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## REVIEW

### Bioavailability of dietary phenolic compounds: Review

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#### KEYWORDS

Phenols;  
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#### ABSTRACT

Phenolic compounds are ubiquitous in plant-based foods. High dietary intake of fruits, vegetables and cereals is related to a decreased rate in chronic diseases. Phenolic compounds are thought to be responsible, at least in part, for those health effects. Nonetheless, phenolic compounds bioaccessibility and biotransformation is often not considered in these studies; thus, a precise mechanism of action of phenolic compounds is not known. In this review we aim to present a comprehensive knowledge of the metabolic processes through which phenolic compounds go after intake.

## Biodisponibilidad de compuestos fenólicos dietéticos: Revisión

### PALABRAS CLAVE

Fenoles;  
Biotransformación;  
Metabolismo.

### RESUMEN

Los compuestos fenólicos son ubicuos en alimentos de origen vegetal. La alta ingesta de frutas, vegetales y cereales está relacionada con un bajo índice en padecimientos crónicos. Se cree que los compuestos fenólicos son, en parte, responsables de este efecto benéfico. Sin embargo, la bioaccesibilidad y biotransformación de los compuestos fenólicos generalmente no es considerada en este tipo de estudios. Por lo tanto, no se ha podido obtener un mecanismo de acción de los compuestos fenólicos. En este trabajo, presentamos una revisión de literatura de los procesos metabólicos a través de los cuales los compuestos fenólicos son sometidos después de ser ingeridos.

### CITA

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## INTRODUCTION

Phenolic compounds constitute a large and an important group of phenylpropanoids produced by plants as secondary metabolites. Phenolic compounds have an aromatic ring and several hydroxyl groups attached to it. Phenolic compounds can be classified into different groups. They are grouped as a function of the number of phenolic rings that they contain and the radicals that bind these rings to another one<sup>1,2</sup>.

Phenolic compounds have received considerable attention because their dietary intake is related to lower incidence of chronic diseases, such as cancer, diabetes, Alzheimer's disease and cardiovascular diseases. Cereals, fruits, and vegetables are rich sources of phenolic compounds. In fact, the health benefits of their dietary intake have been related, at least in part, to their phenolic compounds content<sup>3</sup>.

## FACTORS AFFECTING THE BIOAVAILABILITY OF DIETARY PHENOLIC COMPOUNDS

In nutrition science, bioavailability is defined as the fraction of an ingested nutrient or compound that reaches the

systemic circulation and the specific sites where it can exert its biological action. Bioavailability depends on proper absorption, release of a dosage form and presystemic elimination. Therefore bioavailability also depends on the route of administration and dosage form used, but can vary from one individual to another<sup>4,5</sup>.

Bioavailability is related to other two concepts bioaccessibility and bioactivity. In this sense, bioaccessibility is described as the amount of any food constituent that is released from the food matrix, detectable in the gut, and that may be able to pass through the intestinal barrier<sup>6</sup>. This is very important because only the compounds that are released from the food matrix or absorbed in the small intestine are potentially bioavailable and bioactive<sup>7</sup>.

Furthermore, it was recently proposed that once a compound is absorbed it is inevitably bioactive, therefore it was suggested that the concept of bioaccessibility includes bioactivity<sup>8</sup>. Nonetheless, it is important to note that the fact that a compound is bioaccessible does not always imply it is bioactive.

It is important to mention that bioavailability is influenced by phenolic structure, food processing and matrix, host, among others; besides all this factors can interact with each other and influence phenolic compounds bioavailability, which makes harder to define the exact mechanisms of action of

phenolic compounds. Nonetheless, in this work we will focus on glycosylation and food matrix.

### Glycosylation

Phenolic compounds exist as free aglycones and glycoside forms. The last one can be as O-glycosides or as C-glycosides, with a number of sugars, glucose is the most commonly encountered, followed by galactose, rhamnose, xylose and arabinose, while mannose, fructose, glucuronic and galacturonic acids are unusual<sup>9,10</sup>.

Aglycones and polyphenols bound to glucose, galactose or xylose are absorbed in the small intestine after deglycosylation by  $\beta$ -glucosidase and lactase phlorizin hydrolase<sup>11</sup>, these enzymes releasing the aglycone within the intestinal lumen for absorption by a diffusion mechanism. Phenolic compounds bound to rhamnose must reach the colon to be hydrolyzed by bacterial rhamnosidases prior to its absorption<sup>12</sup>.

Flavonoids bound to sugars as  $\beta$ -glycosides are considered non-absorbable, only aglycones are able to pass through the gut wall. The major sites of flavonoid metabolism are the liver and the colonic flora. In the liver occurs O-methylation, sulfation and glucuronidation of hydroxyl groups improving flavonoid absorption; moreover, flavonoid glycosides are hydrolysed only by colon microorganisms, after this they can be absorbed<sup>13</sup>.

