



## Bioactive Compounds in Health and Disease – Focus on Rutin

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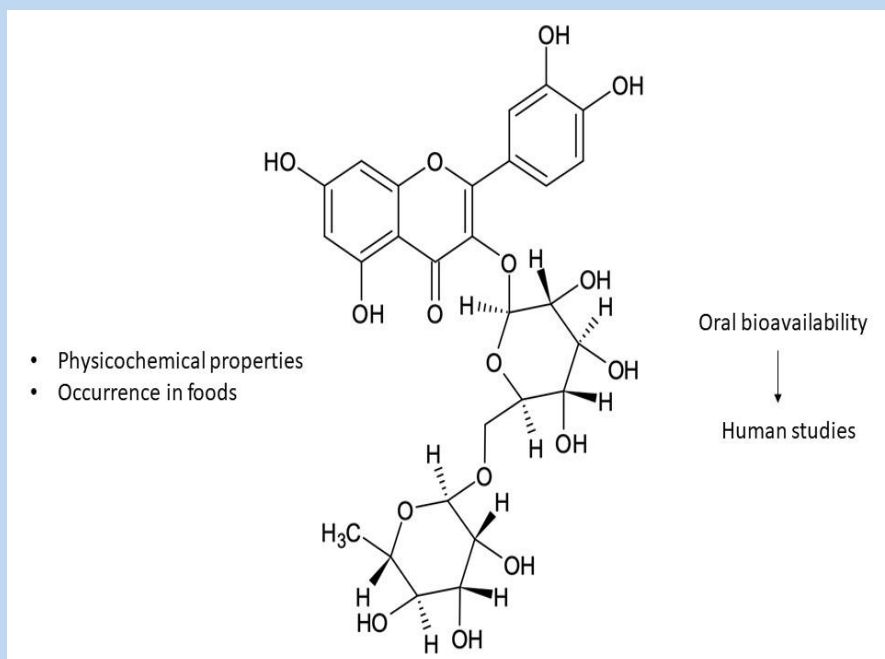
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### ABSTRACT

The flavonoid rutin was first isolated from rue (*Ruta graveolens* L.) and is used therapeutically as a capillary stabilizing and vasoprotective agent to reduce capillary fragility, although no health claims have been approved in the EU. This article briefly focuses on physicochemical properties, occurrence in foods and oral bioavailability of rutin, with emphasis on human studies. According to the available information, rutin can be considered a promising bioactive compound, despite the paucity of clinical trials. In addition to its therapeutic relevance in pathological and pathophysiological conditions, dietary rutin can also contribute to improve the physiological status of the organism in healthy subjects, thus preventing the onset of non-communicable chronic degenerative diseases.

**Keywords:** Flavonoids; polyphenols; phenylpropanoids; bioactive phytochemicals; biological activity; oral bioavailability pharmacokinetics; safety; rutin

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Chemical structure of rutin ( $C_{27}H_{30}O_{16}$ )

Graphical abstract

**INTRODUCTION:** Rutin (quercetin 3-O-rutinoside) is a flavonoid arising from the phenylpropanoid pathway and found in many plant species. It is a rutinoside, a flavonol glycoside derived from quercetin after substitution of the hydroxy group at the C3-position with rutinose, a disaccharide consisting of glucose and a rhamnose molecule (see Graphical abstract). The chemical-physical

properties, toxicity, and occurrence of rutin in selected plant foods are reported in Tables 1-3, respectively. Particularly, high levels of rutin were measured in capers (*Capparis spinosa* L., 332.29 mg/100g FW), olives (*Olea europea* L., 45.36 mg/100 g FW), buckwheat (*Fagopyrum esculentum* Möench, 36.14 mg/100 g FW) and asparagus (*Asparagus officinalis* L., 23.20 mg/100 g FW).

