Evaluating the Bioavailability of Isoquercetin

By Jeremy Appleton, ND

Abstract

Quercetin glucosides are among the most common flavonoids in the human diet. They possess neuroprotective, cardioprotective, chemopreventive, antioxidant, anti-inflammatory, and anti-allergic properties. Quercetin (aglycone) is among the most popular flavonoid supplements. It is not, however, the dominant form appearing in nature, and its bioavailability is poor. Quercetin glucosides, such as isoquercetin, occur naturally and have the same therapeutic effects *in vivo* as quercetin (aglycone), but with better bioavailability.

Introduction

Flavonoids are a group of polyphenolic compounds, which are widely distributed throughout the plant kingdom. More than 5,000 flavonoid compounds have been identified. Many of them, including flavonols, have low toxicity in mammals and will be discussed in this profile. A great many flavonoids have demonstrated health-promoting effects in humans and in animal studies, which will also be addressed.

Glycosides are molecules in which a sugar is bound to a non-carbohydrate moiety, usually a small organic molecule. Glycosides play numerous important roles in living organisms. Many plants store chemicals in the form of inactive glycosides, which can be activated by enzyme hydrolysis. Dietary intake of flavonols is difficult to estimate accurately because values depend on assessment of feeding habits and flavonol content in foods. "Food sources, dietary intakes, and bioavailability of flavonols are also influenced by variations in plant type and growth, season, light, degree of ripeness, food preparation, and processing." However, it has been estimated that adults in the United States typically consume about 1 gram of flavonoids per day. Most of these flavonoids are in the form of glycosides with high molecular weight. The molecular weight and hydrophilicity of all glycosides has the potential to limit their absorption in the small intestine. Many flavonoids, such as rutin, pass unchanged into the large intestine, where they are hydrolyzed by microbially produced glycosidases, yielding quercetin aglycone and its sugar. However, absorption at this point in the intestine is quite limited.

A limited number of clinical trials have been conducted on isolated flavonols (i.e., quercetin, rutin, hydroxyethylrutosides [a semi-synthetic form of rutin]). The most commonly accepted medical use of flavonols is in the maintenance of capillary integrity, for which the flavonols are applied topically, ingested, or taken by both routes concurrently. Flavonols have also demonstrated neuroprotective, cardioprotective, chemopreventive, antioxidant, anti-inflammatory, and anti-allergic activity in numerous preclinical studies. Rutin and quercetin (aglycone), the most commonly used flavonol compounds in nutritional supplements, have poor bioavailability, which may lessen efficacy. Quercetin glucosides, however, have better bioavailability, resulting in potentially increased efficacy compared to the aglycone form.

Although currently less widely available, quercetin glucosides show promise in overcoming some of the limitations of both quercetin aglycone and high–molecular weight rutinosides, expanding the efficacy and range of indications for this class of supplements.

Flavonols

Flavonoids are divided into several classes: flavonols, flavonones, flavones, flavanols, flavan-3-ols and isoflavones. These classifications are made according to the chemical composition of the compounds, specifically the positions of substitute groups present on the parent molecule. Flavonols are yellow, antioxidant pigments found in many flowers and plants. Yellow onion and curly kale are among the richest natural sources. Flavonols are also present in apple, broccoli, lettuce, tomato, grape, berries, tea, and red wine.

Rutin is found in the highest amounts in buckwheat, tomato, apricot, rhubarb, tea, celery, spinach, brussels sprouts and lemon. The rutin used in dietary supplements is typically derived from *Dimorphandra* spp. (Brazil) and *Sophora japonica* (Asia).

The flavonols rutin, quercetin, and isoquercetin are found not only in foods such as apple and onion, but in many medicinal plants, likely contributing to the medicinal qualities of a large number of botanical medicines. Some of the most commonly used plants containing these flavonoids include *Aesculus hippocastanum* (Horse chestnut), *Ruscus aculeatus* (Butcher's Broom), *Ginkgo biloba* (Ginkgo), *Hypericum perforatum* (St. John's Wort), *Calendula officinalis* (Pot marigold), *Arctostaphylos uva ursi* (Uva ursi), *Equisetum arvense* (Horsetail), *Glycyrrhiza glabra* (Licorice), *Foeniculum vulgare* (Fennel), *Aspalathus linearis* (Rooibos), *Humulus lupulus* (Hops), *Tussilago farfara* (Coltsfoot), *Drosera rotundifolia* (Sundew), *Vaccinium myrtillus* (Bilberry), *Bupleurum chinense* (Bupleurum), *Fouquieria splendens* (Ocotillo), and *Morus* spp. (Mulberry).[10]

