

## **Lead Review Article**

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# **Polyphenols: Chemistry, Dietary Sources, Metabolism, and Nutritional Significance**

Laura Bravo, Ph.D.

*Polyphenols constitute one of the most numerous and ubiquitous groups of plant metabolites and are an integral part of both human and animal diets. Ranging from simple phenolic molecules to highly polymerized compounds with molecular weights of greater than 30,000 Da, the occurrence of this complex group of substances in plant foods is extremely variable. Polyphenols traditionally have been considered antinutrients by animal nutritionists, because of the adverse effect of tannins, one type of polyphenol, on protein digestibility. However, recent interest in food phenolics has increased greatly, owing to their antioxidant capacity (free radical scavenging and metal chelating activities) and their possible beneficial implications in human health, such as in the treatment and prevention of cancer, cardiovascular disease, and other pathologies. Much of the literature refers to a single group of plant phenolics, the flavonoids. This review offers an overview of the nutritional effects of the main groups of polyphenolic compounds, including their metabolism, effects on nutrient bioavailability, and antioxidant activity, as well as a brief description of the chemistry of polyphenols and their occurrence in plant foods.*

### **Introduction**

For decades, plant polyphenols have interested scientists because they are essential to plant physiology for their contribution to plant morphology (i.e., pigmentation), they are involved in growth and reproduction and provide plants with resistance to pathogens and predators (by acting as phytoalexins or by increasing food astringency, thus making food unpalatable), they protect crops from plague and preharvest seed germination, and for other reasons. The polyphenolic profiles of plants differ between varieties of the same species. Polyphenols, there-

Dr. Bravo is with the Departamento de Metabolismo y Nutrición, Instituto del Frío (CSIC), Ciudad Universitaria s/n, Madrid 28040, Spain.

fore, have been studied for taxonomic purposes or to determine adulteration of food products. Polyphenols have several industrial applications, such as in the production of paints, paper, and cosmetics, as tanning agents, and in the food industry as additives (as natural colorants and preservatives). In addition, some phenolic compounds, the flavonoids, have applications as antibiotics and anti-diarrheal, antiulcer, and anti-inflammatory agents, as well as in the treatment of diseases such as hypertension, vascular fragility, allergies, hypercholesterolemia, and others.<sup>1-3</sup>

Polyphenolic compounds are ubiquitous in all plant organs and are, therefore, an integral part of the human diet. Until recently, most of the nutritional interest in polyphenolic compounds was in the deleterious effects caused by the ability of certain polyphenols to bind and precipitate macromolecules, such as dietary protein, carbohydrate, and digestive enzymes, thereby reducing food digestibility. Recent interest, however, in food phenolics has increased greatly because of the antioxidant and free radical-scavenging abilities associated with some phenolics and their potential effects on human health. This review offers an overview of the main nutritional effects of polyphenolic compounds as well as a brief description of the chemistry of polyphenols and their occurrence in plant foods.

In reviews of the abundant scientific literature on polyphenolic compounds, particularly those studies of the physiologic effects of plant polyphenols, most experiments are devoted to the study of a specific group of phenolic compounds—the flavonoids. This review provides a general overview of the nutritional significance of flavonoids as well as other types of food polyphenols, including simple phenols and tannins.

### **Chemistry of Phenolic Compounds**

Phenolic compounds or polyphenols constitute one of the most numerous and widely distributed groups of substances in the plant kingdom, with more than 8000 phenolic structures currently known.<sup>4</sup> Polyphenols are products of the secondary metabolism of plants. They arise

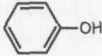

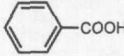
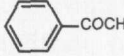
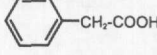
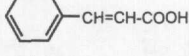
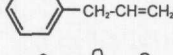
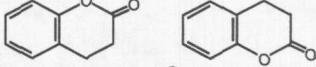
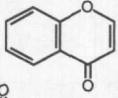
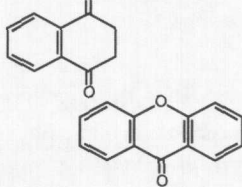
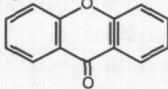
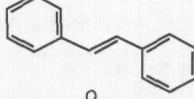
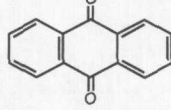
biogenetically from two main synthetic pathways: the shikimate pathway and the acetate pathway.<sup>5</sup> This is an extremely wide and complex group of plant substances.

Natural polyphenols can range from simple molecules, such as phenolic acids, to highly polymerized compounds, such as tannins. They occur primarily in conjugated form, with one or more sugar residues linked to hydroxyl groups, although direct linkages of the sugar unit to an aromatic carbon atom also exist. The associated sugars can be present as monosaccharides, disaccharides, or even as oligosaccharides. Glucose is the most common sugar residue, although galactose, rhamnose, xylose, and arabinose are also found, as well as glucuronic and galacturonic

acids and many others. Associations with other compounds, such as carboxylic and organic acids, amines, and lipids, and linkages with other phenols are also common.

According to Harborne,<sup>5</sup> polyphenols can be divided into at least 10 different classes depending on their basic chemical structure. Table 1 illustrates the basic chemical structure of the main polyphenolic compounds. Flavonoids, which constitute the most important single group, can be further subdivided into 13 classes, with more than 5000 compounds described by 1990<sup>4</sup> (Table 2). A brief description of the main classes of food phenolics follows. For more comprehensive reviews, see references 4–10.

**Table 1.** Main Classes of Polyphenolic Compounds

Class	Basic Skeleton	Basic Structure
Simple phenols	C <sub>6</sub>	
Benzoquinones	C <sub>6</sub>	
Phenolic acids	C <sub>6</sub> -C <sub>1</sub>	
Acetophenones	C <sub>6</sub> -C <sub>2</sub>	
Phenylacetic acids	C <sub>6</sub> -C <sub>2</sub>	
Hydroxycinnamic acids	C <sub>6</sub> -C <sub>3</sub>	
Phenylpropenes	C <sub>6</sub> -C <sub>3</sub>	
Coumarins, isocoumarins	C <sub>6</sub> -C <sub>3</sub>	
Chromones	C <sub>6</sub> -C <sub>3</sub>	
Naftoquinones	C <sub>6</sub> -C <sub>4</sub>	
Xanthones	C <sub>6</sub> -C <sub>1</sub> -C <sub>6</sub>	
Stilbenes	C <sub>6</sub> -C <sub>2</sub> -C <sub>6</sub>	
Anthraquinones	C <sub>6</sub> -C <sub>2</sub> -C <sub>6</sub>	
Flavonoids	C <sub>6</sub> -C <sub>3</sub> -C <sub>6</sub>	
Lignans, neolignans	(C <sub>6</sub> -C <sub>3</sub> ) <sub>2</sub>	
Lignins	(C <sub>6</sub> -C <sub>3</sub> ) <sub>n</sub>	