**Table 1.** Chemical and physical properties of rutin\*

Property	Value
Appearance/physical description	Pale yellow to amber powder
Average molecular weight	610.5175 Da
Monoisotopic mass/exact mass	610.153384912 Da
Melting point	125°C
Water solubility	0.125 mg/mL
LogP(o/x)	-2.020 (est)

\*Source: <https://pubchem.ncbi.nlm.nih.gov/>; <http://www.chemspider.com/>; <https://go.drugbank.com/>; <https://hmdb.ca/>; <http://www.thegoodscentscompany.com/index.html>;

**Table 2.** Acute toxicity of rutin\*

Animal model	Route	LD50
Mouse	Intraperitoneal	200 mg/kg
Mouse	Intravenous	950 mg/kg
Rat	Intraperitoneal	2 g/kg
Guinea pig	Intraperitoneal	2 g/kg

\*Adapted from: <https://pubchem.ncbi.nlm.nih.gov/>

**Table 3.** Occurrence of rutin in selected plant foods\*

Foods	Mean content	
<b>Cereals and cereal products</b>		
Cereals	Buckwheat, groats, thermally treated	8.96 mg/100 g FW (fresh weight)
	Buckwheat, refined flour	5.86 mg/100 g FW
	Buckwheat, whole grain flour	36.14 mg/100 g FW
<b>Vegetables</b>		
Fruit vegetables	Olive (black), raw	45.36 mg/100 g FW
	Tomato (cherry), whole, raw	3.33 mg/100 g FW
	Tomato, whole, raw	0.14 mg/100 g FW
Onion-family vegetables	Onion (red), raw	0.21 mg/100 g FW
	Onion (yellow), raw	0.68 mg/100 g FW
Pod vegetables	Green bean, raw	2.49 mg/100 g FW
Gourds	Zucchini, raw	1.32 mg/100 g FW
Leaf vegetables	Lettuce (green), raw	0.04 mg/100 g FW
Shoot vegetables	Asparagus, raw	23.20 mg/100 g FW
<b>Fruits and fruit products</b>		
Berries	Black raspberry, raw	19.00 mg/100 g FW
	Blackberry, raw	3.89 mg/100 g FW
	Blackcurrant, raw	4.65 mg/100 g FW
	Grape (green)	0.12 mg/100 g FW
	Green currant	6.06 mg/100 g FW
	Red raspberry, raw	11.00 mg/100 g FW
	Redcurrant, raw	0.44 mg/100 g FW
	White currant	0.70 mg/100 g FW
Dried berries	Grape, raisin	0.51 mg/100 g FW
Pomes	Apple (cider), whole	0.25 mg/100 g FW
	Apple (dessert), peeled	0.0000526 mg/100 g FW
	Apple (dessert), whole, raw	0.22 mg/100 g FW

	Pear, whole	0.04 mg/100 g FW
	Quince, peeled, raw	0.51 mg/100 g FW
Pome jams	Quince, jam	0.05 mg/100 g FW
	Quince, jelly	0.00392 mg/100 g FW
	Quince, peeled, jam	0.19 mg/100 g FW
Drupes	Apricot, raw	0.83 mg/100 g FW
	Nectarine, whole	0.10 mg/100 g FW
	Plum, fresh	5.90 mg/100 g FW
Dried drupes	Plum, prune	2.50 mg/100 g FW
Drupe jams	Apricot, jam	1.42 mg/100 g FW
<b>Seeds</b>		
Nuts	Almond	0.25 mg/100 g FW
	Pistachio, dehulled	0.05 mg/100 g FW
Pulses	Lentils, whole, raw	0.52 mg/100 g FW
<b>Seasonings</b>		
Herbs	Fenugreek, fresh	1.86 mg/100 g FW
	Marjoram, dried	2.60 mg/100 g FW
Spices	Capers	332.29 mg/100 g FW
<b>Non-alcoholic beverages</b>		
Fruit juices, berry juices	Sea-buckthorn berry, pure juice	1.30 mg/100 mL
Fruit juices, pome juices	Apple (cider), pure juice	0.01 mg/100 mL
	Apple (dessert), pure juice	0.35 mg/100 mL
Fruit juices, tropical fruit juices	Kiwi, juice from concentrate	0.04 mg/100 mL
	Kiwi, pure juice	0.03 mg/100 mL
Tea infusions	Tea (black), bottled	19.68 mg/100 mL
	Tea (black), infusion	1.62 mg/100 mL
	Tea (green), infusion	1.46 mg/100 mL
<b>Alcoholic beverages</b>		
Beers	Beer, regular	0.09 mg/100 mL
Wine, grapes	Wine, red	0.81 mg/100 mL
	Wine, white	0.19 mg/100 mL
Wine, berries	Blackcurrant, wine	0.45 mg/100 mL

