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Endogenous and exogenous mediators of quercetin bioavailability

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Abstract

Quercetin is a dietary flavonol that has poor and highly variable bioavailability. Epidemiological studies suggest that higher dietary intakes of quercetin decease cardiovascular disease (CVD) risk. However, experimental findings examining its cardioprotective activities are inconsistent, thereby precluding a full understanding of its health benefits. Bioavailability of dietary constituents is a critical mediator of their health benefits. Thus, a better understanding of the factors regulating quercetin bioavailability is expected to support its potential role in managing CVD risk. This review provides an update on the evidence describing endogenous and exogenous factors responsible for the limited and highly variable bioavailability of quercetin. It focuses on pharmacokinetics studies in clinical and animal models, while also describing strategies aimed at improving quercetin bioavailability to better realize its cardioprotective activities *in vivo* that are routinely observed *in vitro*. Although significant advances have been made in understanding determinants of quercetin bioavailability, additional research in controlled trials is needed to more comprehensively examine dose–response effects, whether its cardioprotective activities improve in response to its greater bioavailability, and if the putative health benefits of quercetin are mediated directly or indirectly from one or more of its metabolites generated during xenobiotic metabolism.

Keywords: Quercetin; Bioavailability; Pharmacokinetics; Cardioprotective activities; Metabolism

1. Introduction

Quercetin is a dietary flavonol found widely in fruits, vegetables and nuts [1]. It exists primarily as quercetin glycoside in nature [2] and consists of quercetin aglycone conjugated to sugar moieties such as glucose or rutinose (Fig. 1) [3]. Major dietary sources include lettuce, chili pepper, cranberry, onion, black chokeberry, tomato, broccoli and apple (Table 1) [4], which contribute to an estimated dietary intake of 6–18 mg/day in the United States, China and the Netherlands [5–7]. Benefits of quercetin on human health are controversial due to studies *in vitro* supporting its cardioprotective and anticancer activities (reviewed in Refs. [8,9]), whereas clinical findings are equivocal with some supporting health benefits and others failing to support this relation [10,11]. Quercetin bioavailability, which is generally poor and characterized by high intersubject variability [12,13], is a critical mediator of its bioactivities. Thus, a need exists to better understand the determinants regulating its bioavailability to more fully realize its health benefits. Although factors influencing polyphenol bioavailability have been discussed [14], this review specifically focuses on dietary and endogenous factors contributing to the limited and highly variable bioavailability of quercetin. It also discusses strategies to improve quercetin bioavailability, particularly in the context of advancing an understanding of its putative cardioprotective activities in humans.

2. Quercetin metabolism

Quercetin metabolism is complex and involves intestinal uptake and/or deglycosylation, glucuronidation, sulfation, methylation, possible deglucuronidation and ring fission (Fig. 1). Various quercetin metabolites are generated following its biotransformation. Thus, factors regulating absorption, metabolism and elimination are important mediators of its bioavailability.

2.1. Quercetin absorption

The site and manner in which quercetin is absorbed depends upon its chemical structure. Studies using an *in situ* intestinal perfusion rat model indicate that quercetin aglycone absorption occurs at both the stomach and small intestine [15,16]. Although mechanisms explaining gastric absorption of quercetin aglycone remain unclear, studies in Caco-2 cell monolayers support that intestinal absorption of quercetin aglycone occurs primarily by passive diffusion and secondarily by organic anion transporting polypeptide (OATP) [17]. Contrasting quercetin aglycone, glycosylated forms of quercetin (quercetin glucoside, quercetin rutinoside) are not absorbed in the stomach [15]. At the small intestine, however, specific quercetin glycosides (quercetin glucosides, quercetin galactoside, quercetin arabinoside) are deglycosylated to quercetin aglycone prior to absorption [18]. This

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is mediated by lactase phlorizin hydrolase (LPH), a β-glucosidase residing at the brush border [19]. Subsequently, quercetin aglycone is passively absorbed [20]. Interestingly, quercetin rutinoside is absorbed in the colon following deglycosylation [21], which appears to be mediated by gut microbiota-derived β-glucosidase [22] that generates quercetin aglycone and facilitates its colonic absorption [21]. Studies in an *in vitro* model of anaerobic human fecal fermentation showed that 60% of quercetin rutinoside was degraded to 3,4-dihydroxyphenylacetic acid within 2 h by colonic microbiota [23]. This suggests that most quercetin rutinoside is initially deglycosylated to quercetin aglycone prior to degradation to 3,4-dihydroxyphenylacetic acid rather than being available for colonic absorption as quercetin aglycone. Future studies are expected to better define potential health benefits of quercetin metabolites [24] and the influence of gut microbiota composition on their formation.

Table 1
Quercetin content of select foods.[a]

Food	Quercetin (mg/100 g)
Lettuce (red)	40.27
Chili pepper	32.59
Cranberry	17.34
Onion (red)	17.22
Onion (yellow)	12.65
Black chokeberry	8.90
Tomato	4.56
Broccoli	4.25
Apple	2.47

[a] Data adapted from the Phenol-Explorer database; quercetin aglycone in foods was determined by HPLC after acid or alkaline hydrolysis [4].

