

## **FLAVONOIDS AND OTHER POLYPHENOLS (Quercetin, Rutin, and Hesperidin)**

### POLYPHENOL ABSORPTION

- Polyphenols are abundant micronutrients in our diet, and evidence for their role in the prevention of degenerative diseases is emerging. Bioavailability differs greatly from one polyphenol to another, so that the most abundant polyphenols in our diet are not necessarily those leading to the highest concentrations of active metabolites in target tissues.
- Gallic acid and isoflavones are the most well-absorbed polyphenols, followed by catechins, flavanones, and quercetin glucosides, but with different kinetics. The least well-absorbed polyphenols are the proanthocyanidins, the galloylated T catechins, and the anthocyanins.
- Health-enhancing bacteria in the colon perform reactions that transform more complex plant phenols such as anthocyanins, procyanins, flavanones, flavonols, tannins, and isoflavones into simple phenolic metabolites. The colon is thus a rich source of potentially active phenolic acids that may impact both locally and systemically on gut health. Both the small and large intestine contain absorption sites for phenolic acids, but low post-prandial concentrations in plasma indicate minimal absorption early in the GI tract, and/or rapid hepatic metabolism and excretion. Therefore, any bioactivity that contributes to gut health occurs predominantly in the colon. Several phenolic acids affect the expression and activity of enzymes involved in the production of inflammatory mediators of pathways thought to be important in the development of gut disorders including colon cancer. ----- Supplementing with IMMUNO-SYMBIOTIC is the only way to assure bioavailability of flavonoids.
- Controlled human intervention studies with beverages such as red wine that are rich in polyphenolic compounds have yielded conflicting results. The biological effect of such beverages may be a balance between the pro-oxidant effects of alcohol and its metabolism and the antioxidant effects of polyphenolic constituents.
- There is a long-standing controversy over whether flavonoids are absorbed as the intact glycoside, or whether they have to be hydrolyzed to the free aglycon prior to absorption. Analyses of 12 dietary flavonoids in human urine showed that no flavonoid glycosides are excreted, and that the citrus flavanones and phloretin are excreted in higher amounts than the flavonols. In other words, the benefits of flavonoids do not derive from the flavonoids themselves, but from metabolites produced by the liver, and more

particularly by colonic bacteria (--- IMMUNO-SYMBIOTIC) acting upon those flavonoids.

### HESPERIDIN

- Improves capillary integrity (250 mg) = decreases excess capillary permeability and associated edema. (Leg Dermographics & Edema)
- The capillary fragility group of flavonoids (including particularly hesperidin, quercetin, and rutin) improves capillary integrity, thus benefitting a broad array of pathologies, including cerebral hemorrhage, gastrointestinal hemorrhage, retinal hemorrhage, diabetic hemorrhage, telangiectasia, bleeding gums, lung hemorrhages, varicose and spider veins, bruising, hemorrhoids, and aneurysm.
- The pathology Scurvy actually consists of 27 types of collagen (elastin) breakdown. These symptoms of scurvy are not benefitted by ascorbic acid, but only by the capillary fragility group of flavonoids. ----- Leaky Gut Syndrome is actually in many cases “scurvy of the intestine”.
- Flavonoids reduce lipid peroxidation, with rutin being more effective than hesperidin, which is more effective than quercetin; flavonoids are protective against auto-oxidation of rat cerebral membranes, with quercetin being more effective than rutin, which is more effective than hesperidin.
- Rutin and quercetin (flavonols) and hesperidin (flavanone) in intraperitoneal doses of 80 mg/kg inhibit both acute and chronic phases of inflammation. Rutin is the most active in the chronic phase of inflammation, but is only effective in the chronic process, principally in adjuvant arthritis. On neurogenic inflammation induced by xylene, only hesperidin (and hesperetin) is effective, and the flavanones are the most effective in subchronic inflammatory processes. The most important flavonoid in reducing acute inflammation and swelling induced by carrageenan is quercetin.