Most of *in vivo* studies show gastric absorption of aglycones as quercetin and daidzein, while glycosides are poorly absorbed<sup>12</sup>. However, Hollman and Katan observed that quercetin glycosides from onions were absorbed far well than the pure aglycone. Isoflavones aglycones are absorbed in the stomach, while their glycosides are absorbed in the intestine<sup>11</sup>.

Within the glycosylated polyphenols, anthocyanins appear to be an exception, since the predominant forms in blood are their intact glycosides. Some authors have suggested the existence of a specific mechanism of anthocyanins absorption at the gastric level, which could involve transport via gastric bilitranslocase<sup>12,14,15</sup>.

### Food matrix

The biological properties and bioavailability of some polyphenols depend largely on their release from the food matrix and their subsequent interaction with target tissues. Today, the food matrix is considered as the factor most decisive in the bioavailability and absorption of dietary polyphenols<sup>16</sup>.

Most cereal phenols have covalent interactions with glycosides from the cell wall, forming ester linkages which are not hydrolysed by Phase I and II biotransformation enzymes, thus limiting their release into the colon to be metabolized by intestinal microbiota<sup>17,18</sup>. Such interactions depend on the specific porosity and surface properties of the cell wall that can measure between 4 and 10mm diameter which restricts the penetration of molecules with high molecular weight polyphenols (>10kDa)<sup>19</sup>. These bound phenols are also denominated conjugated.

Free and some conjugated phenolic acids are thought to be readily available for absorption in the human small and large intestines<sup>12,20</sup>, however, those covalently bound to indigestible polysaccharides can only be absorbed after being released from cell structures by digestive enzymes or microorganisms in intestinal lumen<sup>20,21</sup>. The bound phenolic acids have very low bioavailability because the bran matrix severely hinders their access to the necessary enzymes (such as ferulate esterases, xylanases) that contribute to their release in the human gastrointestinal tract<sup>18,21,22</sup>.

In addition, during mastication of plant foods, cells are disrupted and polyphenols are released from cell; this can cause phytochemicals interact with components of dietary fibre as cellulose, hemicellulose and pectin, which affects bioavailability by increasing or decreasing it<sup>23-25</sup>.

Furthermore, some phenolic acids such as chlorogenic and caffeic acids, can form interactions with proteins, however, these interactions proved to be slightly disrupted during an *in vitro* digestion process and does not affect its bioavailability and absorption<sup>26</sup>.

## BIOTRANSFORMATION OF DIETARY PHENOLIC COMPOUNDS

Biotransformation of xenobiotic compounds is the process of converting lipophilic chemicals into hydrophilic chemicals; thus, making the readily absorbed compounds into readily excreted compounds. Exceptions to this process are acetylation and methylation that can decrease the water solubility of certain xenobiotics. Phenolic compounds are categorised into xenobiotic compounds because humans do not produce them. Therefore, they undergo through xenobiotic biotransformation reactions<sup>27,28</sup>.

Xenobiotic biotransformation reactions are divided

into four categories: 1) hydrolysis, 2) reduction, 3) oxidation and 4) conjugation. Nonetheless, oxidation and conjugation reactions are the most important in dietary phenol studies. These reactions can occur whether in the cytosol or cellular organelles such as microsomes or mitochondria, and the main tissues in which these processes occur are small intestine and liver<sup>27</sup>.

The structure of most dietary phenolic compounds reaching the peripheral circulation and tissues is different from the structure of those present in foods, this due to the metabolism to which they are subjected after intake<sup>11,29-31</sup>.

Some enzymes involved in these processes are phenol-sulfotransferases,  $\beta$ -glucosidase, lactase phlorizin hydrolase and UDP-glucuronosyl transferases. The absorption and bioavailability of phenolic compounds depend largely on their metabolism in the small intestine. Moreover, only compounds that are not absorbed in the stomach and small intestine are degraded by the colonic microbiota<sup>29</sup>.

Nevertheless, during mastication and gastric digestion, the structure and interactions of phenolic compounds with food matrix may be modified. This can diminish or improve their bioaccessibility in the small intestine<sup>29,32</sup>.

The resultant metabolites of these conjugation reactions are transported through blood bound mainly to albumin

and distributed to different tissues and organs. The fraction of phenol compounds not absorbed in the small intestine and that reaches the large intestine is metabolized by colonic bacteria. The action of colonic bacteria involves releasing aglycones and breakage of simple aromatic rings which may be absorbed after processing in benzoic acid derivatives and conjugation with glycine molecules, glucuronic acid or sulfate<sup>12,34</sup>.

