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Flavonoids and the gastrointestinal tract: Local and systemic effects

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ABSTRACT

The gastrointestinal (GI) tract plays a central role in the absorption, distribution, metabolism, and excretion of flavonoids, which ultimately define the health effects of these bioactives. These aspects are modulated by the interactions of flavonoids with other dietary components, environmental factors, the host, and the GI microbiota. Flavonoid can target molecules in the luminal content, the different GI tract cell types, and the microbiota. Importantly, flavonoid actions at the GI tract can have an impact systemically, e.g. on glucose homeostasis, lipid and energy metabolism, or cardiovascular risk factors. The beneficial actions of flavonoids at the GI include their capacity to: i) protect the intestinal epithelium against pharmacological insults and food toxins; ii) modulate the activity of enzymes involved in lipid and carbohydrate absorption; iii) maintain the intestinal barrier integrity; iv) modulate the secretion of gut hormones; v) modulate the GI tract immune system; vi) exert potential anti-colorectal cancer activity; and vii) shape microbiota composition and function. Further understanding of the mechanisms mediating the effects of flavonoids on the intestine (and its microbiota) is of critical importance given the relevance of the GI tract on sustaining overall health and of the widespread recommendations of increasing the intake of plant bioactives.

1. Introduction

The gastrointestinal (GI) tract, and particularly the intestinal barrier (Wells et al., 2017), plays a central role in sustaining health. The multiple functions of the intestinal epithelium include: i) nutrient absorption; ii) to act as a barrier providing a line of defense against the entrance of bacteria, bacterial toxins and byproducts, and toxins present in ingested foods; iii) to maintain the GI tract immune homeostasis; and iv) to regulate important aspects of body energy metabolism including satiety and energy expenditure. Furthermore, the microbiota present in the intestinal lumen is a key contributor to whole body physiology.

The cross talk among host, diet, environmental factors, and the microbiota has been found to either sustain health or to underlie the pathophysiology of common diseases and unwanted conditions, e.g., inflammatory bowel diseases (IBD), celiac disease, diabetes, obesity-associated insulin resistance, and non-alcoholic fatty liver disease (NAFLD) (Fasano and Shea-Donohue, 2005; Odenwald and Turner, 2017).

The provision of nutrients and bioactives that can optimize GI functions is a theme of current relevance. In this direction, this review addresses current knowledge of the actions of dietary flavonoids regulating GI tract physiology, including their interactions with the gut microbiota. Chemically, flavonoids are constituted by two aromatic rings (A and B) linked through three carbons that usually form an oxygenated heterocycle (C-ring). This C ring is characteristic of each flavonoid subfamily. Among the subfamilies, monomers differ in the type, location and number of substituents (e.g. hydroxyl groups), and some flavonoids can also form oligomers. We will focus on three major flavonoid subfamilies, i.e. flavanols and their polymers (proanthocyanidins), flavonols and

Abbreviations: CRC, colorectal cancer; DPP-IV, dipeptidyl peptidase IV; EC, (−)-epicatechin; EGCG, (−)-epigallocatechin gallate; GLP-1, glucagon-like peptide-1; GLP-2, glucagon-like peptide-2; GI, gastrointestinal; IBD, inflammatory bowel diseases; LPS, lipopolysaccharides; NAFLD, nonalcoholic fatty liver disease; T2D, type 2 diabetes; TJ, tight junction; TNFα, tumor necrosis factor alpha.

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anthocyanins. These three families were selected based on their abundance in the diet, and the growing body of experimental evidence pointing to their beneficial actions at the GI tract.

2. The GI tract and flavonoid metabolism

We will only discuss general aspects of the role of the GI tract on flavonoid absorption and metabolism; this review will not address specific and chemical aspects of flavonoid metabolism given that they have been recently and extensively reviewed (Crozier et al., 2010; Kay et al., 2017; Williamson and Clifford, 2017). It has been well established that flavonoid bioavailability at the GI tract is determined by flavonoid structure, interactions with the food matrix, the activity of GI hydrolytic enzymes, the composition of the microbiota, and intestinal epithelial cell transporters (reviewed in (Gonzales et al., 2015). Flavonoids can be absorbed as parent compounds, after conjugation (e.g. methylation, sulfation) and/or after other chemical modifications. Flavonoids can be metabolized both by enzymes present in intestinal epithelial cells and to a large extent by the microbiota. Overall, after ingestion, flavonoids have three main potential metabolic fates, which define their molecular targets and their biological activities (Fig. 1). The first is to exert direct effects at the GI tract, which can be mediated by parent compounds or metabolites. Such effects can be of considerable importance given the high concentrations flavonoids can reach in the stomach and in the upper part of the intestine. Examples of these actions are those exerted on GI tract epithelial, endocrine and immune cells, and those exerted on the gut lumen content, e.g. direct antioxidant actions. Local actions can also in part underlie flavonoid systemic actions, e.g. changes in GI tract hormone release, which affects systemic glucose homeostasis. Secondly, flavonoids can interact with the microbiota leading to changes in microbiota profiles, e.g. benefiting the growth of beneficial bacteria. This metabolism of flavonoids by the microbiota leads to the production of smaller molecules that can be absorbed, entering the circulation where they are able to reach distal organs (Williamson and Clifford, 2017) (Fig. 1). For example, the flavan-3-ol (−)-epicatechin (EC) is metabolized by the microbiota to 5C-ring fission metabolites, i.e. 5-(hydroxyphenyl)-γ-valerolactones and 5-(hydroxyphenyl)−γ-hydroxyvaleric acids, which are absorbed and, as evaluated through urinary metabolites, account for 42% of the ingested EC (Borges et al., 2017). Importantly, while flavonoid polymers (e.g. proanthocyanidins) are poorly or not absorbed at the GI tract, their metabolism by the microbiota leads to compounds, e.g. valerolactones and phenolic acids, that are absorbed and can have systemic effects (Appeldoorn et al., 2009; Zhang et al., 2016).

