Absorption, metabolism, and excretion of (−)-epicatechin in humans: an evaluation of recent findings\(^1,2\)

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Flavan-3-ols, such as (−)-epicatechin (I in Figure 1), and their oligomeric derivatives, procyanidins, are major components in the human diet and can occur in substantial amounts, especially in cocoa, tea, apples, red wine, and berries (1). There is a wealth of data linking consumption of such foods, most notably cocoa-based products, with reduced incidences of morbidity and mortality from cardiovascular diseases (2). (−)-Epicatechin can, at least partially, be causally linked with the beneficial effects associated with consumption of flavan-3-ol– and procyanidin-rich foods (2, 3). Unraveling the mechanism by which (−)-epicatechin mediates these effects involves knowledge of the fate of flavan-3-ols within the body after their ingestion.

Although questions remain, human dietary intervention studies have shown that after oral intake, (−)-epicatechin is absorbed into the epithelium of the small intestine, where it undergoes phase 2 metabolism. Depending on the amount ingested, food matrix effects, and other factors (4), the main metabolites—(−)-epicatechin-3′-glucuronide (II), (−)-epicatechin-3′-sulfate (III), and 3′-methyl-(−)-epicatechin-5-sulfate (IV)—reach their peak plasma concentration 1–3 h after intake (5, 6). Subsequent urinary excretion of these and other metabolites has ranged from 21% to 50% of (−)-epicatechin intake.

In this issue of the Journal, Actis-Goretta et al (7) report on the intestinal absorption, metabolism, and excretion of (−)-epicatechin in humans based on the use of a Loc-I-gut intestinal perfusion technique, which has been used previously to investigate certain aspects of drug metabolism (8). A multilumen perfusion catheter was introduced into the small intestine and 3 balloons inflated to isolate two 20-cm segments of the jejunum. The upper balloon was positioned ~20 cm below the papilla of Vater. As a consequence, when (−)-epicatechin was introduced into the proximal and distal segments of the catheter, this enabled biliary excretion of flavan-3-ols to be monitored by analysis of perfusates collected from the lumen above the upper balloon.

Using 6 volunteers, 50 mg (172 μmol) of (−)-epicatechin was introduced into isolated jejunum sections, which were then perfused for 2.5 h. An average of 23.4 mg of unchanged (−)-epicatechin was recovered along with 0.84 mg of metabolites, indicative of low-level efflux of metabolites formed in the enterocytes back into the lumen of the jejunum. This finding shows that ~50% of the administered (−)-epicatechin was absorbed into the systemic circulation. Corroborating previous findings (4), (−)-epicatechin metabolites reached submicromolar peak plasma concentrations 1 h after the initiation of perfusion. Urinary excretion ranged from 1.2 to 5.9 mg, which corresponds to 2.4–11.8% of the amount of perfused (−)-epicatechin. Although the estimated amount of (−)-epicatechin absorption from the jejunum segments and the plasma pharmacokinetics are similar to data obtained in human dietary interventions, urinary excretion of metabolites after perfusion was well below the 21–50% of intake observed after ingestion of differing amounts of (−)-epicatechin from various dietary sources (4). Arguably, this reflects the fact that absorption in the perfusion model occurred in a 20-cm section of jejunum compared with that occurring during passage through the full ~6-m length of the small intestine after ingestion.

Actis-Goretta et al (7) observed that the main metabolite effluxing back into the lumen of the jejunum was (−)-epicatechin-3′-sulfate, whereas (−)-epicatechin-3′-glucuronide was present in higher amounts in plasma and urine. Although the significance of this finding is unclear, it could be postulated that the sulfate formed in enterocytes was preferentially being effluxed back into the lumen of the jejunum, whereas (−)-epicatechin-3′-glucuronide was absorbed into the circulatory system to a greater extent. Over the 2.5-h incubation period, 0.84 mg of metabolites, corresponding to a surprisingly small 1.6% of the perfused (−)-epicatechin, effluxed from the wall of the jejunum back into the lumen. This is much lower than would be anticipated from studies in which either green tea or Concord grape juice was provided to ileostomists, in the course of which ~90% of the (−)-epicatechin recovered in ileal fluid was sulfated (9, 10). To put the perfusion figure into perspective, compared with the ileal fluid data, and assuming a constant efflux per centimeter of duodenum/jejunum, an ~30-fold greater efflux of (−)-epicatechin-3′-sulfate would have been anticipated.

One novel aspect of the study is that the use of the perfusion model enabled enterohepatic recirculation of flavan-3-ols to be directly determined for the first time. Over the 2.5-h perfusion period, 2.6–18.4 μg of metabolites were excreted in the bile of individual volunteers. This is equivalent to 0.005–0.04% of the perfused (−)-epicatechin, showing that enterohepatic recirculation

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of metabolites of the flavan-3-ol is, at best, a minor event, assuming that the perfusion model is adequate for drawing conclusions in the context of dietary intake under lifelike conditions. In consideration of this question, and because dietary intake of (−)-epicatechin will almost always lead to the concomitant ingestion of other flavan-3-ol stereoisomers and procyanidins, it would be important to establish the impact this may have on the data obtained with the perfusion model. The same is true when considering the role of the dietary background, a known factor in the regulation of enzymes involved in flavan-3-ol absorption and metabolism. It is tenable that adherence to a low–flavan-3-ol diet would be important to establish the impact of dietary intake on health.

Overall, the use of the perfusion model provided valuable insights into the metabolism and excretion of dietary (−)-epicatechin after its absorption from the small intestine. However, studies in ileostomists indicate that ~50% of ingested (−)-epicatechin is not absorbed in the small intestine and passes to the large intestine where colonic microbiome-mediated catabolism results in the formation of 5-(hydroxyphenyl)-γ-valerolactones and hydroxyphenylvaleric acids (11, 12). Research is therefore required on the formation of these colonic catabolites, their plasma pharmacokinetic profiles, and potential bioactivity, because this represents an important part of the (−)-epicatechin bioavailability equation, and thus an essential element for the assessment of the impact of flavan-3-ol intake on health.

The author had no conflicts of interest to declare.

REFERENCES