### QUERCETIN

- One of the major polyphenol constituents of red wine (along with catechin)
- Non-citrus
- 250 mg constitutes a therapeutic dose
- Molds (Aspergillus) = rutin inhibits fungal infection & mold toxin synthesis
- Histamine inhibitor (Red Dermographics)
- Controls excess release of Leukotrienes and Prostaglandins
- Quercetin inhibits LPS-induced PGE2 production in vitro. (IMMUNO-SYMBIOTIC)

- Improves Intestinal Barrier function
- Increases efficacy and decreases toxicity of chemotherapy
- Controls excess release of Mast Cells (Red Dermographics)
  
- Quercetin = anti-inflammatory and Mast Cell inhibitory flavonoid
  - Quercetin inhibits the action of phospholipase A2 and release of Arachidonic Acid in activated mast cells. (Prostaglandin Imbalance)
  - As an inhibitor of mast cell secretion, quercetin causes a decrease in the release of tryptase and the pro-inflammatory Th2 cytokine Interleukin-6, and the downregulation of histidine decarboxylase from mast cells. Quercetin could likely benefit neurological diseases mediated by mast cell degranulation.
  - Quercetin upregulates heme oxygenase activity (see bilirubin below), thus inhibiting mast cell degranulation and reducing allergic reactivity.
  - Quercetin blocks the IL-1 stimulation of IL-6 production (a pathway that is independent of IgE-induced mast cell degranulation).
  - Quercetin inhibits IgE-mediated pro-inflammatory mediator release from mast cells. Release of IL-6, IL-8, and TNF- $\alpha$  is inhibited by 82-93%; tryptase release is inhibited by 79-96%; histamine release is inhibited by 52-77%. --- There are benefits for both allergic and inflammatory diseases.
  - Antigen-induced intestinal longitudinal muscle contractions are significantly mediated via thromboxane A2. The effect of antigen on longitudinal smooth muscle contractions were reduced by the mast cell stabilizing agent quercetin (and by histamine 1 blockers). (But the smooth muscle contracture is more than 3x as sensitive to thromboxane A2 than to histamine.) Quercetin (and H1 receptor blockers) also reduced the intestinal longitudinal muscle contractions induced by muscarinic agonists. (If anti-carbachol, then both anti-muscarinic and anti-nicotinic.) (Anti-carbachol = anti-muscarinic and anti-nicotinic = anti-Parasympathetic)
  - Quercetin is related to disodium cromoglycate in inhibiting anaphylactic histamine release from intestinal mast cells. (It offers similar anti-histamine activity in basophils.) Quercetin is a more effective mast cell inhibitor in mucosal mast cells than in peripheral mast cells. (Acacetin and chrysin are more effective than quercetin in peripheral mast cells.)
  - Quercetin inhibits histamine release and also inhibits the associated elevation of intracellular calcium. It thus decreases TNF- $\alpha$ , IL-1 $\beta$ , IL-6, and IL-8.
  - Quercetin inhibits the induction and function of antigen-induced histamine release from cytotoxic T lymphocytes, and from mast cells, and from basophils from subjects with hay fever. The beneficial effects of quercetin are blocked by addition to the system of copper, and to a certain extent manganese and cobalt. (Anti-Anaerobic trace minerals at

the cellular level block quercetin's action --- therefore, quercetin is anti-Dysaerobic at the cellular level.)

- Maintains presynaptic acetylcholine retention at neuromuscular junctions of the GI tract
- Protects DNA from oxidation; quercetin = 78%, luteolin = 91%, myricetin = 90%, vitamin C = 12%, but additive with quercetin
- Inhibits protein kinase C (carcinogenic process); inhibits tyrosine kinase (tumor spread)
- Xanthine oxidase and xanthine dehydrogenase (uric acid production in the liver) inhibition (--- probably anti-Dysaerobic)
- Flavonoids reduce lipid peroxidation, with rutin being more effective than hesperidin, which is more effective than quercetin; flavonoids are protective against auto-oxidation of rat cerebral membranes, with quercetin being more effective than rutin, which is more effective than hesperidin.
- In mice, quercetin shows no protective effect against LDL oxidation or atherosclerotic lesion formation, while the glycoside quercetin 3-(6-malonylglucoside) is very effective.
- Quercetin attenuates the development of atherosclerosis by reducing the susceptibility of LDL to aggregation. It has no direct antioxidant effects on LDL, but reduces its tendency to oxidize by binding LDL particles into aggregates.
- Quercetin inhibits LPS-induced (--- IMMUNO-SYMBIOTIC) Nitric Oxide production in macrophages through suppression of Nitric Oxide Synthase expression.
- Quercetin (as well as apigenin and luteolin) inhibit platelet aggregation by binding to thromboxane A2 receptors. (Electrolyte Stress & Prostaglandin)
- Rutin and quercetin (flavonols) and hesperidin (flavanone) in intraperitoneal doses of 80 mg/kg inhibit both acute and chronic phases of inflammation. Rutin is the most active in the chronic phase of inflammation, but is only effective in the chronic process, principally in adjuvant arthritis. On neurogenic inflammation induced by xylene, only hesperidin (and hesperetin) is effective, and the flavanones are the most effective in subchronic inflammatory processes. The most important flavonoid in reducing acute inflammation and swelling induced by carrageenan is quercetin.