**Table 2. Classification of Food Flavonoids**

Flavonoid	Basic Structure
Chalcones	
Dihydrochalcones	
Aurones	
Flavones	
Flavonols	
Dihydroflavonol	
Flavanones	
Flavanol	
Flavandiols or leucoanthocyanidins	
Anthocyanidin	
Isoflavonoids	
Biflavonoids	
Proanthocyanidins or condensed tannins	

### Simple Phenols and Flavonoids

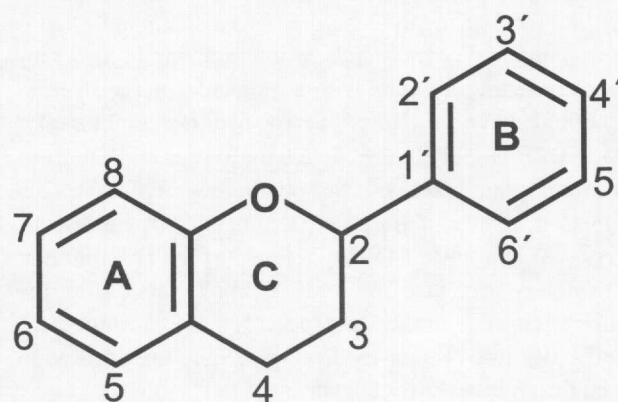
Among the most common and important low-molecular-weight phenolic compounds are simple phenolic derivatives and flavonoids. Simple phenols ( $C_6$ ), such as phenol itself, cresol, thymol, resorcinol, orcinol, etc., are widespread among different plant species, including hydroquinone and derivatives (e.g., arbutine, sesamol) and phloroglucinol. Phenolics with a  $C_6-C_1$  structure (Table 1), such

as phenolic acids (e.g., gallic, vanillic, syringic, *p*-hydroxybenzoic) and aldehydes (e.g., vanillin, syringaldehyde, *p*-hydroxybenzaldehyde), also are fairly common in higher plants and ferns. Phenylacetic acids and acetophenones ( $C_6-C_2$ ) are, however, less frequently described in the literature. All of these compounds can be found free, although their corresponding methyl and ethyl esters and glycosides occur very commonly in free and/or bound forms.<sup>5</sup>

Phenylpropanoid derivatives ( $C_6-C_3$ ) also are an important group of low-molecular-weight phenolics. Chromones are less known than coumarins, with the latter occurring naturally as glycosides (e.g., umbelliferone, aesculetin, scopoletin). The most important phenylpropanoids are the hydroxycinnamic acids (*p*-coumaric, caffeic, ferulic, sinapic) and derivatives. Cinnamyl alcohols (coniferyl alcohol or guaiacyl, sinapyl alcohol or syringyl, and *p*-coumaryl alcohol or *p*-hydroxyphenyl) form the basic constituent of lignins, and thus represent one of the major groups of plant phenolics. Phenylpropanoids and more simple phenols (benzoic acid and benzaldehyde derivatives) are usually covalently linked to cell wall polysaccharides (predominantly ester-linked to arabinose units of hemicellulose) or to the so-called core lignin.<sup>11,12</sup>

Flavonoids (Table 2) represent the most common and widely distributed group of plant phenolics. Their common structure is that of diphenylpropanes ( $C_6-C_3-C_6$ ) and consists of two aromatic rings linked through three carbons that usually form an oxygenated heterocycle. Figure 1 represents the basic structure and the system used for carbon numbering of the flavonoid nucleus. Biogenetically, the A ring usually comes from a molecule of resorcinol or phloroglucinol synthesized in the acetate pathway, whereas ring B is derived from the shikimate pathway.<sup>13</sup> Flavonoids occasionally occur in plants as aglycones, although they are most commonly found as glycoside derivatives.

Among the flavonoids, flavones (e.g., apigenin, luteolin, diosmetin), flavonols (e.g., quercetin, myricetin, kaempferol), and their glycosides are the most common

**Figure 1.** Basic structure and numbering system of flavonoids.

compounds. They are widespread in the plant kingdom, with the exception of algae and fungi. Flavonols occur as *O*-glycosides, but flavone *O*-glycosides and *C*-glycosides are very common,<sup>14</sup> with the latter characterized for possessing a carbon-carbon linkage between the anomeric carbon of a sugar molecule and the C-6 or C-8 carbon of the flavone nucleus. Unlike *O*-glycosides, sugars in *C*-glycosides are not cleaved by acid hydrolysis. Flavanones (e.g., naringenin, hesperidin) also can occur as *O*- or *C*-glycosides and are especially abundant in citrus foods and prunes. The variability of this group of flavonoids is noteworthy, with about 380 flavonol glycosides and 200 different quercetin and kaempferol glycosides described to date.<sup>4</sup> Isoflavones (e.g., genistein, daidzein), with ring B of the flavone molecule attached to the carbon 3 of the heterocycle, especially occur in legumes.

Flavonoids (e.g., catechin, epicatechin, gallo catechin) are the monomeric constituents of the condensed tannins, although they are also very common as free monomers. Anthocyanins are the most important group of water-soluble plant pigments and are responsible for the color of flowers and fruits of higher plants. The term anthocyanin refers to the glycosides of anthocyanidin (e.g., pelargonidin, malvidin, cyanidin). In addition to glycosylation, common linkages with aromatic and aliphatic acids, as well as methyl ester derivatives, also occur. Anthocyanins and polymeric pigments formed from anthocyanins by condensation with other flavonoids are responsible for the color of red wine.<sup>15</sup>

Simple phenols and flavonoids represent the vast majority of plant phenolics. Most of these compounds are of relatively low molecular weights and are soluble according to their polarity and chemical structure (degree of hydroxylation, glycosylation, acylation, etc.). Some of them, however, can be linked to cell wall components (polysaccharides, lignin). Because of the nature of the ester linkages, these compounds can be solubilized in alkaline conditions or are otherwise retained in the fiber matrix.

