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Review

Interindividual differences in phytochemical metabolism and disposition

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Abstract

Many phytochemicals, the bioactive nonnutrient compounds found in plant foods, possess biologic effects associated with reduced risk of various diseases such as cancer. Genetic variation in pathways affecting absorption, metabolism, and distribution of phytochemicals is likely to influence exposure at the tissue level, thus modifying disease risk in individuals. Few studies have examined these gene-phytochemical interactions in humans. In this review, we discuss the sources of variation in metabolism and disposition of phytochemicals, and focus on two aspects of phytochemical handling that have received some attention: the impact of intestinal bacteria and genetically polymorphic phase II, conjugating enzymes.

Keywords: Phytochemical; Gut bacteria; Genetic polymorphism; Phase II biotransformation enzyme; Interindividual variation

Contents

1. Introduction

Phytochemicals are bioactive nonnutrient chemical compounds found in plant foods, such as fruits, vegetables, grains, and other plant foods. They can be categorized into various groups, i.e., polyphenols, organosulfur compounds, carotenoids, alkaloids, and nitrogen-containing compounds. The polyphenols are some of the most studied compounds and can be further divided into flavonoids (including flavonols, flavones, catechins, flavanones, anthocyanidins, and isoflavones), phenolic acids, stilbenes, coumarins, and tannins [1].

Many phytochemicals are potent effectors of biologic processes and have the capacity to influence disease risk via several complementary and overlapping mechanisms [1–5]. In theory, genetic variation in pathways affecting absorption, metabolism, and distribution of phytochemicals is likely to influence exposure at the tissue level. Similarly, genetic variation in the pathways within which these compounds interact can alter biological response. However, beyond a few well-recognized conditions (e.g., glucose-6-phosphate dehydrogenase and vicine and covicine: favism), little is known about the biologic effects of genetic variation on these gene-phytochemical interactions in humans, particularly as it relates to cancer risk. Further, some phytochemicals undergo bacterial modification to produce metabolites that are more biologically active than the parent compounds. Few studies have systematically addressed the factors that contribute to the substantial variation in the metabolism and disposition of phytochemicals *in vivo*. Two aspects of phyto-

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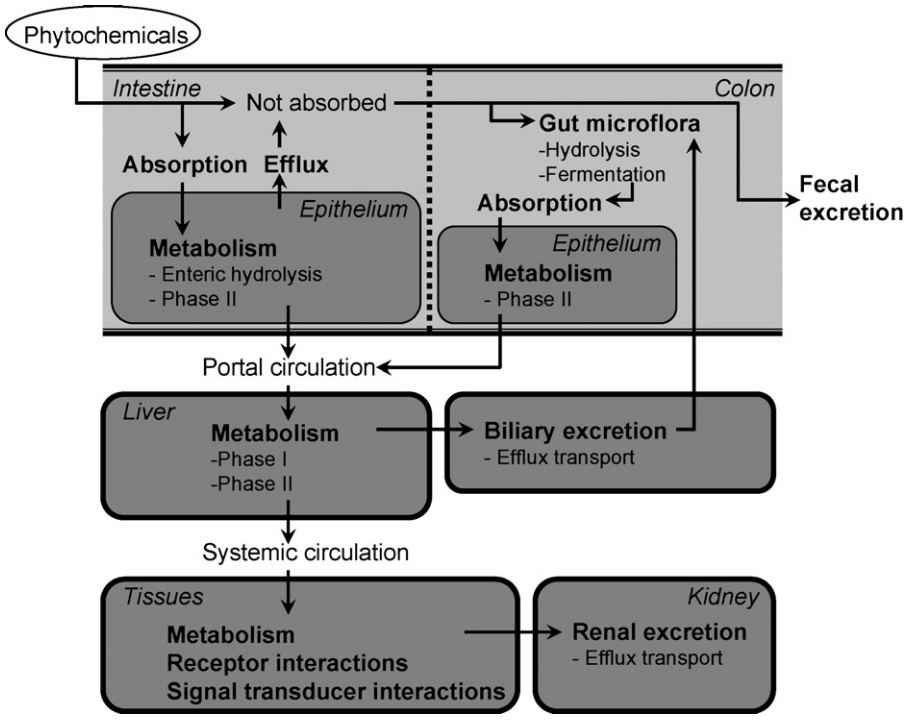

Fig. 1. Sources of variation in phytochemical metabolism and disposition.

chemical handling that are receiving some attention, particularly in relation to specific phytochemicals, are the impact of intestinal bacteria and genetically polymorphic phase II, conjugating enzymes.

2. Sources of variation in phytochemical metabolism and disposition

Researchers investigating the pharmacokinetics of phytochemicals in humans have observed substantial variation (reviewed in [6,7]). Circulating concentrations of phytochemicals, such as psoralens, lignans, and the flavonoids naringenin and hesperitin, can vary widely among individuals even in the context of controlled feeding studies [8–10]. The process of phytochemical disposition, like that of disposition of drugs and other xenobiotics, involves absorption, metabolism, distribution, and excretion, and each of these parts may contribute to pharmacokinetic variability (Fig. 1) [11].

Many phytochemicals are present in plant foods as glycosides or other conjugates and need to be hydrolyzed in order to be absorbed [7]. This hydrolysis can be carried out by brush border membrane-bound β-glucosidases (e.g., lactase phlorizin hydrolase) or by gut bacterial β-glucosidases in the lower small intestine and colon. Once absorbed, aglycones undergo extensive first-pass metabolism in the gut epithelium or liver, with many compounds being conjugated with glutathione, glucuronic acid or, to a lesser extent, sulfate. Conjugation in the intestinal epithelium and liver by UDP-glucuronosyltransferases (UGT) and sulfotransferases (SULT) results in conjugates that are excreted in urine and bile. Those that are re-excreted through the bile duct are deconjugated by bacterial β-glucuronidase and can undergo enterohepatic recycling.

The transcellular transport of ingested food ingredients across the intestinal epithelium is another important factor determining bioavailability upon oral intake. For many phytochemicals and other xenobiotic compounds, this transcellular transport is dependent on the activity of membrane-bound, ATP-binding cassette (ABC) transport proteins, which are able to export the compounds from intestinal cells. ABC transporters can efflux a variety of conjugated and unconjugated compounds from the intestinal cells, either to the basolateral blood side, facilitating absorption, or back into the intestinal lumen, reducing bioavailability. The intestinal ABC transporters include P-glycoprotein (Pgp/MDR1/ABCB1), multidrug resistance proteins (MRPs/ABCCs) and breast cancer resistance protein (BCRP/ABCG2/ABCP/MXR) and these transporters are typically located specifically in the apical (intestinal luminal side) or basolateral (blood/plasma side) membrane of the enterocytes [12]. Animal and cell-based studies have demonstrated a role for P-gp and BCRP and other transporters in regulating the uptake of various flavonoids and other phytochemicals [13,14]. Polymorphisms have been identified in ABCB1, ABCC1, ABCC2, and ABCG2; however, their impact on drug disposition *in vivo* are not well understood [15–17] and the implications for their effects on phytochemical efflux are unknown.

As with other xenobiotics, some phytochemicals undergo phase I reactions in the liver. Several studies have shown, using human liver microsomes or monitoring metabolites *in vivo* in pharmacokinetic studies, that hydroxylation can occur at various positions on lignans, isoflavones, and other flavonoids, producing an array of novel secondary oxidation products [18–22]. However, oxidation products appear to be minor metabolites of most polyphenols, probably due to rapid conjugation of the would-be phase I substrates in the intestinal epithelium and the