- Quercetin and rutin (7.5 mg/kg, per os) decrease both the immediate and late-phase increase in airway resistance in asthma. These flavonoids also significantly inhibit histamine (15 mg/kg) production as well as recruitment of neutrophils and eosinophils during the late-phase response. Quercetin and rutin are about half as effective as dexamethasone (3 mg/kg).
- Photosensitized hemolysis of human RBCs is suppressed by quercetin and rutin, accompanied by inhibition of lipid peroxidation. --- Indicating that flavonols can function as antioxidants in biological systems by terminating radical chain reactions and removing singlet molecular oxygen. This antioxidant function is a mechanism by which quercetin and rutin decrease excess permeability and fragility of capillaries. (Leg Dermographics & Edema)
- The capillary fragility group of flavonoids (including particularly hesperidin, quercetin, and rutin) improves capillary integrity, thus benefitting a broad array of pathologies, including cerebral hemorrhage, gastrointestinal hemorrhage, retinal hemorrhage, diabetic hemorrhage, telangiectasia, bleeding gums, lung hemorrhages, varicose and spider veins, bruising, hemorrhoids, and aneurysm.
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- Cardioprotective actions of two bioflavanoids, quercetin and rutin, in experimental myocardial infarction in both normal and type 1 diabetic rats. J Pharm Pharmacol, 2009. ----- “Revascularization therapy is the mainstay of treatment in the management of myocardial infarction in normal and diabetic patients. We attempted to evaluate the cardioprotective actions of quercetin and rutin in ischemia-reperfusion hyper-induced myocardial infarction in both normal and diabetic rats. Quercetin and rutin significantly limit the infarct size in both normal and diabetic animals in similar fashion. However, rutin offers complete cardio protection at a dose of 10 mg/kg in terms of limiting infarct size. Both flavonoids partially but significantly attenuate the lipid peroxidation. In addition, treatment shows moderate improvement in heart rate in both normal and diabetic rats.”
- Two week quercetin supplementation (1,000 mg daily) of trained cyclists after a 3 day period of heavy exertion resulted in increased granulocyte oxidative burst activity, and a significant decrease of C-reactive protein and Interleukin-6 and Interleukin-10.
- Supplementation with quercetin decreased upper respiratory tract infections in trained cyclists during a 2 week period after intensified exercise.

- Quercetin increases exercise tolerance in mice.
- Oral administration of quercetin leads to accumulation in brain tissue and attenuates the increased oxidative stress in the hippocampus and striatum of rats exposed to chronic forced swimming.
- Quercetin reverses acute stress-induced behavioral changes and reduces brain glutathione levels in mice.

## RUTIN

- Improves capillary integrity = decreases excess capillary permeability and associated edema (Leg Dermographics & Edema)
- Decreases platelet aggregation (Electrolyte Stress & Prostaglandin)
- Binds Iron = antioxidant --- prevents Fe<sup>+2</sup> from binding to H<sub>2</sub>O<sub>2</sub>
- Inhibits VEGF (angiogenesis)
- Anti-inflammatory
- Decreases cytotoxic effect of oxidized LDL
- Molds (Aspergillus) = rutin inhibits fungal infection & mold toxin synthesis
- 350 mg of rutin administered by intraperitoneal route results in significant drop in triglycerides. Rutin combined with nicotinic acid also lowers cholesterol better than nicotinic acid alone.
- Flavonoids reduce lipid peroxidation, with rutin being more effective than hesperidin, which is more effective than quercetin; flavonoids are protective against auto-oxidation of rat cerebral membranes, with quercetin being more effective than rutin, which is more effective than hesperidin.
- In rats with induced myocardial infarct, pre-treatment with rutin protected against increased heart weight, prevented increased heart concentrations of cholesterol, triglycerides, and free fatty acids, and a decrease of phospholipids. In these myocardial infarct rats, rutin also prevented the increase in serum cholesterol, triglycerides, phospholipids, LDL cholesterol, vLDL cholesterol, and the decrease in HDL cholesterol. Rutin had no effect on these parameters in normal control rats.
- Rutin and quercetin (flavonols) and hesperidin (flavanone) in intraperitoneal doses of 80 mg/kg inhibit both acute and chronic phases of inflammation. Rutin is the most active in the chronic phase of inflammation, but is only effective in the chronic process, principally in adjuvant arthritis. On neurogenic inflammation induced by xylene, only hesperidin (and hesperetin) are effective, and the flavanones are the most effective in subchronic inflammatory processes. The most important flavonoid in