### Tannins

Unlike the previously described groups of plant phenolics, tannins are compounds of intermediate to high molecular weight. Tannins with a molecular mass of up to 30,000 Da have been found in carob pods (Leguminosae).<sup>16</sup> Tannins are highly hydroxylated molecules and can form insoluble complexes with carbohydrates and protein. This function of plant tannins is responsible for the astringency of tannin-rich foods, because of the precipitation of salivary proteins. The term "tannin" comes from the tanning capacity of these compounds in transforming animal hides into leather by forming stable tannin-protein complexes with skin collagen.

Plant tannins can be subdivided into two major groups: (1) hydrolyzable and (2) condensed tannins. A

third group of tannins, the phlorotannins, are found only in marine brown algae and are not commonly consumed by humans.<sup>17</sup>

**Hydrolyzable tannins.** Hydrolyzable tannins consist of gallic acid and its dimeric condensation product, hexahydroxydiphenic acid, esterified to a polyol, which is mainly glucose.<sup>18</sup> These metabolites can oxidatively condense to other galloyl or hexahydroxydiphenic molecules and form high-molecular-weight polymers. As their name indicates, these tannins are easily hydrolyzed with acid, alkali, and hot water and by enzymatic action, which yield polyhydric alcohol and phenylcarboxylic acid. According to the nature of the latter, hydrolyzable tannins can be further subdivided into gallotannins, which are derived from gallic acid, or ellagitannins, which are derived from hexahydroxydiphenic acid and which take their name from the lactone ellagic acid. The best-known hydrolyzable tannin is tannic acid (Figure 2), which is a gallotannin consisting of a pentagalloyl glucose molecule that can further esterify with another five gallic acid units.

**Condensed tannins.** Condensed tannins or proanthocyanidins are high-molecular-weight polymers. The monomeric unit is a flavan-3-ol (catechin, epicatechin, etc.), with a flavan-3,4-diol or leucoanthocyanidin molecule as its precursor. Oxidative condensation occurs between carbon C-4 of the heterocycle and carbons C-6 or C-8 of adjacent units.<sup>18</sup>

Much of the literature on the condensed tannin content of different plants refers only to oligomeric proanthocyanidins (dimers, trimers, tetramers), because of the difficulty in analyzing highly polymerized molecules. Proanthocyanidins, however, can occur as polymers with degrees of polymerization of 50 and greater. The most commonly described condensed tannins have molecular weights of approximately 5000 Da, although, as previously mentioned, polymers with molecular weights greater than 30,000 Da have been discovered.<sup>16</sup> Autooxidative or enzymatic polymerization of flavan-3-ol and flavan-3,4-diol units has been suggested as the process leading to the formation of condensed tannins.<sup>19</sup> Interflavanoid linkages

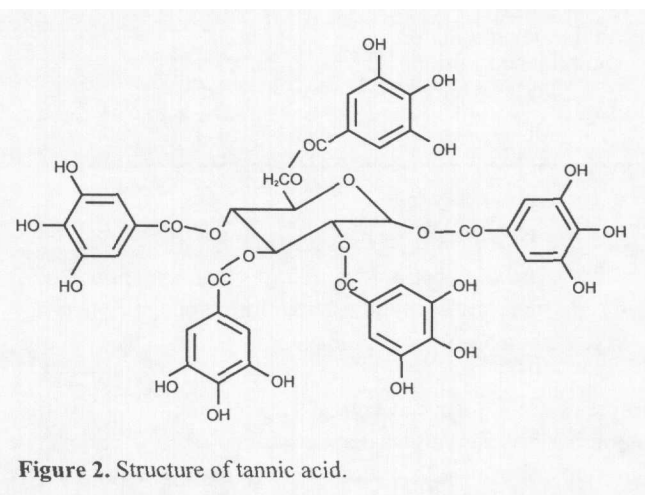


Figure 2. Structure of tannic acid.

are acid labile and yield anthocyanidins during acid hydrolysis in alcoholic solutions. This reaction is used for determination of proanthocyanidin molecules. Phlobaphene-like substances also are formed when condensed catechins are heated in mineral acid solutions from the further polymerization of these compounds.<sup>1</sup>

Oligomeric proanthocyanidins and low-molecular-weight hydrolyzable tannins are soluble in different aqueous and organic solvents, such as acetone, methanol, and water. However, high-molecular-weight condensed and hydrolyzable tannins are insoluble. In addition, when tannins form complexes with protein or cell wall polysaccharides, they remain insoluble. This insolubility of tannins is responsible for significant errors in the quantification of the polyphenolic content of plants, because polyphenols usually are analyzed in extracts, often omitting the quantification of insoluble or nonextractable tannins.

### Polyphenols in Foods

Polyphenols are almost ubiquitous in plant foods (vegetables, cereals, legumes, fruits, nuts, etc.) and beverages (wine, cider, beer, tea, cocoa, etc.). Their levels vary greatly even between cultivars of the same species. For example, the formation of flavone and flavonol glycosides greatly depends on light; therefore, the highest concentrations of these compounds are found generally in leaves and outer parts of plants, with only trace amounts in the subterranean parts of plants.<sup>14</sup> The presence of polyphenols in plant foods is largely influenced by genetic factors and environmental conditions. Other factors, such as germination, degree of ripeness, variety, processing, and storage, also influence the content of plant phenolics.<sup>1,14,15,18,19</sup>

Polyphenols are partially responsible for the sensory and nutritional qualities of plant foods. The astringency and bitterness of foods and beverages depends on the content of polyphenolic compounds. Oxidation of polyphenols during processing or storage will result in either beneficial or undesirable characteristics in food products. For example, oxidative changes such as the browning of cocoa during processing or the oxidative polymerization of tea polyphenols during the manufacture of black tea result in the development of distinctive and desirable organoleptic properties. Conversely, the enzymatic browning reaction of phenolic compounds (catalyzed by polyphenol oxidase) and nonenzymatic browning reactions are responsible for the formation of undesirable color and flavor in fruits and vegetables.<sup>20,21</sup>

There is a large body of literature on the polyphenolic composition and content of plant foods and beverages. Because of the complexity of this wide group of plant metabolites, however, many polyphenols remain unidentified. Moreover, it is difficult to compare data within the literature, owing to the lack of agreement on an appropriate method to analyze the different types or families of

polyphenolic compounds. As a result, information in the literature on the content and composition of polyphenols in plant foods is not only incomplete but sometimes also contradictory and difficult to compare.