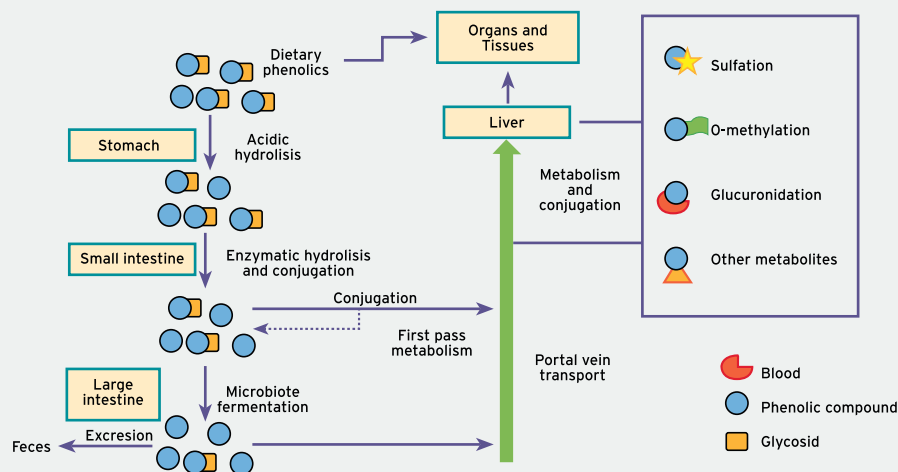
Conjugation of hydroxycinnamic acids *in vivo* has implications for the bioactivity of these compounds, because the antioxidant capacity of hydroxycinnamic acids is given by the presence of free hydroxyl groups and these are the main sites of glucuronidation and sulfation<sup>35</sup>.

### Phase I: Metabolism of Dietary Phenolic Compounds

Phase I biotransformation reactions are oxidation, reduction and hydrolysis. These reactions may increase, decrease or nullifying the biological activity of phenolic compounds<sup>27</sup>.

Reactions of phase I aim at changing the structure of the xenobiotic molecules. This modification is achieved by the introduction of hydroxyl functional groups, amino, carboxyl, among others. The purpose of this process is to increase the polarity of the xenobiotic phenolic compound for easy excretion<sup>27</sup>.

**Figure 1.** Schematic simplified representation of the metabolic pathway of plant phenols in humans after ingestion. Adapted from Vacek *et al.*<sup>33</sup>



**Hydrolysis:** Hydrolytic reactions mainly target functional groups as carboxylic acid ester, amide, lactone and others. Some of the major hydrolytic enzymes in mammals are carboxylesterases. Nevertheless, aldehyde dehydrogenases, carbonic anhydrases, carboxypeptidases, lipases and proteases have shown to have hydrolytic activity<sup>27</sup>.

The enzyme lactase-phlorizin hydrolase (LPH) is found in humans. It is present mostly in the luminal side of the enterocytes of the small intestine. LPH hydrolyses lactose to glucose and galactose. It has also been reported that LPH can hydrolyse flavonoid-O- $\beta$ -D-glycosides; this process causes a decreased polarity in the resulting aglycones, which can increase flavonoids cellular absorption<sup>36,37</sup>. Nevertheless, the activity of LPH can be inhibited by stearic factors and it may not hydrolyse glycosides like rhamnosides<sup>29</sup>.

**Oxidation:** Oxidative reactions are the most important of the phase I biotransformations of phenolic compounds. These reactions are mainly mediated by the enzymatic oxidative system regulated by microsomal cytochrome P-450 (CYP450). Human CYP450 is an enzyme with a broad spectrum of substrates. CYP3A4, a subfamily enzyme of CYP450 is involved in the metabolism of xenobiotics in gut. It has been reported that CYP3A4 interacts with dietary phenolic compounds. This suggests that coadministration of drugs and phenolic compounds may stimulate some toxicity consequences<sup>38</sup>.

The metabolic action of CYP450 on phenolic compounds depends largely on their functional groups, molecular weight, stereostructure, glycosylation, polymerization, and conjugation with other phenolic compounds<sup>38,39</sup>. Moreover, flavonoids rich in hydroxylic groups are less likely to be metabolized by CYP450; paradoxically, tea catechins (flavonoids rich in hydroxyl groups) are reported to inhibit CYP450<sup>40</sup>.

Phenolic compounds metabolism is still under-studied. However, the potential health benefits of phenols urges more studies on the subject.

### Phase II: Metabolism of Dietary Phenolic Compounds

Phase II biotransformation reactions include the addition of various chemical radicals to xenobiotic compounds. The transferred radicals are derived from endogenous, polar and high availability molecules in the body. The ultimate purpose of this process is to increase the polarity of the xenobiotic molecules. This increased polarity facilitates the excretion of xenobiotics through urine<sup>27,30</sup>.