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- Rutin has antiradical and antioxidant activity in both iron- and ascorbate-driven fenton systems, radiation, xanthine/xanthine oxidase systems, and, has DPPH radical scavenging activities.
- Superoxide anion scavenging activity is strongest with rutin, and second strongest with quercetin (and naringin), and only moderate with hesperidin. The superoxide anions are strong inhibitors of prostacyclin production, so, flavonoids facilitate anti-aggregatory PGI2 formation.
- Supplementation with rutosides was given to patients with chronic venous insufficiency (CVI) without diabetes (1500 mg/day) and patients with CVI plus diabetes (2 g/d). In the CVI patients without diabetes, there was a statistically significant decrease in capillary filtration rate, and an even greater decrease in capillary filtration rate in the diabetic patients taking a somewhat larger dose of rutosides. During the 5 year study, venous edema reduced substantially and deterioration of the distal venous system was prevented. There was also prevention of ulcerations. Rutoside supplementation after only 4-8 weeks caused an increase in subnormal PO<sub>2</sub> and a decrease in elevated PCO<sub>2</sub>, indicating microcirculatory improvement. There was a significant decrease in ankle swelling of 41% after 8 weeks. (Leg Dermographics & Edema)
- Intravenous arachidonic acid and serotonin increase vascular permeability (an indication of inflammation) (Leg Dermographics & Edema), and that increase is reduced by aspirin. It is also totally abolished by vitamin C and the flavonoid compound troxerutin (100 mg/kg), whereas vitamin E has only a partial effect (40-100% inhibition). The anti-inflammatory potential of flavonoids is highlighted here.
- Photosensitized hemolysis of human RBCs is suppressed by quercetin and rutin accompanied by inhibition of lipid peroxidation. --- Indicating that flavonols can function as antioxidants in biological systems by terminating radical chain reactions and removing singlet molecular oxygen. This antioxidant function is a mechanism by which quercetin and rutin decrease excess permeability and fragility of capillaries. (Leg Dermographics & Edema)

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- Flavonoids such as rutins decrease inflammatory edema. The benefit of decreasing excess vascular permeability is associated with inhibiting the leakage of albumen from the serum into the interstitium. (Leg Dermographics & Edema)
- Rutosides decrease vascular permeability associated with excess histamine, bradykinin, and fibrin degradation products. (Leg Dermographics & Edema)
- (From Harvard Magazine) Harvard researchers found that rutin has potent anti-clotting powers that could help prevent heart attack and stroke. “Researchers discovered rutin’s anti-thrombotic property when they screened a set of 5,000 compounds for their ability to block the action of vessel-clogging thrombin. Rutin was at the very top of the list. ....Indeed, if scientists had tried to design a clot-preventing molecule, they could scarcely have created one more perfect than rutin.”
- The Harvard Review states that “Even with the use of existing anti-clotting therapies, such as aspirin, clopidogrel (Plavix), and warfarin (Coumadin), each year there are approximately 400,000 recurrent episodes in the US among patients who previously experienced a stroke or a heart attack...” --- “...a safe and inexpensive (rutin) could reduce recurrent clots and help save thousands of lives.”
- (The Journal of Clinical Investigation) Rutin is identified as a novel strategy for preventing thrombosis, and thus as therapy for prevention and treatment of stroke and heart attack, as well as deep venous thrombosis (DVT) and pulmonary embolism.
- PDI (protein disulfide isomerase) (found in all cells involved in blood clotting) is a key component of the pathological formation of thromboembolism. Rutin is the most potent PDI inhibitor, and not only inhibits PDI action directly, but also prevents PDI from entering cells. Rutin retains its anti-thrombotic properties when it is metabolized following oral ingestion. Rutin inhibits both platelet accumulation and fibrin generation during thrombus



formation. Clots occur in both arteries and in veins. Clots in arteries are platelet-rich, while those in veins are fibrin-rich. Thus, rutin is a single agent that can treat and prevent both types of clots.