Table 3<sup>1,21</sup> lists the polyphenolic content of different foods and beverages. Most of the polyphenols listed are phenolic acids and flavonoids (including anthocyanins, procyanidins, flavanones, flavanols, etc.); fewer are tannins. Nonetheless, as mentioned previously, tannins are often underestimated when polyphenols are analyzed only in food extracts.

As illustrated in Table 3, the polyphenolic content of plant foods can vary by several orders of magnitude. In legumes and cereals, the main polyphenols are flavonoids, phenolic acids, and tannins. Polyphenolic content in cereals is usually less than 1% of dry matter, except for some sorghum (*Sorghum bicolor*) cultivars, which can have as much as 10%. Legumes with higher polyphenolic content are the dark varieties, such as red kidney beans, black beans (*Phaseolus vulgaris*), and black gram (*Vigna mungo*). Legumes also contain isoflavones, whereas vegetables are composed primarily of flavonoid glycosides. These are present mainly in the outer parts of the plant;<sup>14</sup> roots and tubers have very low concentrations of flavonoids, with the exception of certain plants, such as onions and liquorice.<sup>22</sup> Berries are characterized by their high anthocyanin content, whereas fruits such as apples and citrus fruits are rich in phenolic acids and flavonoids, respectively. The predominant phenolic compound in fruits is flavonol, and the highest concentrations occur in the skin.<sup>1,21,22</sup> Nuts are rich in tannins; the polyphenols in oil seeds are mainly phenolic acids, and olive oil contains both phenolic acids and hydrolyzable tannins.<sup>23</sup>

The polyphenolic content of fruit juices is usually in the range of 2–500 mg/mL, although juices from certain orange varieties have much higher values (up to 7000 mg/mL) owing to their extremely high flavanone (hesperidin) contents.<sup>21,24</sup> Fermentation of tea leads to important differences in the polyphenolic composition of tea leaves: green tea is very rich in flavanols, whereas black tea contains large amounts of oxidized polyphenols (theaflavins and thearubigins).<sup>24,25</sup> Chlorogenic acid is the main phenolic constituent of coffee beans. The major polyphenol in cocoa beans is the flavanol epicatechin, and cocoa beans are also rich in anthocyanins and tannins. The polyphenols in wine include phenolic acids, anthocyanins, tannins, and other flavonoids. There are significant variations between the polyphenolic content of white and red wines (200–300 versus 1000–4000 mg/mL, respectively) and between young and aged wines, with important differences in the nature of the polyphenols present in aged wines compared with those found in free-run grape juices and young wines.<sup>15,26</sup>

**Table 3.** Polyphenolic Content of Different Plant Foods and Beverages<sup>1,21</sup>

Food/Beverage <sup>a</sup>	Total Polyphenols	Food/Beverage <sup>a</sup>	Total Polyphenols
<b>Cereals (mg/100 g dm)</b>		<b>Fruits (mg/100 g fm)</b>	
Barley	1200–1500	Blackcurrant	140–1200
Corn	30.9	Blueberry	135–280
Millet	590–1060	Cherry	60–90
Oats	8.7	Cowberry	128
Rice	8.6	Cranberry	77–247
Sorghum	170–10,260	Gooseberry	22–75
Wheat	22–40	Grape	50–490
		Grapefruit	50
		Orange	50–100
		Peach	10–150
		Pear	2–25
		Plum	4–225
		Raspberry	37–429
		Red currant	17–20
		Strawberry	38–218
		Tomato	85–130
<b>Legumes (mg/100 g dm)</b>		<b>Fruit juices (mg/L)</b>	
Black gram	540–1200	Apple juice	2–16
Chickpeas	78–230	Orange juice <sup>b</sup>	370–7100
Cowpeas	175–590		660–1000
Common beans	34–280		
Green gram	440–800		
Pigeon peas	380–1710		
<b>Nuts (% dm)</b>		<b>Beverages</b>	
Betel nuts	26–33	Tea leaves (% dm)	
Cashew nuts	33.7	Green	20–35
Peanuts	0.04	Black	22–33
Pecan nuts	8–14	Tea, cup (mg/200 mL)	150–210
		Coffee beans (% dm)	0.2–10
		Coffee, cup (mg/150 mL)	200–550
		Cacao beans (% dm)	12–18
		Wine (mg/L)	
		White	200–300
		Red	1000–4000 (6500)
		Beer (mg/L)	60–100
<b>Vegetables (mg/100 g fm)</b>			
Brussels sprouts	6–15		
Cabbage	25		
Leek	20–40		
Onion	100–2025		
Parsley	55–180		
Celery	94		
<b>Fruits (mg/100 g fm)</b>			
Apple	27–298		
Apricot	30–43		

<sup>a</sup>dm=dry matter; fm=fresh matter.

<sup>b</sup>Values for different orange varieties.

### Dietary Intake of Polyphenols

Currently, there is no accurate information available on dietary intake of polyphenols; only a few estimations are available in the literature. Kühnau<sup>1</sup> estimated the average daily intake of dietary flavonoids in the United States to be between 1 and 1.1 g/day, depending on the season. Hertog et al.<sup>27</sup> calculated the intake of two types of flavonoids—flavonols and flavones—in the Dutch diet, and found it to be 23 mg/day. This figure is significantly smaller than Kühnau's estimation of 115 mg/day for these two flavonoids, which is allegedly overestimated because of the unreliability of the analytic methods employed during the 1970s.<sup>28</sup> More recently, Leth and Justesen<sup>29</sup> estimated the intake of flavones, flavonols, and flavanones in Denmark to be 28 mg/day, similar to that reported by Hertog et al. These studies, however, only contemplate the intake of some types of flavonoids and do not consider other phenolic compounds. Moreover, it should be noted that the actual content of polyphenols in foods is usually underestimated because of omission of the analysis of insoluble polyphenols, which may be quantitatively more important

than flavonoids. Thus, accurate estimation of total polyphenolic intake is not available.

### Bioavailability of Polyphenolic Compounds

It is important for a nutritionist to know not only a person's daily intake of dietary polyphenols but also the bioavailability of those ingested polyphenols, since their nutritional significance and potential systemic effects will greatly depend on their behavior in the digestive tract. This is not a straightforward matter, however, and little is known about the absorption of polyphenols in the gastrointestinal tract, whether they are retained in the body after absorption, and what their biologic significance might be.