The enzymes involved in phase II metabolism of dietary polyphenols are uridine 5'-diphosphoglucuronosyltransferase, sulfotransferases and catechol O-methyltransferase. The resultant molecules are conjugated with sulfate, glucuronide and/or methylation groups<sup>27,30</sup>.

Phenolic-conjugated compounds differ from the parental molecule in size, polarity and ionic form. Therefore, the physiological behaviour of conjugated molecules is different from the native compound. Hence, there is an increasing need in knowing the possible contribution on health of these compounds. One way to achieve this is using phenolic-conjugated compounds in *in vitro* studies<sup>30</sup>.

**Glucuronidation:** The process of glucuronidation is the main conjugation reaction in humans. Glucuronidation incorporates to xenobiotic compound the glucuronic acid molecule through uridine diphosphate glucuronic acid (UDPGA) as substrate. The reaction may also use UDP-glucose, UDP-xylose and UDP-galactose as a substrate<sup>27</sup>. The enzyme responsible for catalysing glucuronidation process is UDP-glucuronosyltransferase. This enzyme is found in the microsomal fraction of tissues as liver, kidney, skin, brain and small intestine<sup>41</sup>.

The site of glucuronidation is an electron rich nucleophilic heteroatom O, N or S. Therefore, the substrates for glucuronidation contain functional groups such as aliphatic alcohols and phenols (forming ethers O-glucuronide)<sup>42</sup>. Therefore, glucuronidation is one of the main conjugation reactions of phenolic compounds metabolism in humans<sup>43</sup>.

Steffen *et al.* (2008)<sup>44</sup> reported that glucuronide metabolites of (-)-epicatechin bind to a lesser degree to serum albumin than their aglycone counterpart does. Therefore, this can increase their absorption in enterocytes through  $\beta$ -glucuronidase or LPH activity. Moreover, aglycones lipophilicity is higher than flavonoids glycosides, therefore they can be more readily absorbed. Additionally, it would be interesting to study glucuronidation of phenolic acids and its effect on their bioaccessibility and bioactivity<sup>44</sup>.

**Acetylation and Methylation:** The acylated flavonoids such as epicatechin and epicatechin gallate are absorbed without prior hydrolysis or deconjugation<sup>11</sup>. Studies have shown that approximately 50% of the amount of (-)-epicatechin that reaches the intestinal cells are absorbed with a percentage of metabolites (especially sulfate conjugates) eliminated by efflux into the intestinal

lumen, and there exist a relatively modest elimination of (–)-epicatechin by bile, also have been observed a potential absorption of (–)-epicatechin and elimination by efflux in another segment of the gut lumen<sup>45</sup>.

Methylation differs from other conjugation reactions because it generally decreases hidrosolubility of phenolic compounds, also it masks functional groups that may be targeted by other conjugating enzymes<sup>27</sup>.

As previously stated, flavonoids are mainly glucuronidated, nevertheless, methylated metabolites have also been detected, for example, perfusion studies with catechin or epicatechin have found O-methylated and glucuronidated forms. This process is thought to be mediated by catechol O-methyltransferase (COMT)<sup>46,47</sup>.

The O-methylation of flavonoids is a natural xenobiotic transformation by the O-methyl transferases, they are high selective enzymatic systems in plants, microbes and mammals<sup>48</sup>. Methylation of phenolic compounds significantly increases their ability to be transported across biological membranes, making them more stable to metabolic changes; this can also increase their biological efficacy, particularly its antitumor activity in cell culture studies. In this sense, O-methylated flavonoids exhibited a superior anticancer activity than the corresponding hydroxylated derivatives in cell culture studies, being more resistant to the hepatic metabolism and showing a higher intestinal absorption<sup>49</sup>. Moreover, methylated flavonoids showed effects on transport proteins which play a central role in the defense of organism against toxic compounds (multidrug resistance proteins)<sup>50</sup>. It has been suggested that increasing the degree of methylation and decreasing the number of free hydroxyl groups that are available for conjugation with glucuronic acid and sulfate groups, stability and ability to transport across biological membranes is increased<sup>51</sup>.

## CONCLUSIONS

Several epidemiological studies relate a decreased rate of chronic diseases in population with high intake of fruits, vegetables and cereals. Phenolic compounds are a group of antioxidant phytochemicals that are present in those plant-based foods; a large number of studies relate health promoting effects of plant-based foods to phenolic compounds. Nevertheless, there is a lack of knowledge on the metabolism of these compounds; these have led to a

poor understanding of phenols mechanism of action. There is a need to go further into this kind of research in order to create better strategies to take advantage of phenols health promoting properties.

## COMPETING INTERESTS

Authors state that there is no conflict of interest when drawing the manuscript.

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