Structure and Activity of Flavonols

Quercetin

Quercetin is a natural antioxidant, producing its antioxidative actions by inhibiting lipid peroxidation through blockade of the enzyme xanthine oxidase, chelating iron, and directly scavenging hydroxyl, peroxy, and superoxide radicals.[11,12,13] Flavonols, including quercetin, also protect the antioxidative defense mechanism by increasing the absorption of vitamin C.[14] Quercetin inhibits structural damage to proteins and the release and production of oxidative products generated by the respiratory burst in phagocytes.[15,16] Quercetin is an aglycone, meaning that it lacks a glycoside side chain. In contrast, naturally occurring quercetin compounds are primarily glycosides, with only very small quantity occurring as an aglycone. Once absorbed from the gut, most quercetin compounds are metabolized to quercetin glucuronides, the primary

metabolic form detected in plasma. As will be discussed later, isoquercetin (quercetin glucoside, a type of glycoside) is comparatively much more bioavailable than quercetin aglycone, the commonly available form as a supplement. Highly efficient hydrolysis of the glucoside chain in the absorptive endothelium of the small intestinal brush border yields quercetin aglycone within the enterocytes. This means that ingested isoquercetin itself does not reach the portal circulation; it enters the circulation either as quercetin aglycone or as a quercetin glucoside. Therefore, the therapeutic profile of isoquercetin is identical to that of quercetin. This article will therefore consider the therapeutic applications of isoquercetin together with those of quercetin.

Isoquercetin

As mentioned, quercetin does not principally occur in the form in which it is available as a dietary supplement (an aglycone). Instead, it occurs mostly as quercetin glycosides, with glucoside chains usually occurring at the 3 or 4 position of the pyrone ring.[17] Isoquercetin is one of the naturally occurring glucosides of quercetin. It has the molecular formula $C_{21}H_{20}O_{12}$ and a molar mass of 464.38 g/mol. It is also known as quercetin-3-O-glucoside, quercetin-3-O-ß-D-glucoside, and hirsutrin. Isoquercetin is also sometimes called isoquercitrin, a nearly identical quercetin-3-monoglucoside. Technically the two are different (isoquercetin has a pyranose ring whereas isoquercitrin has a furanose ring), but functionally the two molecules are indistinguishable. The literature often considers them as one and uses the names interchangeably, a convention followed hereafter in this article.
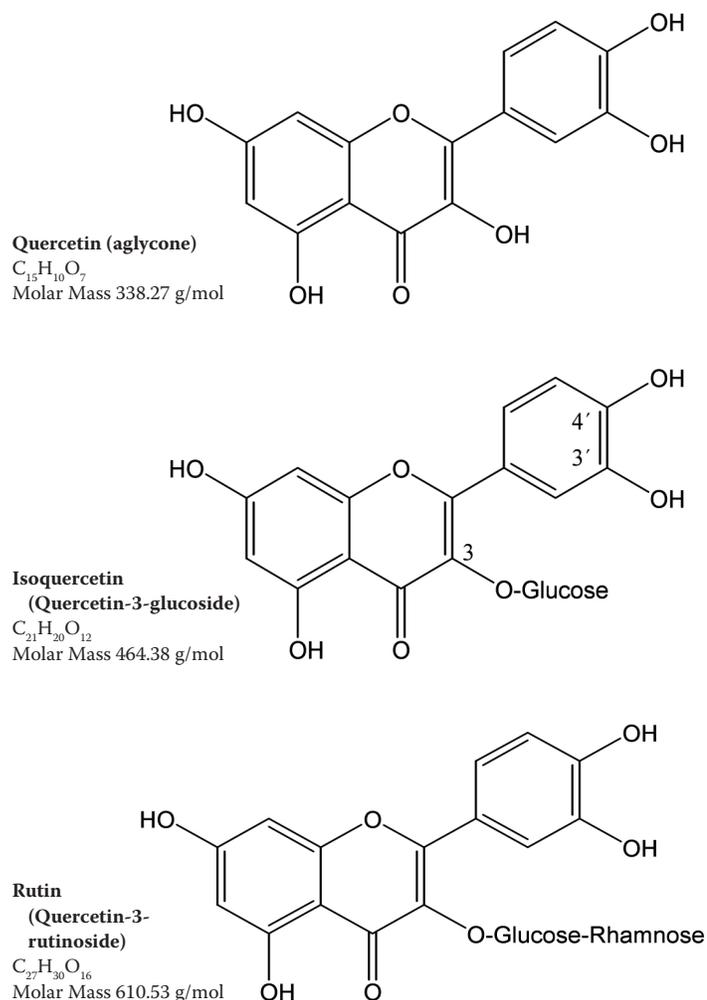