The absorption and metabolism of food phenolics are determined primarily by their chemical structure, which depends on factors such as the degree of glycosylation/acylation, their basic structure (i.e., benzene or flavone derivatives), conjugation with other phenolics, molecular size, degree of polymerization, and solubility. The enormous variability of this group of substances, as well as



their occurrence in plant materials as a complex mixture of phenolic compounds, creates great difficulties in the study of their bioavailability and their physiologic and nutritional effects.

Efforts in this respect, however, have been made. Experiments reported in the literature have used extracts of different plant materials that contain a mixture of soluble phenolic compounds or pure standards used as supplements in complex foods administered either to laboratory animals or to human volunteers. When plant extracts are used, it is possible to gain information on the effect of their constituent polyphenols as a group, but not on the digestive fate and specific effects of individual polyphenols. Conversely, differences in the absorption, metabolism, and physiologic effects of food phenolics administered as supplements, compared with polyphenols that are part of a complex food matrix, cannot be ruled out. Finally, the extrapolation of animal data to humans is not clear. Attention also should be given to the fact that in most cases, and mainly because of the difficulty in their analysis and characterization, the study of the digestive fate and physiologic effects of insoluble polyphenols—highly polymerized or bound tannins—is usually neglected. All of these limitations represent difficulties to overcome in studying the bioavailability of polyphenolic compounds and their nutritional significance; caution in interpreting results is necessary.

Both *in vivo* and *in vitro* studies using polyphenolic compounds with different chemical structures and solu-

bility illustrate their varying susceptibility to digestion, fermentation, and absorption within the gastrointestinal tract.<sup>30-41</sup> These findings prompted the authors to suggest a classification of polyphenolic compounds for nutritional purposes. Such classification distinguishes between extractable and nonextractable polyphenols. Extractable polyphenols are low- and intermediate-molecular-mass phenolics that can be extracted using different solvents (water, methanol, aqueous acetone, etc.) and include some hydrolyzable tannins and proanthocyanidins. Nonextractable polyphenols are high-molecular-weight compounds or phenols bound to dietary fiber or protein that remain insoluble in the usual solvents.<sup>41,42</sup>

When different samples containing both extractable polyphenols and condensed tannins (nonextractable polyphenols) were treated *in vitro* with digestive enzymes ( $\alpha$ -amylase, amyloglucosidase, and protease) and dialyzed to simulate intestinal digestion and absorption, the presence of both nonextractable and extractable polyphenols was observed in the insoluble and soluble fractions obtained (Table 4<sup>30-35</sup>). These results suggest the nonavailability of some polyphenolic compounds, mainly nonextractable polyphenols.

These results were confirmed by *in vivo* studies of rats fed fruit products (apple pulp and grape pomace) that contained both nonextractable and extractable polyphenols<sup>36,37</sup> or products with only nonextractable polyphenols (carob pod concentrate, which is rich in highly polymerized condensed tannins) and extractable polyphenols

**Table 4.** Presence of Extractable (EPP) and Nonextractable Polyphenols (NEPP) in Different Plant Materials and in Soluble and Insoluble Fractions Obtained After Enzymatic Treatments (% dry matter)

	Sample % Dry Matter	Insoluble Fraction		Soluble Fraction	
		% Dry Matter	% Original Sample	% Dry Matter	% Original Sample
Carob pod <sup>30</sup>					
NEPP	17.9	17.1	95.5	ND	—
EPP	1.3	ND <sup>a</sup>	—	0.72	55.48
Carob pod concentrate <sup>21</sup>					
NEPP	27.6	12.7	46.0	ND	—
EPP	1.36	ND	—	0.59	43.4
Spanish sainfoin <sup>32</sup>					
NEPP	7.0	5.6	80.0	ND	—
EPP	1.1	ND	—	0.30	27.3
Apple pulp <sup>33</sup>					
NEPP	1.6	1.00	62.5	ND	—
EPP	0.34	ND	—	0.21	61.7
White grape pomace <sup>34,35</sup>					
NEPP	14.5	ND	—	ND	—
EPP	4.02	1.70	42.3	1.14	28.4
Red grape pomace <sup>34,35</sup>					
NEPP	36.4	ND	—	ND	—
EPP	3.29	1.44	43.8	0.68	20.7

<sup>a</sup>ND=not determined.

(catechin and tannic acid).<sup>38-41</sup> Nonextractable polyphenols were extensively recovered in feces, confirming the resistance of these compounds to intestinal digestion and/or absorption (Table 5<sup>36-40</sup>). Conversely, extractable polyphenols were excreted only in minor amounts, suggesting that extensive digestion and/or absorption of these polyphenolic compounds occurs in the gut. Similar results were obtained by Degen et al.,<sup>43</sup> who found that extractable polyphenols from *Acacia saligna* were virtually absent in sheep and goat feces, whereas condensed tannins were excreted in substantial amounts.

Differences in the percentage of excretion between extractable and nonextractable polyphenols may result because of chemical differences (i.e., molecular size, degree of polymerization of soluble and insoluble polyphenols, nature of the phenolic bound to other food components in nonextractable polyphenols, etc.). Distinct absorption of various extractable polyphenols, depending on their extractability with different solvents, was reported by Jimenez-Ramsey et al.<sup>44</sup> These authors used <sup>14</sup>C-labeled phenolics from sorghum grains (*Sorghum bicolor*) extracted in water, ethanol, or aqueous acetone. When the polymeric <sup>14</sup>C-proanthocyanidin fraction (insoluble in water and ethanol, but soluble in aqueous acetone) was fed to chickens, no radioactivity was detected in plasma or tissues, with all the radioactivity recovered in the excrement and in the gastrointestinal tract and its contents. These results illustrate the nonabsorbable nature of some soluble tannins with a low degree of polymerization (condensed tannins or proanthocyanidins). Conversely, the <sup>14</sup>C-nontannin phenolic fractions (monomeric and oligomeric polyphenols soluble in water and ethanol) were partially absorbed from the intestinal tract and the label was extensively detected in all tissues and plasma.

