Rutin

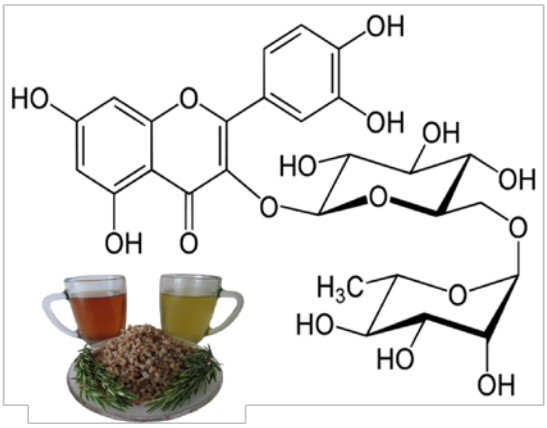


Fig.1. Structure of rutin (Quercetin-3-o-rutinoside)

Rutin, composed of quercetin and the disaccharide rutinose (rhamnose and glucose), is a flavonol glycoside widely distributed in plants (Fig.1).

Its common name derives from *Ruta graveolens* a plant that contains high amounts of rutin, however other names such as rutoside, quercetin-3-O-rutinoside or sophorin have also been used.

Rutin's biological role in plants relates mostly to its protection against UVB radiation as the positive correlation between exposure to UVB and the synthesis of rutin has been observed[53]. Interestingly, the leaves at the top of the plant contain more rutin than the lower leaves. It appears that factors such as geographic locations (high altitude) and even the position of leaves on the plant can determine the rutin content and thus the therapeutic efficacy of a plant.

Traditional and folk medicine have used rutin-rich plants for centuries in the form of beverages or foods. Today, due to its versatile properties, rutin has been found as a constituent in over 130 registered medicinal preparations[20]. It exhibits numerous significant benefits including anti-oxidant, anti-inflammatory, cardiovascular and neuroprotective effects, and anti-diabetic and anticancer activities[7, 81].

Rutin is found in many foods like tartary buckwheat seeds, asparagus, red pepper, apples, cherries, aronia berries and citrus fruits, among others and its abundance is characteristic for the inflorescence and leaves of many herbs such as rue, rosemary, dandelion or sage, and black and green tea are rich sources of rutin (Fig.2.)[5, 53, 65, 96].

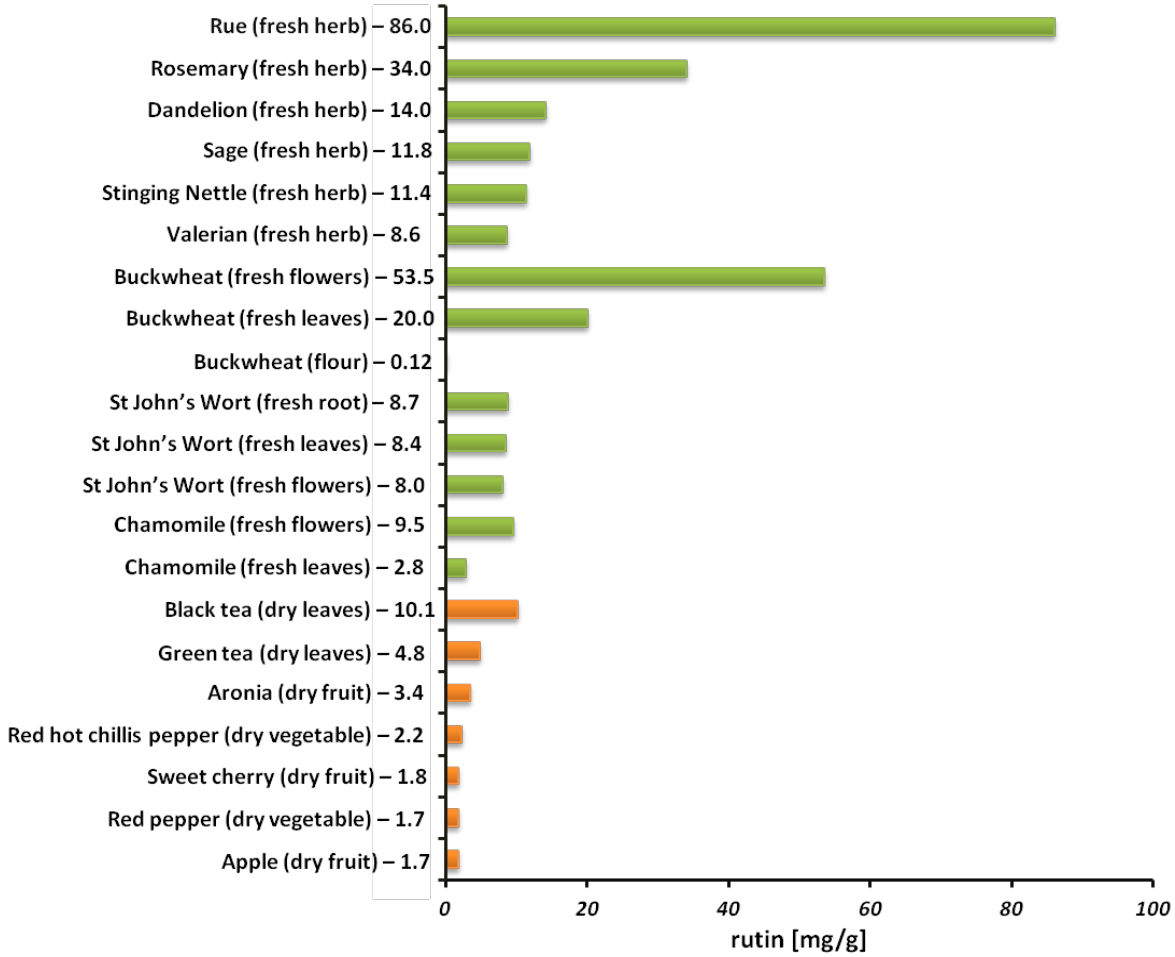


Fig.2. Rutin content in plant products (herb=flowers+leaves+stems) [5,65,96]