Quercetin (aglycone)
$C_{15}H_{10}O_7$
Molar Mass 338.27 g/mol

Isoquercetin
(Quercetin-3-glucoside)
$C_{21}H_{20}O_{12}$
Molar Mass 464.38 g/mol

Rutin
(Quercetin-3-rutinoside)
$C_{27}H_{30}O_{16}$
Molar Mass 610.53 g/mol

Fig. 1 Quercetin, Isoquercetin and Rutin.

Therapeutic Properties of Quercetin and its Glucosides: Indications and Clinical Applications

Cardioprotection

In a clinical study done by Edwards and colleagues, quercetin supplementation reduced blood pressure in hypertensive subjects.[1] However, contrary to prior animal studies, there was no quercetin-evoked reduction in systemic markers of oxidative stress as was expected. The authors suggest the possibility of elevated oxidative stress in vascular and renal compartments of their hypertensive subjects, as has been seen in animal models of hypertension. They suggest that high oxidative stress in these compartments may have left little residual systemic effect of the antioxidants.

Quercetin supplementation has been shown to inhibit LDL oxidation in humans, though it does not appear to modify *levels* of LDL.[2,3] Administration of quercetin glucoside to human subjects demonstrated that quercetin was bioavailable, with plasma concentrations attained in the range known to affect platelet function. Platelet aggregation was inhibited 30 and 120 min after ingestion of quercetin glucoside.[4] Dietary flavonoids, such as quercetin and (-)-epicatechin, have also been shown to augment nitric oxide status and reduce endothelin-1 concentrations, thereby improving endothelial function.[5]

Blood Vessel Protection

One time-tested therapeutic indication for flavonols is the protection and restoration of blood vessel integrity. Endothelial oxidation, inflammation, and capillary fragility can set the stage for thrombosis and venous insufficiency. Isoquercetin has demonstrated dose-dependent protective effect against oxidative endothelial injury.[6] It has also been shown to protect venular endothelium from inflammatory products released by activated blood platelets and polymorphonuclear granulocytes.[7]

Neuroprotection

The brain is particularly susceptible to oxidative damage because of its high utilization of oxygen, its high levels of unsaturated lipids and transition metals like iron, and its relatively inefficient antioxidant defenses.[8] Reactive oxygen radicals and lipid peroxides have been implicated in the pathogenesis of neurological pathology, including brain trauma, ischemia, and neurodegenerative disorders. Agents capable of scavenging free radicals and inhibiting lipid peroxides, and thereby protecting neurons from oxidative injury, may help prevent and treat neurodegenerative disorders caused by oxidative stress. Flavonoids have demonstrated protection of the brain through their ability to modulate intracellular signals, promoting cellular survival.[9]

Isoquercetin has demonstrated potential protective effects against oxidative neuronal injuries and brain ischemia. Dok-Go and colleagues found quercetin and its 3-methyl ether metabolite prevented xanthine oxidase-induced oxidative neuronal cell injury, scavenged free radicals, and inhibited lipid peroxidation. Quercetin 3-methyl ether, a methanolic extract of quercetin, was a more potent neuroprotectant than any of the other flavonoids tested.[10] Heo and Lee observed that quercetin decreased oxidative stress-induced neuronal cell membrane damage more effectively than vitamin C.[11] Quercetin has also attenuated carotid hypoperfusion injury to white matter in rats, suggesting protective effects against ischemic stroke.[12] Krasteva and colleagues found that isoquercetin and related flavonoids increase cerebral blood flow and possess antihypoxic activity, and may account for of the application of flavonoid-containing botanical agents like *Ginkgo biloba* in memory loss.[13] Further supporting this, quercetin and its glucosides have been shown to exert protective effects against cognitive decline related to aging, vascular dementia, and Alzheimer disease.[14,15] Therapeutic effects in tardive dyskinesia in rats have also been noted.[16]