Nonextractable polyphenols that are different from highly polymerized tannins (i.e., polyphenols bound to protein or dietary fiber) can be liberated under certain circumstances and thus made available for digestion. In an interesting in vivo study using insoluble <sup>14</sup>C-labeled phenolic groups bound to cell wall polysaccharides from spinach (*Spinacia oleracea*), Buchanan et al.<sup>45</sup> showed that ferulic and *p*-coumaric acids were released from the cell wall. Some phenolic acids were released in the upper intestine, partially because of the alkali-labile nature of their ester bindings with cell wall polysaccharides and partially because of the action of fermentative bacteria in the small intestine (especially in the terminal ileum). These free phenolics were promptly absorbed by the intestinal mucosa, with significant amounts of <sup>14</sup>C-label present in the body tissues or excreted in urine. However, most <sup>14</sup>C-labeled phenolic groups reached the large intestine, where radioactivity was solubilized from cell wall and free phenolic groups (coumaric and ferulic) were released upon bacterial fermentation of cell wall polysaccharides. Radioactivity could be detected in body tissues and urine, suggest-

**Table 5.** Fecal Excretion of Extractable (EPP) and Nonextractable Polyphenols (NEPP) in Rats Fed Different Polyphenol-containing Diets

	Intake (g/week)	Excretion	
		g/week	% of intake
Apple pulp <sup>36</sup>			
NEPP	0.51	0.35	68.6
EPP	0.014	0.002	14.3
Grape pomace <sup>37</sup>			
NEPP	5.31	5.21	98.1
EPP	0.19	0.06	31.6
Carob pod concentrate <sup>38</sup>			
NEPP	6.11	5.97	97.7
Tannic acid <sup>39,40</sup>			
EPP	2.06	0.10	4.6
Catechin <sup>39</sup>			
EPP	2.11	0.07	3.1

ing absorption and metabolism of these polyphenols. A fraction of <sup>14</sup>C, made up of phenols resistant to microbial degradation and not absorbed in the intestine, was excreted in feces.

### Metabolism of Phenolic Compounds

It seems evident that some polyphenolic compounds, either extractable polyphenols or solubilized phenolics, are metabolized within the gastrointestinal tract. Aglycones and free simple phenolic compounds, flavonoids (quercetin, genistein) and phenolic acids, can be directly absorbed through the small intestinal mucosa.<sup>46-49</sup> Free phenolics (cinnamic acid and derivatives such as *p*-coumaric, ferulic, caffeic, etc.) have been shown to be absorbed through the intestinal tract in both in vivo experiments of rats<sup>48</sup> and in vitro experiments of isolated rat jejunum.<sup>49</sup> Conversely, glycosides must be hydrolyzed to their corresponding aglycones before absorption. Because mammals lack the appropriate  $\beta$ -glycosidases, it was thought that absorption in the small intestine did not occur.<sup>50-52</sup> It has been shown, however, that partial absorption of quercetin glycosides takes place in the upper intestine, probably owing to the action of glycosidases from bacteria that colonize the terminal ileum.<sup>28,47,53</sup> Most glycosides, however, pass into the large intestine, where they are hydrolyzed by the cecal microflora, rendering free aglycones. The mediation of bacterial enzymes in the bioavailability of phenolic glycosides was clearly proved by Griffiths and Barrow,<sup>54</sup> who showed that flavonoid glycosides were excreted as such in the feces of germ-free rats. Bacterial fermentation of carbohydrates would also liberate phenolics bound to dietary fiber, which would be metabolized like the extractable polyphenols.

In the colon, aglycones are absorbed through the gut



epithelium and methylated and/or conjugated with glucuronic acid or sulfate in the liver. The main organ involved in the metabolism of polyphenols is the liver, although the implication of other organs such as the kidneys or the intestinal mucosa cannot be ruled out, since they contain the enzymes involved in polyphenol metabolism.<sup>52</sup>

Conjugated and 3'-*O*-methylated derivatives have been detected in the plasma of rats administered flavanols (catechin<sup>51,52</sup>), flavonols (quercetin, rutin, and isorhamnetin<sup>46,55,56</sup>), and isoflavones (genistein<sup>57</sup>). These metabolites are secreted in the urine or in the bile. In this case, they can enter an enterohepatic cycle when deconjugated by the action of the colonic microflora and reabsorbed. Alternatively, they can be fully metabolized and converted into simple phenolic acids after hydrolysis of their flavone structure (opening of the heterocycle) mediated by bacterial enzymes. The hydroxylation pattern will determine the susceptibility of polyphenols to bacterial degradation, with the absence of hydroxyl groups preventing ring cleavage.<sup>28,51</sup> The phenolic acids formed as fission products, such as free soluble phenolics, are absorbed through the intestinal mucosa and excreted in the urine.<sup>28,50-52,58</sup>

Although evidence of the absorption and metabolism of polyphenols in the gut exists, less is known about the efficiency of such uptake and the permanence of phenolic compounds or their conjugates and derivatives in the body. Animal studies with <sup>14</sup>C-labeled phenolics indicate that only partial absorption takes place. Thus, only 20% of the <sup>14</sup>C-quercetin administered to rats was absorbed, 30% was excreted, and the remaining 50% was metabolized, yielding phenolic acids and CO<sub>2</sub>.<sup>59</sup> Similarly, King et al.<sup>47</sup> reported an absorption of about 20% of the soy isoflavones administered to rats, with a fecal excretion of approximately 21% of the ingested dose. No differences between the aglycone and the glycoside were observed in this experiment. Conversely, Buchanan et al.<sup>45</sup> showed that 19% of the gavaged <sup>14</sup>C-phenolics (*p*-coumaric and ferulic acids) bound to cell wall polysaccharides were excreted in rat feces. About 20% of the dose was excreted in urine and more than 34% of the label was incorporated into body tissues 18 hours after gavage; long-term permanence of phenolic compounds was not studied.

Human experiments, although restricted to the study of flavonoids, also show only partial absorption of polyphenols. Absorption of orally administered quercetin in healthy ileostomized individuals varied between 24% and 52% of the ingested aglycone and glycoside, respectively.<sup>53</sup> Soybean isoflavones administered to humans were absorbed by healthy volunteers in a range varying from 9% to 21%, depending on the isoflavone.<sup>60</sup> Blood concentrations of total catechins of 0.17 μmol/L after ingestion of black tea and up to 0.55 μmol/L after green tea were reported recently;<sup>61</sup> these data agree with those reported by Lee et al.,<sup>62</sup> who estimated that the absorption of tea cat-

echins corresponded to about 0.2–0.9% of the ingested dose.