Absorption and assimilation: According to human studies, rutin is poorly absorbed in the small intestine, achieving its plasma metabolites peak nine hours after ingestion[39, 76]. It is believed that the delay is caused by the presence of the sugar moiety (rutinose) that must first be hydrolyzed by colonic microflora. Then liberated quercetin can be absorbed from the colon or be further degraded into phenolic compounds by gut microorganisms[76].

Once absorbed, quercetin undergoes glucuronidation, methylation and sulfation processes in enterocytes and hepatocytes before entering the bloodstream to be transported to other tissues[10, 29, 34, 35]. In the blood quercetin conjugates are carried and distributed by albumins (main blood proteins) to virtually every tissue, including brain tissue due to the ability to cross the blood-brain barrier. Animal studies have shown quercetin presence in the colon, liver,

kidneys, muscles, lungs and brain[25]. Quercetin and its metabolites are eliminated mostly by the kidneys and excreted with urine[75].

The relative bioavailability of rutin is about 20% that of quercetin glucosides (quercetin with glucose moiety)[34], while its elimination half-life (time required to eliminate 50% of the total amount of the substance) is almost identical for all glycosides ranging from 11 to 28 hours[34, 63], with the possibilities of their accumulation in plasma with repetitive intakes. However, quercetin conjugates are not the only beneficial metabolites of rutin. The activity of colonic microorganisms yields the majority of rutin metabolites, mainly in the form of phenylacetic acids that exert inter alia anti-oxidative activity similar to that of vitamin E[76]. Some, such as 3,4-dihydroxytoluene (DHT), have been verified as strong anti-inflammatory agents[99]. Moreover, unlike rutin they are easily absorbed and their total urinary excretion could be as much as 50% of the ingested dose[93].

In summary, the consumption of fruits, vegetables and herbs rich in rutin provides a whole spectrum of its active metabolites with wide health benefits.

Health Benefits

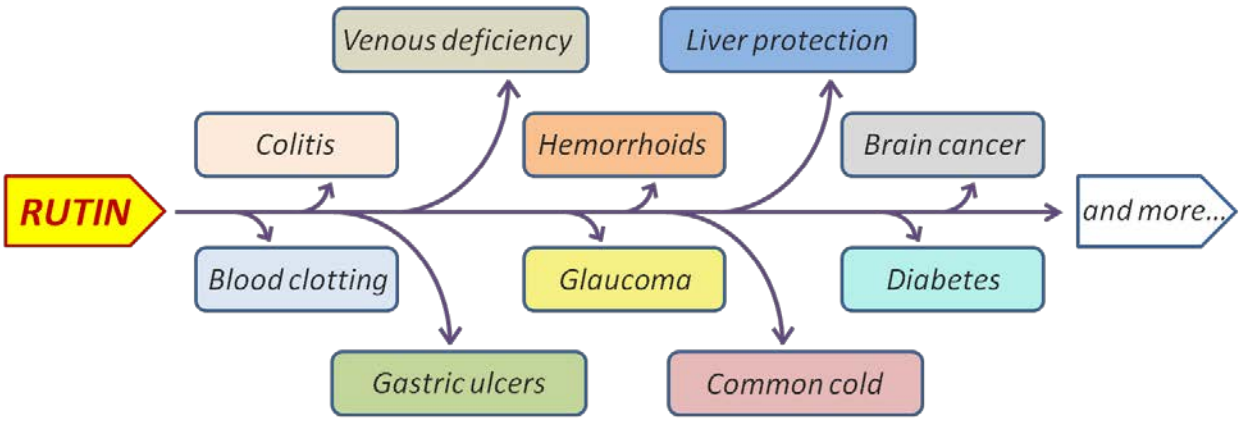


Fig.3. Pleiotropic effects of rutin

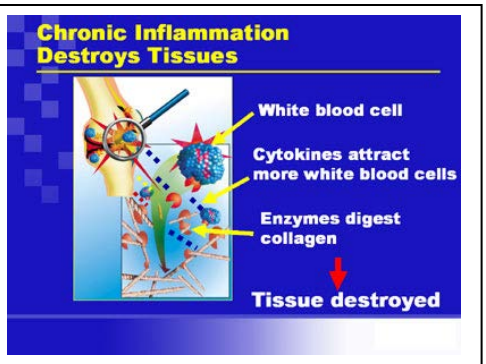
Antioxidant effects: Rutin is a potent antioxidant, decreasing oxidative stress (see description box) and thus preserving the structural and functional integrity of cells. Both *in vitro* and *in vivo* studies have found and elucidated at least three mechanisms behind it. First, due to its chemical structure rutin can directly scavenge reactive oxygen species (ROS) and stop the progression of the deteriorating chain reaction[38]. Second, it can up-regulate cellular oxidative defense systems by increasing expression and activity of many antioxidant enzymes such as superoxide dismutase (SOD) or catalase; and it increases the production of glutathione (GSH) the body's major antioxidant[6, 48, 62]. In addition, rutin has been found to be an inhibitor of an enzyme called xanthine oxidase which is involved in generating ROS[52].

