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Invited Review

Isoquercitrin: Pharmacology, toxicology, and metabolism

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ABSTRACT

The flavonoid isoquercitrin (quercetin-3-*O*-β-D-glucopyranoside) is commonly found in medicinal herbs, fruits, vegetables and plant-derived foods and beverages. This article reviews the occurrence, preparation, bioavailability, pharmacokinetics, toxicology and biological activity of isoquercitrin and "enzymatically modified (α-glucosylated) isoquercitrin" (EMIQ). Pure isoquercitrin can now be obtained on a large scale by enzymatic rutin hydrolysis with α-L-rhamnosidase. Isoquercitrin has higher bioavailability than quercetin and displays a number of chemoprotective effects both *in vitro* and *in vivo*, against oxidative stress, cancer, cardiovascular disorders, diabetes and allergic reactions. Although small amounts of intact isoquercitrin can be found in plasma and tissues after oral application, it is extensively metabolized in the intestine and the liver. Biotransformation of isoquercitrin includes deglycosylation, followed by formation of conjugated and methylated derivatives of quercetin or degradation to phenolic acids and carbon dioxide. The acceptable daily intake of (95%) isoquercitrin and of EMIQ was estimated to be 5.4 and 4.9 mg/kg/day, respectively. Adverse effects of higher doses in rats included mostly (benign) chromaturia; nevertheless some drug interactions may occur due to the modulation of the activity and/or expression of drug metabolizing/transporting systems. With respect to the safety, affordability and beneficial pharmacological activities, highly pure isoquercitrin is a prospective substance for food supplementation.

Contents

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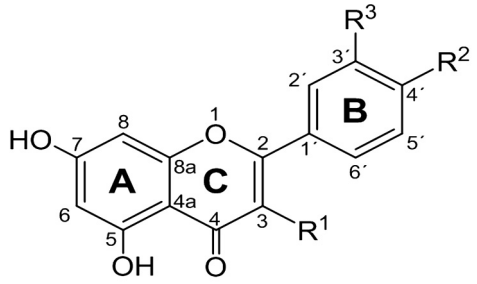
1. Introduction

Isoquercitrin (quercetin-3-*O*-β-D-glucopyranoside; Fig. 1, Table 1) is, together with rutin (quercetin-3-*O*-rutinoside), one of the major glycosidic forms of the natural flavonol quercetin (3,5,7,3′,4′-pentahydroxyflavone; Fig. 1). In recent decades, quercetin has been the subject of a large number of biological studies (Boots et al., 2008; Dajas, 2012; Gibellini et al., 2011; Harwood et al., 2007; Okamoto, 2005; Russo et al., 2012). In contrast, the biological activity of quercetin glycosides has been studied to a lesser extent. For instance, in 2012, the Web of Science database shows 1489 records on quercetin, 482 records on rutin and only 49 records on isoquercitrin. However, isoquercitrin has been attracting increasing research attention (Fig. 2) due to its presence in plant-derived food and a growing array of its biological activities. Moreover, our recently developed biocatalytic method for the production of pure isoquercitrin from rutin (Gerstorferová et al., 2012; Křen et al., 2010; Weignerová et al., 2012) attracts the interest of the food and pharmaceutical industry. While pharmacological reviews of rutin have been published recently (Chua, 2013; Sharma et al., 2013), no survey on isoquercitrin is available to date. In this review we summarize the current knowledge of the biochemical and pharmacological activities of isoquercitrin, and also its safety and/or possible adverse effects with respect to its potential use in food supplementation.

Searches in several scientific literature databases, including PubMed, Web of Science and Scopus, were conducted through March–December 2013 and papers related to isoquercitrin occurrence, production, physicochemical properties, bioavailability, metabolism, potential toxicity and pharmacological activity were selected. Articles dealing with "enzymatically modified isoquercitrin" (EMIQ, a quercetin-glycoside mixture consisting of isoquercitrin and its α-glucosylated derivatives (Salim et al., 2004)), called sometimes "α-glucosyl isoquercitrin", and "enzymatically decomposed rutin" (consisting partly of isoquercitrin and quercetin (Hasumura et al., 2004)) were also included in this review.

1.1. Occurrence and production/preparation

It is reasonable to assume that isoquercitrin, being the monoglucoside of the most abundant natural flavonoid quercetin, is ubiquitously distributed in the plant kingdom. For instance, isoquercitrin is one of the bioactive components of the medicinal plant St. John's wort (*Hypericum perforatum* L.; Paulke et al., 2006) and it is commonly found in fruits, vegetables, cereals and various plant-derived beverages such as tea and wine (Hasumura et al., 2004). The first isolation of isoquercitrin was accomplished from the seed pods of *Cercis canadensis* L. (eastern redbud; Douglass et al., 1949). Recently, the occurrence of isoquercitrin has been reported e.g. in *Rosa soulieana* Crépin flowers (Yang et al., 2013), *Eucommia ulmoides* Oliv. leaves (Dai et al., 2013), *Crataegus pinnatifida* Bge. (Chinese hawberry) fruits (Juříková et al., 2012), *Crataegus azarolus* L. (azarole) leaves (Belkhir et al., 2013), flowering shoots of *Caragana arborescens* Lam. (Siberian peashrub; Olennikov et al., 2013), leaves of *Arbutus unedo* L. (strawberry tree; Males et al., 2013), in various *Allium* species (Vlase et al., 2013b, 2013a), in extracts from amaranth leaves, flowers, stems and seeds (Kraujalis et al., 2013), and in pistachio nuts (*Pistacia vera* var. Kerman; Fabani et al., 2013). Phenol-Explorer, the first comprehensive database on polyphenol content in foods (Neveu et al., 2010), lists 36 items containing between 0.0067 (kiwi juice) and 41.95



	R^1	R^2	R^3
Quercetin	OH	OH	OH
Isoquercitrin	*O*-β-D-glucopyranosyl-	OH	OH
EMIQ	[α-D-glucopyranosyl]$_{0\text{-}7}$-(1,6)-*O*-β-D-glucopyranosyl-	OH	OH
Rutin	α-L-rhamnopyranosyl-(1,6)-*O*-β-D-glucopyranosyl-(rutinosyl-)	OH	OH
Quercitrin	*O*-α-L-rhamnopyranosyl-	OH	OH
Hyperoside	*O*-β-D-galactopyranosyl-	OH	OH
Spiraeoside	OH	*O*-β-D-glucopyranosyl	OH
Isorhamnetin	OCH_3	OH	OH
Tamarixetin	OH	OCH_3	OH
Kaempferol	OH	OH	H

Fig. 1. Structures of selected quercetin derivatives and other flavonoids related to isoquercitrin and its metabolism.