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Bioactive Compounds in Health and Disease – Focus on Rutin

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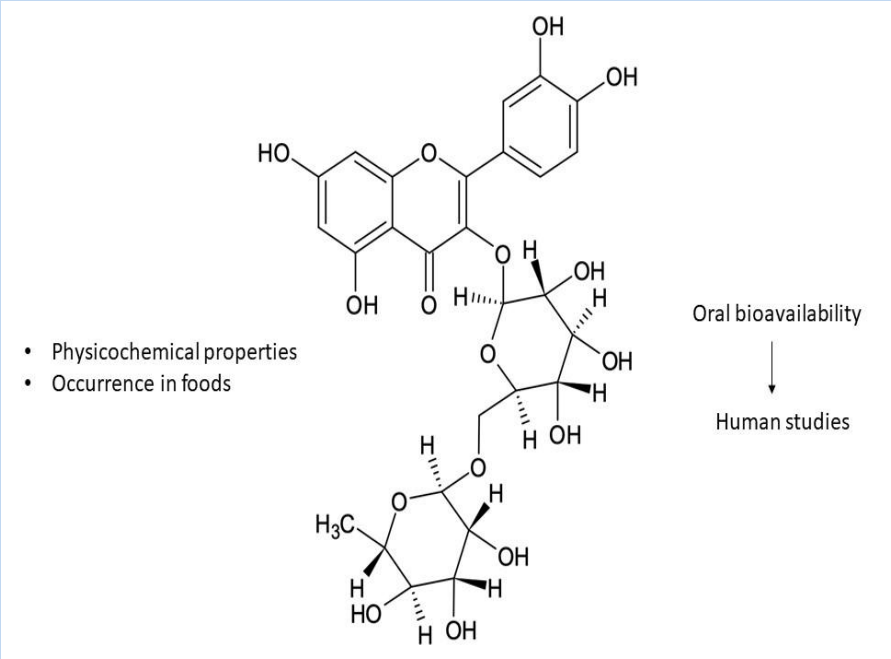
ABSTRACT

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

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
Cereals and cereal products		
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
Vegetables		
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
Fruits and fruit products		
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
Seeds		
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
Seasonings		
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
Non-alcoholic beverages		
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
Alcoholic beverages		
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 (µmol) 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
Hippuric acid**	2700
Homovanillic acid	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 (hig-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 ≥ 23 and <30 kg/m^2 [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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Author Contribution: All authors conceived and write the MS.

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