Oxidative stress

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

Therefore, it is not surprising that there is a growing field of evidence demonstrating rutin's therapeutic potential in many health conditions in which oxidative stress is an underlying cause, e.g., diabetes, and cardiovascular or neurodegenerative diseases[6, 61, 78, 106]. Moreover, rutin can protect the body and its organs (heart, kidneys and liver) subjected to oxidative damage during radiation and chemotherapy and also ameliorate many side effects associated with these medical treatments[48, 72, 80, 105].

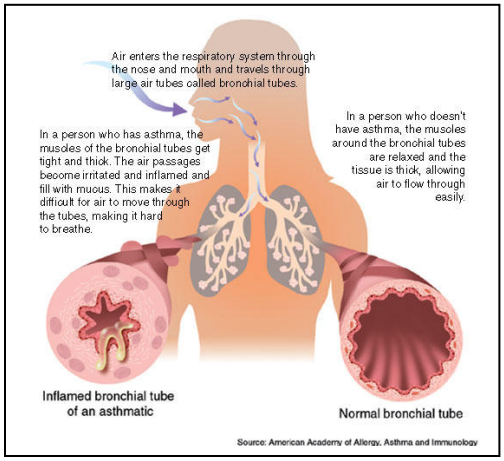
Anti-inflammatory effects: Rutin and its derivatives exert pleiotropic anti-inflammatory effects[18, 19, 27, 32, 99, 111]. Various *in vivo* studies demonstrated that rutin can result in significant reduction of pro-inflammatory markers including enzymes such as cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) as well as their upstream inducer called nuclear factor kappa B (NFkB).



COX-2 is involved in the production of inflammatory mediators such as prostaglandins and is therefore a primary target for classic non-steroid anti-inflammatory drugs (NSAIDs). iNOS, on the other hand, is an enzyme that produces nitric oxide (NO) which plays an important role in the defense against various pathogens. However, the overproduction of NO can be harmful and may lead to undesirable conditions such as life threatening septic shock or autoimmune disorders[111].

Multiple experiments including topical administration of rutin on UVB radiated skin[18], as well as oral[32], subcutaneous, or intra-peritoneal injections[27, 111] confirm its anti-inflammatory efficacy. In an animal model of chronic ulcerative colitis, rutin treatment significantly decreased the production of the COX-2 and iNOS by 90% and 52%, respectively[32]. Moreover, both *in vitro* and *in vivo* studies demonstrated its potent inhibition of the protein called high mobility group box 1 (HMGB1) release [112]. HMGB1 acts as a late mediator of advanced inflammatory conditions including sepsis, arthritis, ischemia, colitis, diabetes and cancer[114]. All of these findings indicate that rutin may mitigate inflammatory conditions and should be considered as a complementary or alternative adjunct treatment.

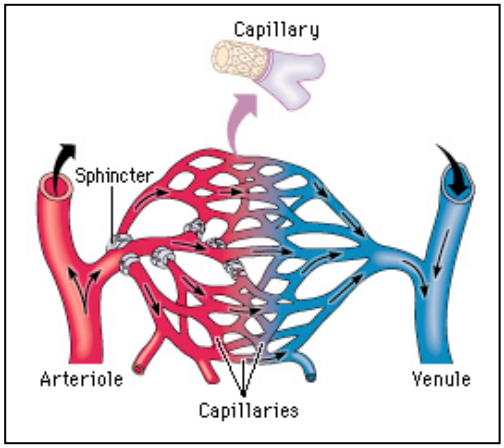
Allergy: Many researchers have proven Rutin to be a safe and effective remedy for allergy relief, and thus it is often incorporated in anti-allergy preparations[16, 46, 51, 67]. Although allergic reactions are complex with many factors involved, histamine is believed to play a critical role in the process by increasing the permeability of capillaries with the subsequent consequences that exacerbate the symptoms. Rutin can inhibit the production and release of histamine from immune cells known as mast cells and basophiles and calm the inflammatory response[46, 67].



Moreover, in an experimental model of asthma, rutin not only blocked the histamine release but also reduced the number of leucocytes in lung tissue and relaxed smooth muscle cells in airway passages[46]. In recent studies on allergic rhinitis (hay fever), it was discovered that rutin notably decreased the level of another permeability promoting factor called vascular endothelial growth factor (VEGF)[51]. This effect was accompanied by reduced levels of specific inflammatory and allergy promoting cytokines and chemokines.

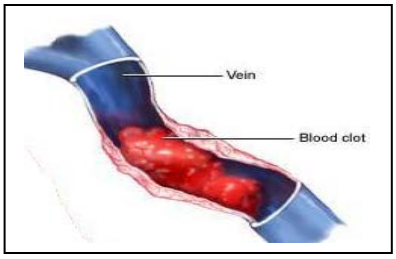
Finally, topical application of rutin to counteract skin allergy revealed additional benefits of this flavonoid[16, 67]. Application of rutin in atopic dermatitis (AD) and allergic contact dermatitis (ACD) resulted in attenuation of the allergic reaction through inhibition of mast cell infiltration to the affected site, and reduction of histamine level as well as other inflammatory mediators.