The third potential fate is the biotransformation of flavonoids by intestinal epithelial cells. In this case, conjugates formed in the intestinal epithelium can either be transported into the bloodstream or alternatively, secreted back into the gut lumen, e.g. secretion to the lumen of EC sulfated by epithelial cells (Actis-Goretta et al., 2013), where they may be further metabolized and/or exert local biological actions.

Thus, the initial metabolism of flavonoids at the GI tract is highly relevant to flavonoid health effects as metabolism can modify flavonoid absorption and flavonoid metabolites can be biologically more or less active than the parent compounds. In summary, flavonoids and their metabolites can exert their biological actions both locally and systemically.

3. Flavonoids and the GI tract in health and disease

Flavonoids' actions at the GI tract can target the lumen content and/or the different cell types that are involved in sustaining GI tract physiology. The intestinal monolayer is mainly composed of: i) intestinal epithelial cells involved in nutrient absorption, immunoglobulin transcytosis, preservation of barrier integrity and regulation of trans- and paracellular transport; ii) goblet cells which produce the mucins that act as the first physical barrier against bacteria and toxins and iii) Paneth cells which secret bactericidal peptides. Immune cells located at the lamina propria act in conjunction with the above mucosal cells to integrate the GI

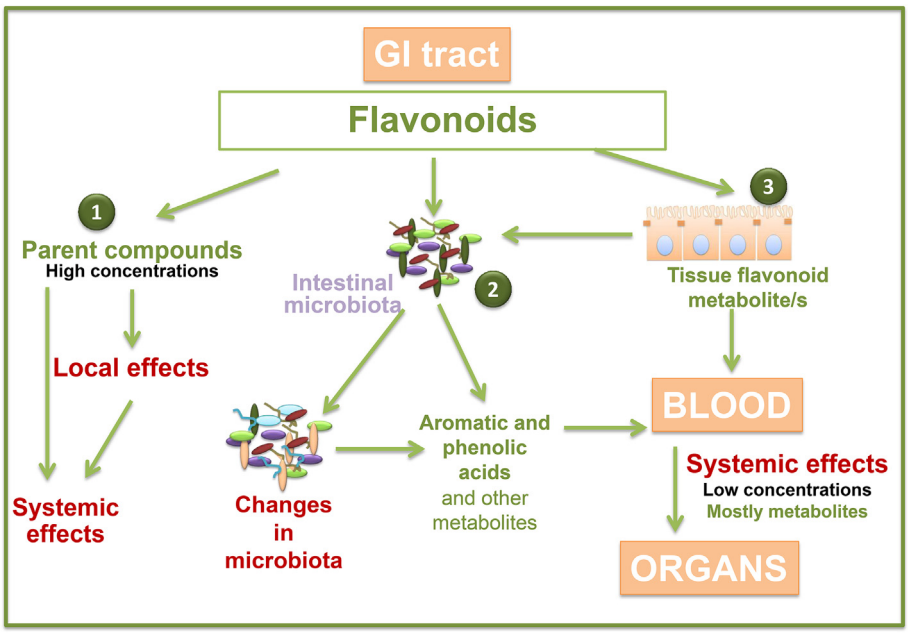

Fig. 1. Fate of dietary flavonoids at the GI tract. At the GI tract dietary flavonoids can (**1**) as parent compounds exert local effects favored by their high concentrations, (**2**) interact with the microbiota changing its profile and/or be metabolized mainly to aromatic and phenolic acids which can be absorbed (systemic effects) and/or exert local effects, and (**3**) be metabolized, usually to conjugates of the parent compounds by intestinal epithelial cells; subsequently metabolites may be absorbed (systemic effects) or excreted to the gut lumen (local effects). Local effects can also extend systemically, e.g. when they lead to the secretion of gut hormones with systemic actions.

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