2.2. Xenobiotic metabolism of quercetin

Quercetin is a dietary xenobiotic and its biotransformation occurs through xenobiotic metabolism [25]. In general, xenobiotic metabolism consists of three phases acting independently and/or additively to limit xenobiotic absorption and accumulation: phase I modification, phase II conjugation and phase III elimination [26]. Phase I metabolism of quercetin has not been reported, but it is structurally similar to the flavone apigenin, which participates in cytochrome P450 metabolism, the primary class of phase I metabolizing enzymes [27]. Phase II conjugation of quercetin at the small intestine involves glucuronidation, sulfation and methylation, as evidenced by the appearance of

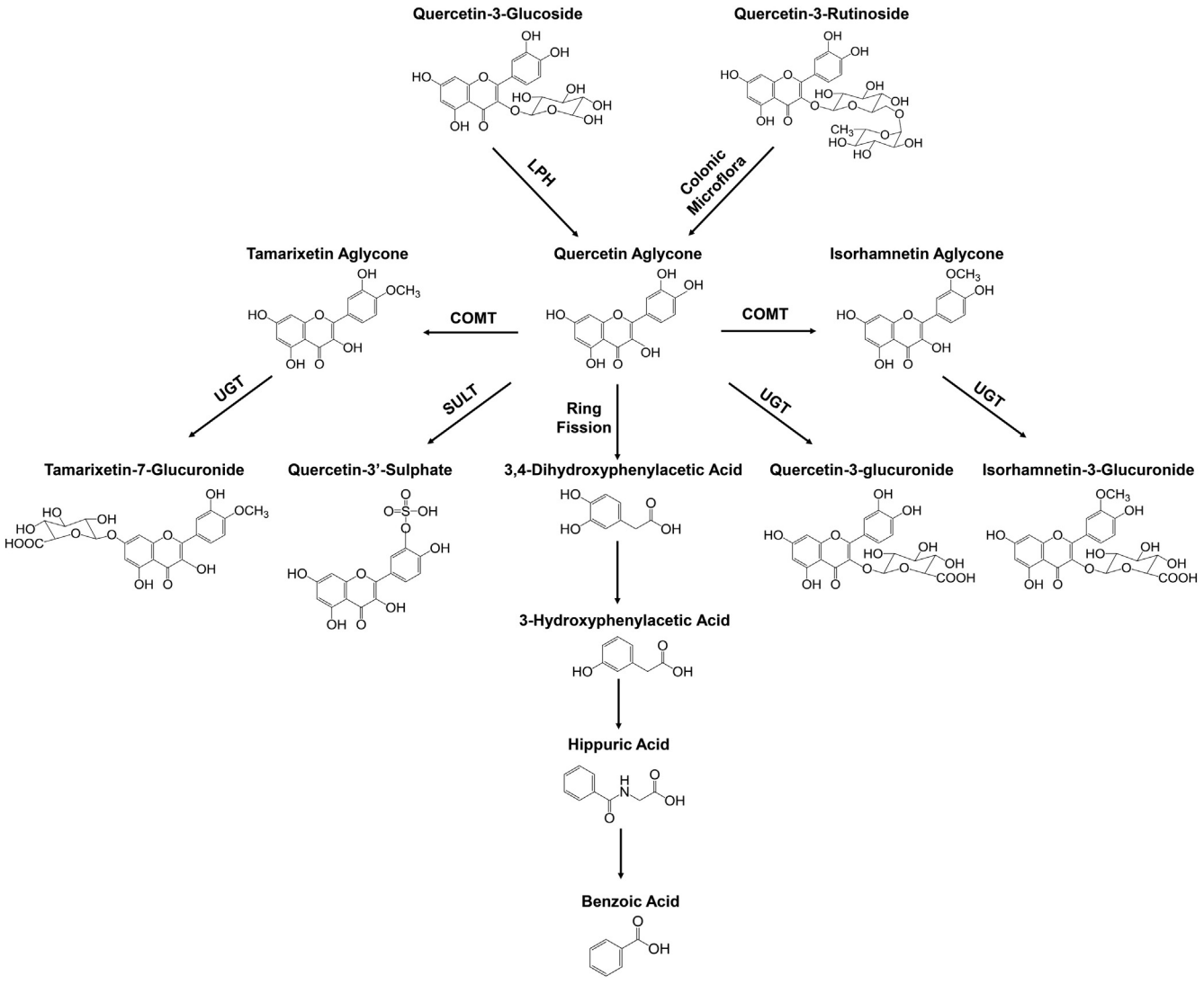

Fig. 1. Schematic representation of quercetin biotransformation. Adapted from several references [35,37,105,106]. Abbreviations: COMT, catechol-*O*-methyl transferase; LPH, lactase phlorizin hydrolase; SULT, sulfotransferase; UGT, uridine 5′-diphospho-glucuronosyltransferase.