Vascular benefits: Generally, rutin has been known for its benefits in strengthening capillaries and blood vessels. This makes rutin highly beneficial for the whole body and especially in any condition associated with capillary weakness or venous deficiency. Therefore, rutin has been used in treating bruises, spider veins, and varicose veins along with amelioration of the concomitant symptoms such as edema (swelling)[13, 42]. Rutin was also found to bring relief in dealing with hemorrhoids (swollen veins in the anus and rectum)[100], and when administrated to patients after a hemorrhoidectomy (hemorrhoid surgery) it has been claimed to have superior effects in improving hemorrhoidal and post-surgical symptoms[8].



Cardiovascular health: Since oxidative stress, inflammation and weakened vessels are strongly related to heart diseases, many research studies have demonstrated multifactorial activity of

rutin that positively affects different aspects of cardiovascular health[90]. The list starts from the inhibition of LDL oxidation and further progression of atherosclerosis[58, 69]. In addition, rutin has been found to stimulate nitric oxide (NO) production in endothelial cells (cells of the inner blood vessel wall) resulting in vasodilation (widening of blood vessels), which is crucial for healthy blood flow and the resulting blood pressure lowering effect[56, 104]. Additionally, rutin exerts antihypertensive effect through inhibition of angiotensin-converting enzyme (ACE), which plays a key role in the regulation of arterial blood pressure, and is a main target for medications like captopril and imidapril[37].



Furthermore, after high-throughput screening of over 5000 compounds, rutin has been found to have the unique ability to inhibit blood clot formation[23, 44]. It has been noticed that rutin inhibits both platelet accumulation and fibrin generation during thrombus formation. This is important since clots occur in both arteries and veins; however, arterial clots are platelet-rich, while those in the veins are fibrin-rich[84]. Hence, rutin as a single agent can prevent and treat both types of clots which is essential considering the fact that in the US alone every year there are approximately 400 000 recurrent episodes of stroke or heart attack among patients who are already on anti-clotting therapies (e.g., aspirin, warfarin). Therefore, owing to all aforementioned benefits, rutin should be considered as a natural, safe and effective solution in many cardiovascular problems.

Neuroprotection: There have been numerous studies showing the benefits of rutin in supporting healthy brain and nervous tissue function. This is partially related to the fact that most of the neuropathology has been associated with oxidative stress and brain inflammation, followed by neurodegeneration and neuronal cell death.

One example is epilepsy, which is a chronic disorder characterized by recurrent, unprovoked seizures[95]. In an animal model of seizures, rutin administration (intracerebroventricular injection) showed a dose-dependent reduction in number and severity of seizure onsets[70].

Also in chronic cerebral hypoperfusion (reduction in cerebral blood flow), which is a causative factor for the development of cognitive decline and dementia in the elderly, there was a

marked improvement in cognitive function along with alleviation of oxidative, inflammatory and neuronal damage in rats supplemented with rutin[85].

Memory loss is also characteristic for patients suffering from Alzheimer's disease. It is believed that neurodegenerative progression is caused by extracellular amyloid β (Aβ) plaque formation and the soluble Aβ oligomers are thought to be the most neurotoxic form of all Aβ aggregates[109]. In test tube experiments, rutin has been shown to decrease Aβ aggregation and cytotoxicity along with attenuation of oxidative stress and inflammatory response. Moreover, oral rutin supplementation in animals resulted in a significant reduction in memory deficit as well as increased activation of antioxidant defense mechanisms and inhibition of brain inflammation[17, 109].

Parkinson's disease (PD) is another neurodegenerative condition that can be affected by rutin. Sympthoms of PD are caused by death of dopaminergic (dopamine producing) neurons in substanctia nigra (a region of the midbrain) that progressively impairs motoric ability. In both *in vitro* and animal studies, rutin pretreatment showed a significant protection against neurotoxic effects of oxidopamine (a substance used to destroy dopaminergic neurons)[50,60]. Rutin significantly decreased the level of reactive oxygen species[78] and promoted survival mechanisms in neurons through down-regulation of the apoptotic genes (promoting cell death) and up-regulation of the anti-apoptotic genes[60, 78]. It was also found that rutin up-regulated the tyrosine hydroxylase (TH) gene, which is important in dopamine biosynthesis[60]. All of these findings indicate the need for further research and ignite hope for patients dealing with neurodegenerative conditions.

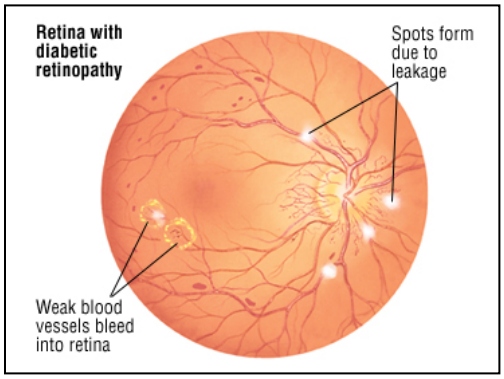
Cancer: Rutin was found to trigger a range of various effects in cancer from undesirable[28], to weak[26], to very encouraging[79]. The test tube experiments revealed and verified several cellular pathways and mechanisms by which rutin can trigger death of cancer cells[80]. Its efficacy against leukemia[45, 57, 86] and colon[3, 108] cancer has been demonstrated in both *in vitro* and *in vivo* studies. Interestingly, after simple enzymatic modification, i.e., deglycosilation of rutin to quercertin-3-glucoside (Q3G), the obtained derivative (Q3G) displayed more potent than rutin

and quercetin anti-proliferative effects against many human tumor cell lines including brain, ovary, breast, prostate, kidney, lung and colon[24, 113].