\*Source: <http://phenol-explorer.eu/>

The oral bioavailability of dietary rutin was demonstrated in 12 healthy subjects after administration of tomato puree (25 g/day containing 2.7 mg/25 g of flavonoids), together with olive oil (5 g) for 14 days. The measured mean concentration of rutin in plasma was 0.10 µmol/L,

with large inter-individual variation (0.08 - 0.30 µmol/L), whereas the flavanol was not detected in 4 subjects [1]. However, in humans, rutin is not well absorbed in the small intestine, but is transported to the colon (about 80%) where metabolism takes place.

In 20 healthy subjects, about half of ingested rutin (440 mg/day for 7 days) was first deglycosylated to quercetin (the aglycone), and then metabolized to phenylacetic acids after cleavage of the quercetin ring by the colonic microflora. The latter were subsequently absorbed from the colon and further metabolized in the liver and kidneys. Indeed, the presence of homovanillic

acid (3-methoxy-4-hydroxyphenylacetic acid) in the urine is indicative of methylation, an important metabolic reaction that occurs in the liver (Table 4) [2]. Similarly, the very high levels of hippuric acid (N-benzoylglycine) measured in this study are consistent with the hepatic conjugation of benzoic acid with glycine to form hippuric acid [3].

**Table 4.** Urinary metabolites after rutin administration (440 mg/day for 7 days) in healthy subjects\*

Rutin metabolites	Concentration ( $\mu\text{mol}$ ) in 24-h urine after 1 week
2,4-Dihydroxybenzoic acid	16
2-Hydroxy-2-phenylacetic acid	6
2-Hydroxyhippuric acid	6.2
2-Hydroxyphenylacetic acid	8.2
3,4-Dihydroxyphenylacetic acid	52
3,5-Dihydroxybenzoic acid	47
3-Hydroxyphenylacetic acid	259
4-Hydroxybenzoic acid	29
4-Hydroxyphenylacetic acid	150
Benzoic acid	9
Ferulic acid	27
<b>Hippuric acid**</b>	2700
<b>Homovanillic acid</b>	103
Phenylacetic acid	22
Protocatechuic acid	13
Sinapic acid	26
Syringic acid	8.3
Vanillic acid	80

\*Source: <http://phenol-explorer.eu/>; [2]

\*\*In bold are the main hepatic metabolites of rutin

Despite the plethora of *in vitro/in vivo* studies on the efficacy of rutin, for example as an anticancer and neuroprotective agent [4-6], more clinical trials are needed to substantiate the preclinical evidence. In fact,

over the past five years, we have found 614 articles in PubMed using 'rutin' [in title] as a search term, with only 4 clinical trials. Similarly, only 2 recruiting and not yet recruiting clinical trials were recorded in the US registry

(<https://www.clinicaltrials.gov/>) (Table 5), whereas no clinical trials on rutin were registered in the EU registry.

Two out of four published articles were randomized controlled trials (RCTs) focusing on rutin supplementation in patients with type 2 diabetes mellitus [7,8]. In one study, 500 mg of rutin daily for 3 months significantly reduced fasting blood glucose (FBG), insulin, glycosylated hemoglobin (HbA1c), low-density lipoprotein cholesterol (LDLc), triglycerides, very low-density lipoprotein, total cholesterol (TC), LDLc:HDLc (high-density lipoprotein cholesterol) ratio, interleukin 6 and malondialdehyde, while HDL-c and total antioxidant capacity significantly increased in the rutin group compared to the placebo group [8]. Similarly, in the other study, rutin 60 mg in combination with vitamin C 160 mg administered three times a day in addition to the usual

oral antidiabetic treatment for 8 weeks significantly reduced FBG, compared with the control (only antidiabetic treatment), but had no effect on HbA1c, FBG, TC, fasting insulin, and oxidative stress in diabetic patients [7].