Antidepressant Activity

Early identification of therapeutic activity of isoquercetin came from studies in which the flavonol was extracted from *Hypericum performatum* (St. John's wort). In fact, isoquercetin bears striking structural similarities to the main active constituents of St. John's wort, particularly hyperoside.[17] It has long been known that the antidepressant activity of the herb is due not only to hypericin, but to other constituents, including flavonoids.[18] Isoquercetin is part of the flavonoids fraction of St. John's wort that has been shown in animals to exhibit antidepressant activity, possibly by modulating HPA-axis regulation of ACTH and cortisol.[19,20]

Prevention of Diabetic Complications

Isoquercetin inhibits the formation of advanced glycation end-products (AGEs), one of primary pathologic mechanisms involved in diabetic complications and morbidity of aging.[21] Treatment with quercetin significantly attenuated renal dysfunction and oxidative stress in diabetic rats as well as the neuropathic pain that accompanies the disease.[22,23]

Anti-inflammatory Effects

Quercetin is clinically used in the treatment of chronic prostatitis and related inflammatory conditions. In one study, quercetin supplementation provided significant symptomatic improvement in a majority of men with chronic pelvic pain syndrome.[24] Quercetin therapy (500 mg twice daily for 4 weeks) also demonstrated significant symptomatic improvement in patients with interstitial cystitis and chronic pelvic pain syndrome in another study.[25]

Quercetin and quercetin glycosides have demonstrated beneficial effects in animal models of inflammation. Isoquercetin demonstrated slightly better anti-inflammatory efficacy than quercetin on the expression of COX-2 mRNA and inflammatory cell exudation, though overall effects of the two were roughly comparable in this *in vitro* study.[26]

Quercetin and rutin inhibit the generation of inflammatory mediators (leukotriene LTB4 and prostaglandin E2) in human neutrophils.[27] These flavonoids may therefore find application in the treatment of inflammatory conditions associated with excessive leukotriene production, such as rheumatoid arthritis and inflammatory bowel disease.[28]

Quercetin has been shown to inhibit cytokine and inducible nitric oxide synthase expression through inhibition of the NF-kappaB pathway, which further accounts for its anti-inflammatory capacity.[29] Quercetin may also exert anti-inflammatory via systemic inhibition of TNF-α.[30]

Allergies

Quercetin has been shown to stabilize mast cells against degranulation, resulting in a decrease in histamine release.[31] In addition, anti-inflammatory actions, such as inhibition of neutrophil lysosomal enzyme secretion and leukotriene production,[32,33] has led to the use of quercetin as a leading nutritional intervention for perennial allergic rhinitis.[34]

Absorption and Bioavailability

Absorption and bioavailability studies of quercetin and its glucosides have been conducted primarily in animals, such as rats and pigs.[35,36,37,38,39] A few researchers have investigated the absorption and bioavailability of flavonoids in humans.[40]

Bioavailability Studies in Humans

Comparative pharmacokinetics in humans demonstrates that the absorption of quercetin, isoquercetin, and rutin in humans involves different mechanisms. Rutin has the lowest relative bioavailability and is not significantly absorbed before 2 hours, showing peak plasma concentrations at 6 hours after intake. Metabolites of isoquercetin appear within 30 minutes in the systemic circulation; a rapid rise to a peak at 30 minutes is seen with isoquercetin, suggesting active or enhanced transport; quercetin aglycone exhibits a slow rise to a plateau at 1–4 hours, indicating absorption by passive diffusion from the stomach and through the intestines.[41,42]

Hollman and colleagues in the Netherlands assessed the relative bioavailability and absorption of flavonoids from onions (glucose-conjugated quercetin), apples (both glucose conjugates and non-glucose conjugates), or pure quercetin-3-rutinoside in humans.[43] They found that absorption and bioavailability were highest for the quercetin glucosides, such as isoquercetin, lower for quercetin aglycone, and lowest for non-glucose quercetin glycosides such as rutin. No published study has directly compared the relative bioavailability of isolates of isoquercetin, quercetin aglycone, and rutin in humans, though some animal studies have.