Another recent finding may be especially important for individuals carrying a mutant allele of the BRCA2 gene[59]. The presence of this mutation has been linked to higher risk of breast and ovary cancer. Interestingly, researchers discovered that quercetin and rutin are able to reduce this risk and provide a significant protection. This should be taken into account as part of the prevention approach as well as clinical treatment in patients with this mutation.

The most interesting, but still neglected, results came from the human study with a homeopathic medicine Ruta 6, isolated from *Ruta graveolens* in a combination with calcium phosphate - $Ca_3(PO_4)_2$[79]. This unique combination resulted in a complete regression of tumors in six of the seven glioma (brain tumor) patients. These results provide strong support for further investigations since glioma is a highly aggressive brain tumor with a very poor prognosis.

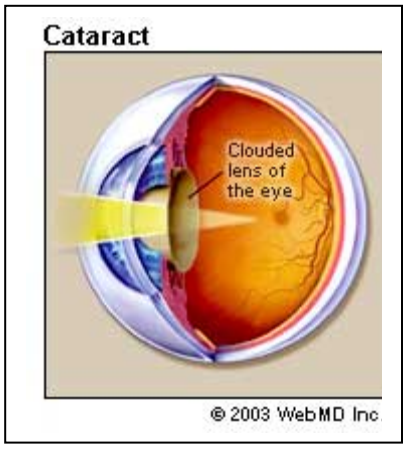
Diabetes: This chronic metabolic condition results in multiple systemic complications affecting cardiovascular and neuronal systems, among others. In numerous studies rutin exerted protective effects and ameliorated many diabetic-related pathologically changed parameters[6, 21, 58, 74, 106]. Animal studies demonstrated its beneficial effects on diabetic cardiomyopathy (DCM). DCM is a type of coronary heart disease that develops in diabetic individuals and is characterized by structural and functional changes in heart tissue[106]. These changes include elevation of inflammatory and oxidative stress markers, abnormal metabolic profile, aberrant myocardial enzymes, and enhanced apoptotic cell death. Interestingly, rutin has been found to ameliorate these changes, improve myocardial dysfunction and protect the heart tissue[106].



Another aspect of rutin application in diabetes relates to retinopathy[21, 74]. Diabetic retinopathy is a neurodegenerative disease of the eye. It is caused by the microvascular retinal changes that result in blood-

retinal barrier damage and increased permeability of the retinal blood vessels that eventually can lead to blindness. Notably, rutin supplementation demonstrated stimulation of beneficial pro-survival cell factors such as nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF) and glutathione (GSH), and the reduction of undesirable ones like vascular endothelial growth factor (VEGF) or thiobarbituric acid-reactive substances (TBARS)[21, 74]. In ddition, human studies have demonstrated a definite improvement in vascular permeability and overall opthalmological (eye) examination in 25% of the cases[9]. All of the anti-diabetic properties of rutin have been attributed in part to its ability to inhibit the enzyme called aldose reductase (ALR2)[87]. This enzyme can convert glucose which remains unused in the cellular bio-energy cycle, into sorbitol (sugar alcohol). Subsequently sorbitol is metabolized to fructose by another enzyme called sorbitol dehydrogenase. If sorbitol accumulates in the cell (it cannot cross the cell membrane) it causes its osmotic swelling, changes cell membrane permeability and oxidative stress. Therefore, inhibition of ALR2 (and sorbitol production) may prevent these undesirable changes and their subsequent complications such as the aforementioned cardiovascular and eye problems as well as nephropathy, and neuropathy[87, 102]. Since rutin has been found to be a very potent and, more importantly, specific inhibitor of ALR2, it holds promise as an effective agent in preventing and treating diabetic complications.

Eye health: Considering the general aspects of eye health (aside from diabetes), rutin has been shown to be valuable in prevention and treatment of such eye diseases as macular degeneration, cataracts, and glaucoma[43, 68, 92, 107]. With its ability to scavenge free radicals and up-regulate cellular antioxidant systems, rutin can protect the eye lens from premature protein degradation, opacification and eventually vision impairment. In addition, in combination with forskolin another natural compound, rutin demonstrated up to 15% reduction in intraocular pressure in glaucoma patients. Therefore, many doctors often recommend rutin for enhancing eye health.



Gastric ulcers: According to another research study rutin demonstrates very promising anti-ulcer effects[40]. Animal studies have shown that formation of gastric ulcers induced by various physical and chemical agents can be significantly inhibited by rutin. The intestinal damage by these agents resembled that caused by NSAIDs (aspirin), alcohol, stress and other factors[40]. These results showed a dose-related anti-ulcer protection ranging from 22% to 78% depending on the gastric ulcer model (induction factor).

Human Studies

Table 1 presents a short description of clinical studies with rutin in patients with various health conditions. For clarity, in most clinical studies rutin was used in the form of a mixture of semi-synthetic derivatives of rutin called hydroxyethylrutosides (HRs), obtained by substituting rutin hydroxyl groups with O-β-hydroxyethyl groups. Standardized mixtures of HRs consist of mono-HRs, di-HRs, tri-HRs, and tetra-HRs, which differ in the number of their hydroxyethyl substituents (Fig.4). These HRs mixtures exist under different brand names such as Venoruton, Paroven, and others.