In another study, a mixture of flavonoids including diosmin (150 mg), troxerutin (300 mg), rutin (250 mg), hesperidin (150 mg) and quercetin (150 mg) was used safely and effectively to manage bleeding from hemorrhoidal disease with minimal adverse events [9]. In the last clinical trial, monoglucosyl rutin (200 and 400 mg/day for 8 weeks), an enzymatically modified, water-soluble form of rutin, significantly reduced abdominal visceral fat in healthy subjects with a body mass index of  $\geq 23$  and  $<30$  kg/m<sup>2</sup> [10].

**Table 5.** Clinical trials (recruiting and not yet recruiting) on rutin recorded on US registry\*

Title (identifier number)	Intervention/treatment	Condition	Primary outcome(s)
Evaluation of the effect of rutin and vitamin C on the oxidative stress in hemodialysis patients (NCT04955145)	Two tablets containing rutin 60 mg and ascorbic acid 160 mg three times daily for 4 months	End stage renal disease	Plasma levels of malondialdehyde, C-reactive protein, glutathione peroxidase, tumor necrosis factor-alpha and erythrocyte sedimentation rate
Evaluation of the effect of systemic proteolytic enzyme therapy (NCT05681312)	Tibrolin™ (trypsin 48 mg, bromelain 90 mg) and rutin 100 mg for five days	Post operative pain	Pain after surgery, facial swelling and trismus 7 days after surgery

\*<https://www.clinicaltrials.gov/>

## CONCLUSION:

Compelling evidence indicates that foods rich in flavonoids are healthy [11,12]. Rutin, in particular, can really be considered a promising bioactive component of many functional foods [13]. Based on clinical evidence, it may have beneficial effects on the improvement of metabolic parameters, in particular glycaemia, as well as

the inflammatory and oxidative status in diabetic patients. In addition to requiring further RCTs on rutin, a future trend is the use of this flavonoid in combination with conventional therapies, to potentiate the effectiveness of the latter. For instance, rutin *i)* can sensitize tumor cells resistant to anticancer drugs,

reducing their side effects [4,14]; *ii*) reduce hyperglycemia (%HbA1c) in combination with the antidiabetic drugs acarbose and canagliflozin [15]; *iii*) improve diabetic neuropathy by potentiating the anti-inflammatory drug nimesulide [16]; and *iv*) manage osteoarthritis symptoms in combination with oral proteolytic enzymes [17].

Another relevant issue is the oral bioavailability of rutin which can be successfully improved with nanoformulations. The latter, in fact, can deliver bioactive compounds to specific target(s), facilitating their controlled release, as demonstrated for other phytochemicals including curcumin, also reducing the administered dose [18]. Rutin nanohybrids made of phenylboronic acid conjugated to nanomagnesia (MgO nanoparticles) exhibited a significant preclinical anticancer activity to chemoresistant breast cancer cells via oxidative burst (i.e., reactive oxygen species generation) and apoptotic cell death, whereas no notable systemic toxicity was documented in mice [19]. In

another *in vitro/in vivo* study, rutin nanoencapsulation in an innovative nanovesicle composed of saturated fatty acids and phytosterols increased oral bioavailability of the flavonoid in rats after a single administration. This nanoformulation has also been shown to be cytotoxic to hepatocellular carcinoma cells via cell cycle arrest [20]. Unfortunately, a reference anticancer drug was not used in either of these *in vivo* experiments. In any case, safety of nanoformulations must be ascertained, in terms of nanotoxicology, chronic exposure and interaction with drugs.

