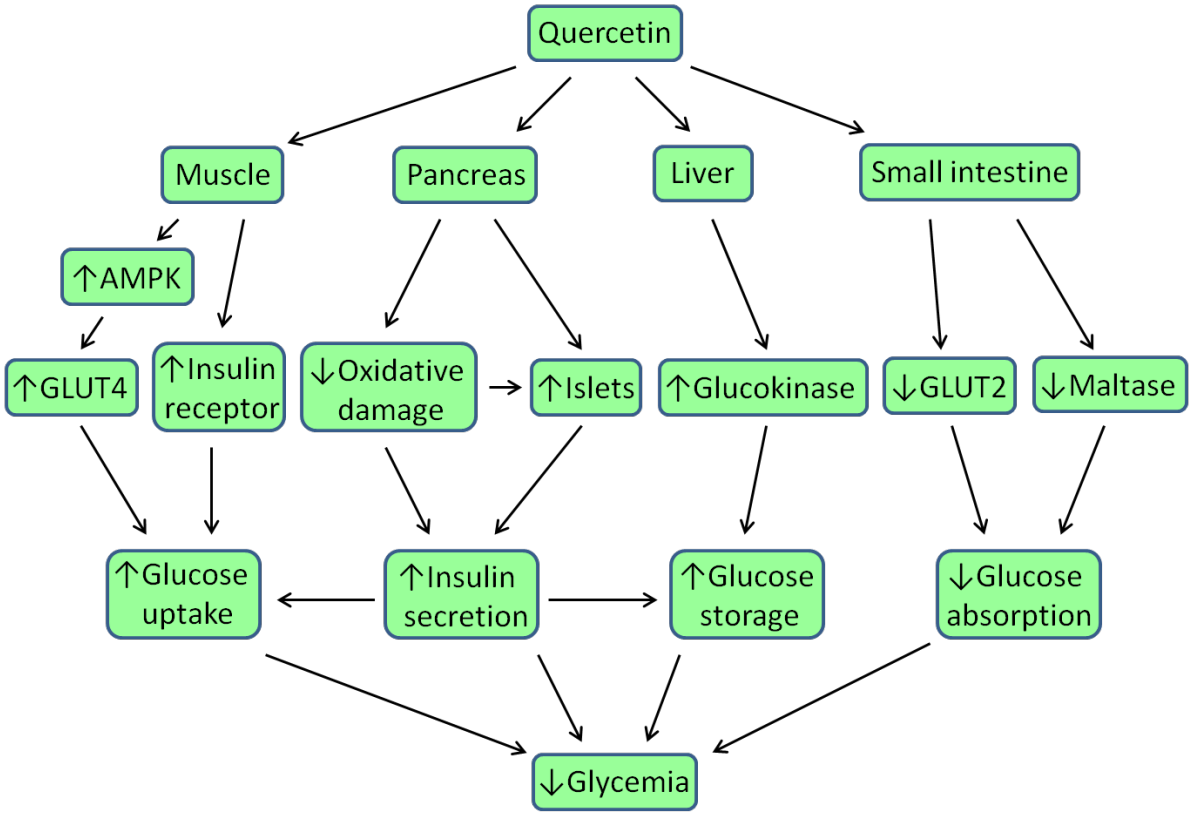


Fig. 6. Proposed mechanisms for anti-diabetic effects of quercetin [1, modified].

Anti-microbial: Antiviral effects of quercetin are exhibited at multiple stages of the viral life cycle.

Since the common cold is caused by rhinovirus infection, pretreatment of airway epithelial cells with quercetin inhibited Akt phosphorylation, viral endocytosis and IL-8 responses[50]. The addition of quercetin after viral endocytosis (infection) reduced levels of negative and positive strand viral RNA, and rhinovirus capsid proteins. Since rhinovirus infection is associated with a shutoff of host protein synthesis due to the cleavage of eukaryotic initiation factor 4GI (eIF4GI,a protein involved in bringing mRNA to the ribosome for translation initiation) by the virus-specific proteinase 2Apro (cysteine protease containing structurally important zinc ion)[49], quercetin strongly abrogated rhinovirus-induced eIF4GI cleavage[50]. In turn, quercetin increased phosphorylation of eIF2α (subunit of eIF2 eukaryotic initiation factor required in the initiation of translation) resulting in the inhibition of viral RNA translation.

This example describes only one of quercetin's antimicrobial mechanisms of action and there are many more that contribute to its potency in fighting pathogenic infections.

Even though the quercetin cellular mechanisms of action presented represent only a small part of available research, it is clear that this molecule displays a wide spectrum of biological functions from scavenging free radicals to changing gene expression.

However, some problems with translation of *in vitro* results into *in vivo* benefits are related primarily to its low bioavailability[115, 121]. Enzymatically modified isoquercitrin enhances the absorption and bioavailability of quercetin due to the presence of glucose moiety. But there is another method called co-crystallization that improves the pharmacokinetic properties of quercetin as well as its therapeutic efficacy[154, 173]. Dozens of quercetin co-crystals have been made and tested in the laboratory. They are both natural (e.g., quercetin-caffeine) and synthetic (e.g., quercetin-metformin) compounds and they often work in synergy. This all indicates a dramatic widening of the health applications of quercetin, beyond considering it as only a nutritional supplement.

Contributed by: Waldemar Sumera, M. Sc.

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