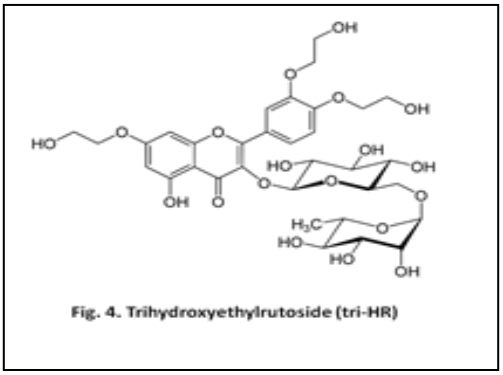


Fig. 4. Trihydroxyethylrutoside (tri-HR)

Abbreviations used in Table 1.

CVI-chronic venous insufficiency; HR-hydroxyethylrutosides (Oxerutins, troxerutin, Venoruton, Paroven); IOP-intraocular pressure; LRR-light reflection rheography; PFRs-plasma free radicals; RAS-rate of ankle swelling; RF-resting flux; RTOG-radiation therapy oncology group; VAR-veno-arteriolar response.

Table 1. Results from human studies with rutin supplementation.

OBJECTIVE	SUBJECTS	FORM AND DOSE OF	PRIMARY RESULTS AND

		RUTIN	CONCLUSIONS
[12] To demonstrate the rapidity of the clinical action of HR in patients with CVI.	Group 1 - moderate CVI and microangiopathy (12 patients); Group 2 - severe CVI and microangiopathy (10 patients).	Group 1 - 1 g of HR per day for 8 weeks; Group 2 - 2 g of HR per day for 8 weeks.	In both groups there was a progressive decrease in laser Doppler RF and RAS. The effect in Group 2 was more rapid. Conclusion: venous microangiopathy and edema were improved by HR treatment within a few days.
[14] To determine whether HR was effective in improving levels of PFRs in patients with CVI and venous microangiopathy.	40 patients with CVI and venous microangiopathy.	Placebo (20 patients) or 1 g of HR twice daily for 4 weeks (20 patients).	No changes in placebo group. Significant decrease of PFRs in treatment group.
[36] To study the efficacy of coumarin/troxerutin for the protection of salivary glands and mucosa during irradiation.	48 patients who had radiotherapy to the head and neck. 23 patients (11 experimental, 12 placebo) completed the study.	Placebo or coumarin/troxerutin.	The RTOG score showed significantly fewer acute side effects of radiation in the coumarin/troxerutin group.
[41] To demonstrate whether HR is effective in improving the microcirculation in subjects with diabetic microangiopathy and neuropathy.	Patients with severe diabetic microangiopathy, neuropathy and edema; patients with microangiopathy, without neuropathy and 20 healthy subjects.	Placebo or 1 g of HR twice daily for 6 months.	Both groups of patients on active treatment showed a significant decrease in RF, RAS and edema, and an increase in VAR. In patients without neuropathy, the variations in RF, VAR, and RAS were larger. The variations in healthy subjects were limited and not significant.
[82] To confirm the efficacy of HR by evaluation of venous parietal tone and microvascular perfusion.	60 patients with CVI.	Placebo (20 patients) or HR (40 patients) for 4 weeks. According to the grade of CVI, patients received 2 g of HR daily in the first 2 weeks and 1 g of HR in the following 2 weeks (grade I); and 3 g of HR in the first 2 weeks and 2 g of HR in the following 2 weeks (grade II).	Changes in venous capacity, LRR, and temperature were significant and favored the HR group. Conclusion: HR is effective in controlling chronic venous hypertension without side effects and with good tolerability.
[100] To assess the clinical efficacy, compliance and safety of Ginko biloba-Troxerutin-Heptaminol Hce in treatment of acute hemorrhoidal attacks.	22 patients, most of them (77%) had grade 1 and 2 hemorrhoids with an average duration of attacks of 3 days.	Ginko biloba-Troxerutin - Heptaminol Hce.	Bleeding, pain, tenesmus and discharge were significantly improved.
[103] To assess the effect of HR on the symptoms of the common cold.	94 patients with common cold symptoms.	Control group (45 patients) received 10 mg of zinc gluconate; active	Symptom score on day 1 was reduced by 11% compared to baseline in

		group (49 patients) received 50 mg of HR and 25 mg of zinc gluconate.	active group and by 1% in the control group. Rhinorrhea (runny nose) score was significantly lower in the active group.
[107] To evaluate the effects of a food supplement containing rutin and forskolin on the IOP.	97 patients with primary open angle glaucoma (POAG).	52 patients in treatment group received 2 tablets per day of a food supplement containing rutin and forskolin in addition to their usual topical drug treatment. Control group, 45 patients continued only with their normal topical therapy.	All patients in treatment group showed a further 10% to 15% decrease of their IOP. IOP values in the control group remained unchanged.
[13] To evaluate the effects of HR on the prevention and control of flight microangiopathy and edema in subjects with varicose veins and moderate CVI flying for more than 11 hours.	38 subjects (20 in treatment group and 18 in control group) with varicose veins and moderate CVI had 11 to 13 hour long flights.	Treatment group received 1 g of HR per day starting 2 days before the flight and 1 g of HR for every 12 hours on day of travel.	The higher level of RF and VAR and the reduction in edema was observed in treatment group. Conclusion: HR is useful for reducing the level of microangiopathy and increased capillary filtration and in controlling edema in patients with venous disease in long flights.
[33] To evaluate the effect of HR on retinal vein occlusion.	27 patients with central retinal vein occlusion and 26 with branch retinal vein occlusion.	Placebo or HR.	HR-treated group showed significant improvement in visual acuity, macular threshold, retinal circulation times, and macular edema. They also had diminished progression of ischemia and decreased red blood cell aggregability.