The presence of the glucoside moiety, whether in the 3′ or 4′ position, appears to be responsible for the increased bioavailability of isoquercetin and other quercetin glucosides, as compared with quercetin aglycone. Isoquercetin (quercetin-3-glucoside) has been shown to have bioavailability comparable to that of quercetin-4′-glucoside.[44] The similarities are such that researchers often refer to the two glucosides interchangeably.[45]

In one study, men with ileostomies consumed a supplement of fried onions (which is rich in quercetin glucosides), pure rutin, or pure quercetin aglycone. The absorption of the flavonoids, defined as oral intake minus ileostomy excretion, was 52% for quercetin glucosides, 24% for quercetin, and 17% for rutin.[46]

Further investigations in which test subjects were fed pure quercetin-4′-glucoside or pure rutin showed similar results.[47] The peak concentration of quercetin equivalents in plasma was 20 times higher and was reached more than 10 times faster after intake of quercetin glucoside (i.e., isoquercetin) compared to rutin. The authors proposed an active transport of the quercetin glucoside with the glucose transporter SGLT1 in the small intestine. In contrast, rutin is thought to be absorbed after deglycosylation in the colon.[48,49] Although not all studies corroborate these results, the preponderance of evidence supports the superior bioavailability of quercetin glucosides compared to quercetin.[50,51]

The influence of plant matrix and sugar moiety of the glycoside on the absorption of flavonoids has been suggested as an important factor for the absorption of quercetin aglycone, but direct study of the influence of the plant matrix found no significant difference in the bioavailability and pharmacokinetic parameters between an onion supplement (containing mainly quercetin-4′-glucoside) and pure quercetin-4′-glucoside.[52,53]

Bioavailability Studies in Animals

Some bioavailability studies of quercetin have been performed in pigs since the anatomy and physiology of porcine and human digestive gastrointestinal tracts are similar. These studies are of particular interest because they directly compare the bioavailability of isoquercetin, quercetin aglycone, and rutin. Bioavailability is highest for isoquercetin, lower for quercetin aglycone, and lowest for rutin. After intravenous and oral application in pigs, the bioavailability of oral quercetin was just 17%, compared with intravenously administered quercetin at 100%.[54] In a similar study, the relative total bioavailability was 148% for isoquercetin. For Q3G and rutin, the relative total bioavailability of quercetin (i.e., conjugated quercetin and conjugated methylethers of quercetin) was 148% and 23% respectively, compared with quercetin aglycone.[55] One study suggested dietary fat content may influence absorption of quercetin derivatives. Pigs were given 3%, 17%, or 32% fat in their diets as well as either isoquercetin or quercetin aglycone. The 17% fat diet has significantly increased absorption compared to the 3% diet, while the 32% diet did not increase the absorption further. Isoquercetin, which is less lipophilic than quercetin aglycone, showed better bioavailability regardless of percentage of fat consumed.[56]

Direct comparisons of the bioavailability of isoquercetin, quercetin aglycone, and rutin have also been made in rats. As with pigs, bioavailability in the small intestine was highest for isoquercetin,

lower for quercetin aglycone, and lowest for rutin.[57] Rats given quercetin, isoquercetin, rutin or quercetin-3-rhamnoside achieved plasma concentration 2.5 to 3 times higher with isoquercetin compared to quercetin aglycone.[58,59]

Mechanisms of Absorption

Quercetin and isoquercetin (and other glucosides like quercetin-4′-glucoside) are primarily absorbed by brush border enterocytes of the small intestine. Quercetin glycosides with sugar moieties *other than* glucose (e.g., rutinosides) are absorbed in lower parts of the intestinal tract after deglycosylation.