- While rutin inhibits PDI, and prevents platelet aggregation and thrombus formation, it has no direct effect on blood coagulation per se. A study published in Molecules in 2012 states, “Two flavonoids, rutin and hesperidin, were investigated in vitro for anti-coagulant activity through coagulation tests: Activated partial thromboplastin time (aPTT), prothrombin time (PT), and thrombin time (TT) --- with the results showing that these complexes had no effects on prothrombin time and thrombin time.” ----- So, flavonoid supplementation can be used on patients already taking aspirin, Plavix, or Coumadin.
- Rutin lowers elevated plasma lipids and elevated hepatic cholesterol.
- (Journal of Bioscience and Bioengineering) In vivo studies show that rutin exerts a significant protective effect against collagen and epinephrine - (or thrombin) induced acute thromboembolism in mice. These results suggest rutin as a potent anti-thrombotic agent for cardiovascular diseases. ----- [Note that rutin is beneficial for the capillary leakage associated with the poor vasomotor tone of a Parasympathetic Imbalance (as revealed on the leg dermographics and edema tests), but also protects against the thromboembolism formation that can precipitated by a Sympathetic Imbalance (or an Electrolyte Stress or Electrolyte Insufficiency Imbalance).]
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- (From Brain Research) The effect of treatment with rutin after induction of focal cortical ischemia was studied. When applied in the acute phase, rutin reduced neurodegeneration in brain lesion periphery. These results indicate that rutin has significant neuroprotective effect when administered after the occurrence of a focal cortical ischemia, suggesting that this flavonoid might be used to treat ischemic damage in the acute phase of stroke. (Previous

studies have shown the efficacy of rutin in pre-treatment models of stroke in stroke prevention.)

- (From the US Department of Agricultural Yearbook of Agriculture from way back in 1947) “In patients suffering from high blood pressure, there is often rupture of weak capillaries, with production of more or less severe hemorrhage. At these times, accidents occur in the retina and cause partial or even complete blindness. Several patients suffering from retinal hemorrhage have been treated with rutin. In 83% of cases, no further rupture of the capillaries occurred. --- Other patients having suffered a stroke were also treated with rutin. In three years, no patient receiving rutin has had a second stroke, although all were suffering from hypertension and in more or less danger of such an accident. --- Rutin restores these conditions to normal, but the affliction may return if rutin is discontinued. Persons who have a natural tendency to increased capillary fragility often relapse some weeks after discontinuing rutin supplementation.”

## PROANTHOCYANIDINS

- Grape pip extract 100 mg: standardized to 95% polyphenols, containing 83% oligomeric proanthocyanidins
- Grape pips = flavonoids + polyphenols + procyanidins

## PYCNOGENOL (proanthocyanidins from pine bark)

- Endothelial (stabilizes collagenous membranes)

## BETA CAROTENE

## ASTAXANTHIN

Polyphenolic compounds are commonly the active ingredient in herbal drugs. They are promoted as being “natural” because these polyphenols occur in small quantities in fruits, vegetables, and spices. In cell culture studies, these polyphenolic drugs are shown to have anti-oxidant, anti-inflammatory, and in some cases anti-cancer effects. Thus, their popularity in health food industry remedies.

However, when taken by humans as herbal drugs, these polyphenolic compounds can have the same opposite effects of those desired --- being pro-oxidant and pro-inflammatory.

These polyphenols (because of their phenol rings) are metabolized by peroxidase enzymes to form pro-oxidant phenoxyl radicals, which destroy (co-oxidize) glutathione and NADH, while enhancing reactive oxidative damage by reactive oxygen species formation. These polyphenols also oxidize RBC oxy-hemoglobin, and cause RBC hemolysis. Among the popular health food store remedies shown to produce these pro-oxidant and pro-inflammatory effects are the ever popular curcumin and resveratrol.

In contrast, polyphenolics with catechol (not phenol) rings enhance the anti-oxidant benefits of vitamin C, and do not oxidize glutathione, but rather increase glutathione conjugate formation. Among the beneficial polyphenols are quercetin and catechin.