Synergy

Reactions in the body are sequenced and complex. To achieve an effective final result there are numbers of various compounds (e.g., substrates, cofactors) and factors (e.g., temperature, pH, compartmentalization) involved. Often the same result may also be accomplished through

alternative pathways. Therefore, both optimal conditions and the availability of all required compounds at the same time (to avoid a missing link) is needed.

Substances that work in synergy can be involved in the same biological pathway or participate in alternative pathways that lead to the same biochemical response. They can support some aspect of the biological process, such as increasing absorption or bioavailability of molecules involved (helping them to get to the reaction place at the required amount and form). Thus, synergy allows for achieving final biological effect without a need for high doses of individual components.

Cellular medicine has applied this principle of biological synergy in searching for most effective, non-toxic ways to enhance and regulate various biological pathways in the body involved in optimum health.

Rutin when combined with specific natural compounds or drugs can exhibit synergistic (Table 2) or additive effects (Table 3). It can also protect cells and organs in the body against the toxic effects of substances, i.e., arsenic, as well as against side effects of medications including antibiotics and chemotherapeutics (Table 4).

Table 2.

Synergistic effects of rutin with select natural compounds and antibiotics.	
Compound(s)/Drug(s)	Effects
[49] ascorbyl palmitate and alpha-tocopheryl succinate in topical preparation	↑skin protection, ↓hydroxyl radicals, ↓superoxide radicals, ↓lipid peroxidation
[66] ascorbic acid	↓LDL oxidation
[66] gamma-terpinene	↓LDL oxidation
[73] ascorbic acid and alpha-tocopherol	↓LDL oxidation
[22] vitamin C and vitamin E	↓lipoperoxidation (membrane phospholipids)
[2] quercetin and morin plus one of the following antibiotics: amoxicillin, ampicillin, cephradine, ceftriaxone, imipenem, methicillin	↓methicillin resistant *Staphylococcus aureus* (MRSA)

Table 3.

Beneficial and additive effects of rutin with select natural compounds or drugs.	
Compound(s)/Drug(s)	Effects
[77] N-acetylocysteine	↑lung protection in patients with adult respiratory distress syndrome (ARDS)
[97] carbazochrome	↓hemorrhoids symptoms
[55,88] vitamin C	↓progressive pigmented purpura (PPP), complete clearance of the skin lesions
[2] morin plus one of the following antibiotics: amoxicillin, cephradine, ceftriaxone, imipenem, methicillin	↓methicillin resistant *Staphylococcus aureus* (MRSA)
[101] quercetin	↓elevated-glucose concentration, ↑insulin production
[30] quercetin and alpha-tocopherol	↑accumulation of quercetin in the brain

Table 4.

Protective effects of rutin against drugs toxicity.	
Compound(s)/Drug(s)	Effects
[72] cyclophosphamide	↓hepatotoxicity, ↓oxidative stress, ↓inflammation
[94] oxaliplatin	↓hepatotoxicity, ↓neurotoxicity
[48] gentamicin	↓nephrotoxicity, ↓oxidative stress, ↓inflammation, ↓apoptosis, ↓autophagy
[105] sodium fluoride (NaF)	↓cardiotoxicity, ↓blood toxicity, ↓dyslipidemia
[91] arsenic	↓neurotoxicity

Safety

Multiple human clinical trials with rutin (in the form of HRs) have shown that it is well tolerated and safe[98].

Rutin doses in clinical practice vary depending on the treated condition and route of administration (see Human Studies section). Common oral doses range from 500 mg to 2000 mg per day and can be safely continued for a period of 6 months[41]. The longest known human study that evaluated the tolerability and safety of HRs with daily administration of 1500 mg or 2000 mg lasted five years and the authors stated that "tolerability and compliance were very

good"[98]. An earlier study using rutin in venous insufficiency in pregnant women, and in the context of premenstrual syndrome (PMS) reported daily intake of 4000 mg for four months[64]. However, today the safety of rutin supplementation during pregnancy - especially in the first trimester - is questionable and some suggest its teratogenic effects[83]. Therefore, pregnant women should consult a doctor before introducing rutin.

Rutin exerts anti-thrombotic activity and in the case of its concomitant administration with warfarin (Coumadin) it has been found to reduce the anti-coagulant effect of this medication, thus caution is advised [15]. Other indicated possible side effects include headache, dizziness, diarrhea, fatigue, upset stomach, or hair loss and allergic reaction[23].

There is a wide spectrum of rutin containing supplements available that differ in form, purity and quality, such as rutin powders and hydroxyethylrutosides (beta rutosides), mixtures with different bioflavonoids and vitamins, or the whole plant extracts. A recent study involving the Graviola plant showed that synergistic interactions among flavonoids significantly improved their therapeutic efficacy (against prostate cancer) which emphasizes the importance of natural synergy of micronutrients [110]. Vitamins, especially vitamins C and E, taken with rutin enhance rutin's effects by providing additional health benefits[22, 49, 55, 73, 88].