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## REFERENCES

- Simonetti, P., C. Gardana, P. Riso, P. Mauri, P. Pietta, and M. Porrini: Glycosylated flavonoids from tomato puree are bioavailable in humans. *Nutrition Research* 2005, 25(8):717-726. DOI: <https://doi.org/10.1016/j.nutres.2005.05.001>
- Olthof, M.R., P.C. Hollman, M.N. Buijsman, J.M. Van Amelsvoort, and M.B. Katan: Chlorogenic acid, quercetin-3-rutinoside and black tea phenols are extensively metabolized in humans. *Journal of Nutrition* 2003, 133(6):1806-1814. DOI: <https://doi.org/10.1093/jn/133.6.1806>
- Penczynski, K.J., D. Krupp, A. Bring, K. Bolzenius, T. Remer, and A.E. Buyken: Relative validation of 24-h urinary hippuric acid excretion as a biomarker for dietary flavonoid intake from fruit and vegetables in healthy adolescents. *European Journal of Nutrition* 2017, 56:757-766. DOI: <https://doi.org/10.1007/s00394-015-1121-9>
- Iriti, M., R. Kubina, A. Cochis, R. Sorrentino, E.M. Varoni, A. Kabała-Dzik, B. Azzimonti, A. Dziedzic, L. Rimondini, and R.D. Wojtyczka: Rutin, a quercetin glycoside, restores chemosensitivity in human breast cancer cells. *Phytotherapy Research* 2017, 31(10):1529-1538. DOI: <https://doi.org/10.1002/ptr.5878>
- Ramalingayya, G.V., S.P. Cheruku, P.G. Nayak, A. Kishore, R. Shenoy, C.M. Rao, and N. Krishnadas: Rutin protects against neuronal damage *in vitro* and ameliorates doxorubicin-induced memory deficits *in vivo* in Wistar rats. *Drug Design, Development and Therapy* 2017, 1011-1026. DOI: <https://doi.org/10.2147/DDDT.S103511>
- Asti, A.L., S. Crespi, T. Rampino, P. Zelini, M. Gregorini, A. Pascale, N. Marchesi, S. Saccucci, C. Colombani, S. Vitalini, and M. Iriti: Yet another *in vitro* evidence that natural compounds introduced by diet have anti-amyloidogenic activities and can counteract neurodegenerative disease depending on aging. *Natural Product Research* 2023, 1-6. DOI: <https://doi.org/10.1080/14786419.2023.2192493>
- Ragheb, S.R., L.M. El Wakeel, M.S. Nasr, and N.A. Sabri: Impact of Rutin and Vitamin C combination on oxidative stress and