Quercetin glucosides are transported into the epithelial cells via sodium-dependent glucose transporter (SGLT1).[60] Luminal hydrolysis of the quercetin glucoside is by the lactase phlorizin hydrolase (LPH) enzyme.[61] LPH is an extracellular ß-glycosidase located on the brush border membrane of intestinal cells. LPH is the only mammalian glucosidase that is present on the luminal side of the brush border, so it can act on dietary glycosides in the lumen, before absorption. Quercetin glucosides are deglycosylated by LPH. The resulting aglycone then enters epithelial cells by passive diffusion. This process is possibly enhanced by the proximity to the cellular membrane.[62,63]

Metabolism

After ingestion of isoquercetin, quercetin, and rutin, quercetin aglycone and intact glycosides of quercetin are not detectable in human plasma and body tissues in significant amounts as these parent compounds. Instead, quercetin occurs principally as glucuronated, sulfated, and methylated quercetin conjugates. This has been demonstrated in humans as well as in animals.[64,65,66] Day and colleagues identified quercetin-3′-O-glucuronide, 3′-O-methylquercetin-3-O-glucuronide, and quercetin-3′-O-sulfate as the major conjugates.[67] Approximately 20–40% of quercetin is methylated in the 3′-position, yielding isorhamnetin.[68,69]

In humans, about 93% of quercetin is metabolized in the gut.[70] Quercetin diglucuronides and glucuronyl sulfates of methylated quercetin in plasma are the major metabolites, and data suggest that the *in vivo* bioactivity of quercetin is due to these metabolites. Research on the neuroactivity of St. John's wort suggests that some of these quercetin metabolites can cross the blood-brain barrier.[71,72]

Why not just eat more onions?

It remains controversial whether or not the food matrix confers advantages in terms of bioavailability of quercetin and its glycosides. As has been demonstrated for other nutrients (e.g., lutein for macular degeneration), epidemiological evidence of a beneficial effect of a particular nutrient does not always translate into a beneficial effect of the isolated nutrient. This leads some nutritionally oriented doctors to shun isolated nutrients in favor of obtaining the nutrients from foods. This is complicated by the findings that some therapeutic quantities of a desired nutrient are not practical to obtain from the diet. Further, food preparation may degrade their bioactivity. In the case of quercetin derivatives, onions are a major source of quercetin glucosides. However, roasting onions for over 60 minutes at 180°C degrades onion quercetin glucosides.[73] Most people prefer not to eat onion raw, at least in large quantities. Moreover, levels of quercetin glucosides vary considerably from one type of onion to another (e.g., they nearly absent from white onions).[74] Quercetin glucoside levels also decrease significantly as onions age.[75] According to Graefe and colleagues in their definitive study of the pharmacokinetics and bioavailability of quercetin glycosides in humans, "The plant matrix of onions has no determinable impact on the absorption of quercetin glucosides."[76]

Contraindications

There are no cases of adverse events from isoquercetin supplementation in the literature. It has been reported that quercetin (aglycone) supplementation can cause elevations of plasma homovanillic acid.[77]

Early *in vitro* research suggested that quercetin aglycone could be a potential mutagen.[78,79,80,81,82,83,84,85,86,87] Although more definitive *in vivo* studies found no mutagenicity and quercetin has been found to be free of reproductive toxicity and developmental toxicity, it is nevertheless prudent that pregnant women not use quercetin supplements, including isoquercetin.[88,89,90,91,92,93,94,95]

Quercetin supplements, including isoquercetin, should also be avoided by people taking cyclosporine, estradiol, nifedipine, or felodipine. In an animal study, oral administration of quercetin (50 mg/kg BW) at the same time as cyclosporine decreased the absorption of cyclosporine by 43%.[96] In another study, however, supplementing with quercetin along with cyclosporine significantly *increased* blood levels of cyclosporine, compared to cyclosporine alone.[97] Naringenin, quercetin, and kaempferol, all present in grapefruit, are inhibitors of cytochrome P-450 metabolism. All of these flavonoids can inhibit metabolism of 17 beta-estradiol.[98] Therefore, people on estrogen replacement therapy should consult with their physician before taking quercetin or any concentrated flavonoid-containing product. Quercetin has also inhibited the metabolism of nifedipine and felodipine by cytochrome P-450 3A4.[99] There are no reports in the medical literature of drug interactions with isoquercetin.

Dosages

A conservative estimate puts the relative bioavailability of isoquercetin at 3–5 times that of quercetin aglycone. Thus it is anticipated that a lower does of isoquercetin would be required for comparable efficacy. As a rule of thumb, isoquercetin could be supplemented in a ratio of 1:5 relative to quercetin aglycone. Thus, for example, in revising a regimen in which 500 mg per day of quercetin aglycone is being given, the physician would recommend an isoquercetin supplement of 100 mg per day.

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