Cellular Mechanisms Involved in Biological Effects of Rutin

Protection against oxidative damage: According to *in* vitro studies[4, 89], glycosylation of flavonoids reduces their antioxidant activity compared with their corresponding aglycones. However, an *in vivo* study in which CCl_4 was administrated to mice to induce liver damage showed that rutin is more effective in amelioration of protein nitrosylation than quercetin, and that the absorption and its metabolic effects are key modulators of *in vivo* activity[27]. The hepatic lesions and necrosis induced by CCl_4 were significantly reduced in mice receiving rutin intraperitoneally. The attenuation of hepatic necrosis was related to the reduction of

nitrosative stress since increased nitric oxide synthesis and superoxide generation can result in the formation of peroxynitrite and nitration of protein tyrosine residues and thus lead to development of hepatic necrosis.

Rutin suppressed the expression of both iNOS and 3-NT (3-nitrotyrosine) more effectively than quercetin. Furthermore, rutin, more strongly than quercetin, stimulated the expression of heme oxygenase-1 (HO-1) which plays a critical role in cell protection against acute and chronic liver injury. This was associated with increased level of its upstream transcription factor Nrf2 and corresponded with the model of liver ischemia-reperfusion injury, suggesting a cell type-dependent activation of this enzyme[1]. Also, treatment with rutin notably suppressed the overexpression of TGF-β1 suggesting the reduction of the fibrinogenic potential in the liver. Finally, through inhibition of transcription factor NFkB activity, rutin decreased the level of inflammatory markers such as TNF-α, COX-2 and iNOS.

Anti-inflammatory effects: Although rutin and its main metabolite, quercetin-3-glucuronide, are well known for their anti-inflammatory effects, little is known about anti-inflammatory activity of phenolic acids that derive from the microbial degradation of rutin in the gut. Recent study suggests that low-molecular-weight phenolic compounds such as 3,4-dihydroxytoluene (DHT), 3,4-dihydroxyphenylacetic acid (DHPAA), hydroxyphenylacetic acid (HPAA) and homovanillic acid (HVA), exert anti-inflammatory effects[99]. Among them DHT was the most potent and inhibited LPS-induced production of NO, iNOS, COX-2 and TNF-α without cytotoxicity (10 μM). The mechanism behind its anti-inflammatory activity revealed that DHT significantly reduced the IkB phosphorylation that preserved inactive complex of IkB-NFkB in the cytoplasm, and prevented NFkB from translocation to the nucleus where it acts as transcription factor for many proinflammatory genes.

Anti-thrombotic effects: One of the unique features of rutin is its potent anti-thrombotic activity exerted by selective inhibition of the protein disulfide isomerase (PDI). PDI is a member of the oxidoreductase family known as endoplasmic reticulum-resident enzymes. These enzymes catalyze post-translational disulfide bond formation and exchange and also act as chaperones during protein folding[44]. PDI has been identified on the cell surface of hepatocytes,

lymphocytes, endothelial cells and platelets. Although the mechanism by which PDI facilitates platelet activation and fibrin formation has yet to be elucidated, it has been shown that PDI is secreted from endothelial cells and platelets during thrombus formation.

Rutin and its metabolite, quercetin-3-glucuronide, have been found to inhibit PDI in a dose-dependent manner with IC_{50} of 6.1 µM and 5.9 µM, respectively[44]. This inhibition is apparently related to the presence of 3-o-glycosidic linkage because isoquercetin, hyperoside, and datiscin, all of which have a 3-o-glycosidic linkage, also inhibited PDI; whereas metabolites that lack a 3-o-glycoside such as isorhamnetin, tamarixetin, quercetin, and diosmetin did not. Inhibition of PDI abrogates both platelet accumulation and fibrin generation at the earliest stages of thrombus formation.

Since PDI is critical for cellular function, the inhibition of PDI would lead to cell death. However, experiments conducted on cultured endothelial cells exposed to rutin concentration as high as 100 µM for at least 72 hours showed no toxicity. This is because the same glycosidic linkage that is required for inhibition of PDI activity impairs cell permeability. In conclusion, flavonols with 3-o-glycosidic linkage preferentially target extracellular PDI and thus can protect from blood clot formation.

Diabetes: As an inhibitor of aldose reductase (ALR2), rutin demonstrates high specificity which is important since many aldose reductase inhibitors (ARIs) not only inhibit ALR2 but other aldo-keto reductases, particularly aldehyde reductase (ALR1) which plays a role in detoxification of reactive aldehydes[87]. Compared to quercetin, rutin exerts much higher specificity and appears to be more potent with IC_{50} value of 13 µM versus 28 µM for quercetin.

Suggested mechanism of inhibition is that rutin binds only to the enzyme substrate complex and does not compete with the substrate and inhibit ALR2 in an uncompetitive manner[87]. Molecular docking studies revealed that rutin possibly interacts with nine amino acid residues at the active site of ALR2, whereas quercetin with six. Compared to well-known synthetic inhibitor fidarestat, which occupies the active site of ALR2 with limited contacts it looks that both flavonoids extended into the hydrophobic cleft called specificity pocket[87].

The authors of this study also investigated the effect of rutin on sorbitol accumulation in human erythrocytes under high glucose conditions. The results demonstrated a dose-dependent reduction in the accumulation of intracellular sorbitol in the presence of rutin, which may be relevant in *in vivo* conditions.

Cancer: Anti-cancer mechanisms of rutin that include different cellular signaling pathways such as Jak-Stat, Wnt, AP-1, NFkB, Akt and more, as well as *in vivo* studies have been well described in the review article "Rutin mediated targeting of signaling machinery in cancer cells" by Aliye Aras Perk and colleagues[81].

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