- glycemic control in patients with type 2 diabetes. *Clinical Nutrition ESPEN* 2020, 35:128-135. DOI: <https://doi.org/10.1016/j.clnesp.2019.10.015>
8. Bazayar, H., L. Moradi, F. Zaman, and A. Zare Javid: The effects of rutin flavonoid supplement on glycemic status, lipid profile, atherogenic index of plasma, brain-derived neurotrophic factor (BDNF), some serum inflammatory, and oxidative stress factors in patients with type 2 diabetes mellitus: A double-blind, placebo-controlled trial. *Phytotherapy Research* 2023, 37(1):271-284. DOI: <https://doi.org/10.1002/ptr.7611>
  9. Corsale, I., P. Carrieri, J. Martellucci, A. Piccolomini, L. Verre, M. Rigutini, and S. Panicucci: Flavonoid mixture (diosmin, troxerutin, rutin, hesperidin, quercetin) in the treatment of I-III degree hemorrhoidal disease: a double-blind multicenter prospective comparative study. *International Journal of Colorectal Disease* 2018, 33:1595-1600. DOI: <https://doi.org/10.1007/s00384-018-3102-y>
  10. Martirosyan, D., and E. Miller. Bioactive compounds: The key to functional foods. *Bioactive Compounds in Health and Disease* 2018, 1(3):36-39. DOI: <https://doi.org/10.31989/bchd.v1i3.539>
  11. Devkota, H.P., A. Kurizaki, K. Tsushiro, A. Adhikari-Devkota, K. Hori, M. Wada, and T. Watanabe: Flavonoids from the leaves and twigs of *Lindera sericea* (Seibold et Zucc.) Blume var. *sericea* (Lauraceae) from Japan and their bioactivities. *Functional Foods in Health and Disease* 2021, 11(1):34-43. DOI: <https://www.doi.org/10.31989/ffhd.v11i1.769>
  12. Madardam, J., S. Wattanachant, and C.T. Yupanqui: Evaluation of the antioxidant activity and nitric oxide production effect of formulated crispy vegetables from thermal processing of *Amaranthus viridis* and *Sauropus androgynous*. *Functional Foods in Health and Disease* 2023, 13(9):409-423. DOI: <https://www.doi.org/10.31989/ffhd.v13i9.1116>
  13. Hashizume, Y., and M. Tandia: The reduction impact of monoglucosyl rutin on abdominal visceral fat: A randomized, placebo-controlled, double-blind, parallel-group. *Journal of Food Science* 2020, 85(10):3577-3589. DOI: <https://doi.org/10.1111/1750-3841.15429>
  14. Satari, A., S. Ghasemi, S. Habtemariam, S. Asgharian, and Z. Lorigooini: Rutin: a flavonoid as an effective sensitizer for anticancer therapy; insights into multifaceted mechanisms and applicability for combination therapy. *Evidence-based Complementary and Alternative Medicine* 2021, Article ID:9913179. DOI: <https://doi.org/10.1155/2021/9913179>
  15. Valdes, M., F. Calzada, J. Martínez-Solis, and J. Martínez-Rodríguez: Antihyperglycemic Effects of *Annona cherimola* Miller and the Flavonoid Rutin in Combination with Oral Antidiabetic Drugs on Streptozocin-Induced Diabetic Mice. *Pharmaceuticals* 2023, 16(1):112. DOI: <https://doi.org/10.3390/ph16010112>
  16. Mittal, R., A. Kumar, D.P. Singh, M. Bishnoi, and T.C. Nag: Ameliorative potential of rutin in combination with nimesulide in STZ model of diabetic neuropathy: targeting Nrf2/HO-1/NF-kB and COX signalling pathway. *Inflammopharmacology* 2018, 26:755-768. DOI: <https://doi.org/10.1007/s10787-017-0413-5>
  17. Henrotin, Y.E., C. Michlmayr, S.M. Rau, A.M. Quirke, M. Bigoni, and M.A. Ueberall: Combination of enzymes and rutin to manage osteoarthritis symptoms: Lessons from a narrative review of the literature. *Rheumatology and Therapy* 2022, 9(5):1305-1327. DOI: <https://doi.org/10.6084/m9.figshare.20058908>
  18. Salehi, B., Rodrigues, C.F., Peron G., Dall'Acqua S, Sharifi-Rad J., Azmi L., Shukla I, Singh Baghel U, Curcumin nanoformulations for antimicrobial and wound healing purposes. *Phytotherapy Research* 2021,35(5):2487-2499. DOI: [10.1002/ptr.6976](https://doi.org/10.1002/ptr.6976).
  19. Singh, T.A., P. Sadhukhan, N. Ghosh, N. Thakur, A. Sharma, N. Tejwan, A. Pabbathi, J. Das, and P.C. Sil. Targeted delivery of rutin into breast cancer cells via using phenylboronic acid functionalized MgO nanoparticles. *Materials Science and Engineering B* 2023, 296:116623. DOI: <https://doi.org/10.1016/j.mseb.2023.116623>.
  20. AbouSamra, M. M., S.M. Afifi, A.F. Galal, and R. Kamel. Rutin-loaded Phyto-Sterosomes as a potential approach for the treatment of hepatocellular carcinoma: In-vitro and in-vivo studies. *Journal of Drug Delivery Science and Technology* 2023, 79:104015. DOI: <https://doi.org/10.1016/j.jddst.2022.104015>.