Only short-term data are available on the permanence of absorbed phenolics in the body. This point is of great importance, because some of the physiologic effects of food polyphenols depend on their circulating levels (i.e., antioxidant capacity). Manach et al.<sup>46</sup> observed that concentrations of quercetin metabolites in the plasma of rats adapted or not adapted to a flavonoid-rich diet did not drastically vary 16 hours after reaching maximum. These authors suggested that the rate of elimination of quercetin metabolites was relatively low and that high plasma concentrations can be easily maintained with a regular supply of flavonoids in the diet.

Van het Hof et al.<sup>61</sup> studied the kinetics of absorption and elimination of tea catechins. These investigators found that maximum blood levels occurred 2 hours after tea ingestion and that elimination half-life varied between 4.8 and 6.9 hours for green and black tea catechins, respectively. These values differed from those reported by Hollman et al.,<sup>63</sup> who found that maximum plasma quercetin concentrations after the ingestion of onions, which are rich in quercetin, occurred after 3.3 hours and that the elimination half-life was 16.8 hours. Therefore, there seem to be important differences in the rate and extent of absorption and elimination of dietary polyphenols, depending on their chemical structure.

### Fermentation of Polyphenolic Compounds

As mentioned previously, fermentative microflora play a crucial role in the metabolism of some polyphenolic compounds. However, not all phenolics are equally susceptible to bacterial degradation, because certain compounds, such as insoluble condensed tannins, are excreted in feces apparently without being affected by the colonic bacteria. In addition to their susceptibility to microbial degradation, dietary polyphenols also can influence intestinal microflora and their fermentative capacity toward other food components.

In vitro fermentation of highly polymerized condensed tannins from carob pod using rat cecal contents as the inoculum showed that these condensed tannins were not affected by fermentative microflora.<sup>41,64</sup> Also, the levels of short-chain fatty acids (SCFA), such as acetic, propionic, and butyric acid, which are the primary end products of colonic fermentation, were not affected by the presence of carob pod condensed tannins in the incubation system. This suggests that highly polymerized phenols do not affect intestinal microflora. Similarly, cecal contents of rats fed diets containing condensed tannins from grape pomace did not affect normal in vitro fermentation of apple pectin used as inoculum.<sup>65</sup> This suggests that condensed tannins do not affect the colonic microflora or their fermenta-

tive capacity.

Conversely, the analysis of cecal contents of rats fed water-soluble condensed tannins from quebracho (*Schinopsis quebracho-colorado*), composed of monomers, dimers, trimers, and oligomers, showed depolymerization of polymers, degradation of monomers, and accumulation of simple phenolic compounds;<sup>66</sup> this indicates bacterial degradation of soluble condensed tannins of a low degree of polymerization. Contrary to highly polymerized compounds, quebracho soluble tannins depressed the production of SCFAs, showing a bacteriostatic effect.

In vitro fermentation of the flavonoid quercetin for 72 hours yielded a reduced production of propionate and butyrate but a high production of acetic acid; this suggests that quercetin is fermented by bacterial microflora with the opening of the aromatic ring, which would explain the high production of acetic acid originating from the complete hydrolysis of the flavonoid and the absence of other SCFAs typically produced during carbohydrate fermentation.<sup>67</sup>

Similarly, in vitro fermentation of the flavonoid catechin and of tannic acid (with gallic acid as the constituent monomeric phenol) also was characterized by a high relative production of acetic acid after 72 hours of fermentation, but not after 24 hours, suggesting that the proposed hydrolysis of the aromatic ring needs long fermentation times.<sup>40,41</sup> Tannic acid caused a reduced production of total SCFAs, indicating an inhibitory effect of this type of phenolic structure on the fermentative microflora. This effect also was observed by Arrigoni et al.,<sup>64</sup> who reported that soluble polyphenols (both flavonoid and gallic acid structures), but not nonextractable polyphenols (condensed tannins), slow down the fermentability of polysaccharides.

On the other hand, in vitro fermentation assays using rumen microbes showed different degradation of quebracho tannins: soluble and extractable proanthocyanidins were partly fermented, whereas nonextractable condensed tannins bound to protein were not degraded.<sup>68,69</sup> Both quebracho and tannic acid decreased the production of SCFAs.<sup>68</sup> Similarly, certain phenolic acids (ferulic, *p*-coumaric, and cinnamic acids) have been reported to inhibit the growth of rumen microorganisms<sup>70</sup> and their fermentative effect on carbohydrates and protein,<sup>71,72</sup> although they are metabolized by the rumen microflora.<sup>73,74</sup>

In summary, the degradation and absorption of polyphenols within the gastrointestinal tract depend on the nature not only of the phenolic compound but also of the intestinal microflora, which fermentative effect on other dietary components will be affected, conversely, by the type of polyphenolic compound.

## Nutritional and Physiologic Effects of Polyphenols

### *Influence of Polyphenols on the Digestibility of Macronutrients*

Probably one of the best-known properties of polyphenolic compounds is their capacity to bind and precipitate protein. Although this protein-binding capacity is common to most polyphenols, thanks to their high degree of hydroxylation, low-molecular-weight phenols are unable to precipitate protein, and it has been shown that oligomers must contain at least three flavonol subunits to effectively precipitate protein.<sup>75</sup> Highly polymerized tannins are the most effective precipitators of protein. Tannin-protein complexes are usually established through hydrogen bonds and hydrophobic interactions, without the contribution of covalent or ionic bonds.<sup>75,76</sup>

With regard to nutrition, tannins traditionally have been considered antinutrients because the presence of tannins in plant foods is usually accompanied by a reduced digestibility of protein and a subsequent increase in fecal nitrogen excretion.<sup>77-81</sup> Similarly, in vitro protein digestibility also is reduced in the presence of condensed tannins.<sup>30,35,82,83</sup> However, the ability of polymeric proanthocyanidins (condensed tannins) to form insoluble protein-polyphenol complexes is limited to those molecules physically accessible to soluble proteins. Highly polymerized tannins (nonextractable polyphenols) are insoluble compounds that usually form part of a complex matrix with cell wall polysaccharides,<sup>84</sup> or insoluble tannin granules,<sup>16</sup> which greatly reduces their protein-binding ability. These effects are more pronounced with soluble oligomeric proanthocyanidins or hydrolyzable tannins,<sup>85</sup> since the simple phenols have no ability to precipitate protein.<sup>75</sup>

The increased fecal nitrogen excretion after ingestion of tannin-containing diets is likely caused by an enhanced elimination of endogenous protein rather than by a reduced digestibility of dietary protein. This was confirmed by Shahkhalili et al.<sup>86</sup> and Mole et al.<sup>87</sup> in experiments of rats fed <sup>14</sup>C- and <sup>15</sup>N-labeled proteins, respectively. Conversely, fecal protein excreted after tannin ingestion is very rich in proline.<sup>88</sup> Salivary proline-rich proteins have a very high affinity for tannins. Secretion of these tannin-binding proteins, which is thought to be a mechanism of adaptation by herbivores consuming high-tannin diets,<sup>89</sup> is induced by the presence of tannins in the diet.<sup>90</sup>

Furthermore, tannins can bind other endogenous proteins in the intestinal tract, such as digestive enzymes, and inhibit them.<sup>85,91-95</sup> This causes a reduction in the digestibility not only of protein<sup>93</sup> but of other macronutrients, such as starch and lipids.<sup>94-96</sup> Inhibition of amylolytic enzymes and the subsequent reduction of dietary carbohydrate hydrolysis can decrease the postprandial glyce-

mic response.<sup>97</sup> Likewise, polyphenols also can form complexes with polysaccharides other than those that form the plant cell wall (i.e., starch)<sup>98,99</sup> and affect the glycemic and insulinemic responses as well.

The effect of food polyphenols on lipid metabolism has not been extensively studied. Both soluble polyphenols and condensed tannins have been shown to increase fecal fat excretion.<sup>36-39,100-103</sup> In addition, hypocholesterolemic effects have been reported in animals fed diets containing grape tannins,<sup>37,102,103</sup> tannic acid,<sup>104</sup> and tea catechins,<sup>105</sup> with increased plasma levels of high-density lipoprotein (HDL) cholesterol and reduced concentrations of low-density lipoprotein (LDL) cholesterol. This hypocholesterolemic action of dietary polyphenols is mediated by an enhanced reverse-cholesterol transport and by reduced intestinal cholesterol absorption and increased bile acid excretion.<sup>101,102</sup> The exact mechanism of action, however, is not known.

### **Influence of Polyphenols on Bioavailability of Minerals**

Polyphenols can form complexes with metal cations through their carboxylic and hydroxylic groups, and thus interfere with the intestinal absorption of minerals. Numerous experiments in both humans and animals have shown that polyphenols strongly inhibit iron absorption.<sup>106-111</sup> This action has been attributed to the galloyl and catechol groups of polyphenolic compounds.<sup>106</sup> Monomeric flavonoids in green and herb teas (catechins),<sup>106-108,110</sup> phenolic acids in coffee (chlorogenic acid),<sup>106</sup> polymerized products in black tea and cocoa,<sup>111</sup> and wine polyphenols<sup>109</sup> have been shown to reduce iron bioavailability. Conversely, tannins from soybean protein, chickpeas, and red kidney beans had no significant effect on iron absorption,<sup>112</sup> suggesting a lack of effect of condensed tannins (nonextractable polyphenols). This finding was not, however, confirmed by Jansman et al.,<sup>113</sup> who reported a reduced absorption of iron and copper in pigs fed condensed tannins from fava beans.

Reduced copper absorption after consumption of tea also has been observed in humans,<sup>114</sup> but contrary results were reported by Vaquero et al.,<sup>115</sup> who observed an increased absorption of <sup>64</sup>Cu and an enhanced retention of copper in the liver of rats fed tea.

Although the chelating action of polyphenols on metals such as copper and iron can have negative effects by reducing their bioavailability, this action can be beneficial in certain circumstances. In the native state, copper and iron can be the initiators of hydroxyl radical production by the Fenton and Haber-Weiss reactions.<sup>116</sup> Chelation of these metals is one of the ways polyphenols exert their antioxidant activity.

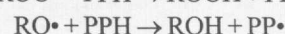
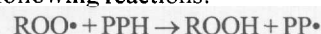
With regard to the effect of polyphenols on the availability of other minerals, chlorogenic and caffeic acids

have been shown to reduce zinc absorption in rats,<sup>117</sup> and negative effects of polyphenols also have been observed on the bioavailability of sodium<sup>118</sup> and aluminum<sup>119</sup> but not manganese,<sup>120</sup> calcium, or magnesium.<sup>113</sup>

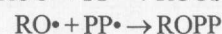
### **Antioxidant Activity of Food Polyphenols**

Recent interest in food phenolics has increased owing to their roles as antioxidants, antimutagens, and scavengers of free radicals and their implication in the prevention of pathologies such as cancer and cardiovascular disease. Epidemiologic studies have shown a correlation between an increased consumption of phenolic antioxidants and a reduced risk of cardiovascular disease<sup>121-123</sup> and certain types of cancer.<sup>123,124</sup> Similarly, moderate consumption of red wine, which is rich in polyphenols, has been associated with a low risk of coronary heart disease.<sup>125,126</sup>

Phenolic antioxidants function as terminators of free radicals and chelators of metal ions that are capable of catalyzing lipid peroxidation. Phenolic antioxidants interfere with the oxidation of lipids and other molecules by rapid donation of a hydrogen atom to radicals, as illustrated in the following reactions:



Moreover, the phenoxy radical intermediates are relatively stable; therefore, a new chain reaction is not easily initiated. The phenoxy radical intermediates also act as terminators of the propagation route by reacting with other free radicals:<sup>127</sup>



However, under certain conditions (high concentrations of phenolic antioxidants, high pH, presence of iron), phenolic antioxidants can initiate an autooxidation process and behave like prooxidants.<sup>127</sup>

The efficiency of polyphenols as antioxidant compounds greatly depends on their chemical structure. Phenol itself is inactive as an antioxidant, but *ortho*- and *para*-diphenolics have antioxidant capacity, which increases with the substitution of hydrogen atoms by ethyl or *n*-butyl groups.<sup>127</sup> Flavonoids are among the most potent plant antioxidants because they possess one or more of the following structural elements involved in the antiradical activity (Figure 3): (1) an *o*-diphenolic group (in ring B), (2) a 2-3 double bond conjugated with the 4-oxo function, and (3) hydroxyl groups in positions 3 and 5.<sup>128-130</sup> Quercetin, a flavonol that combines all of these characteristics, is one of the most potent natural antioxidants. Also, the antioxidant efficiency of flavonoids is directly correlated with their degree of hydroxylation and decreases with the presence of a sugar moiety (glycosides are not antioxidants, whereas their corresponding aglycones are antioxidants).<sup>130</sup>

Flavonoids are very effective scavengers of hydroxyl

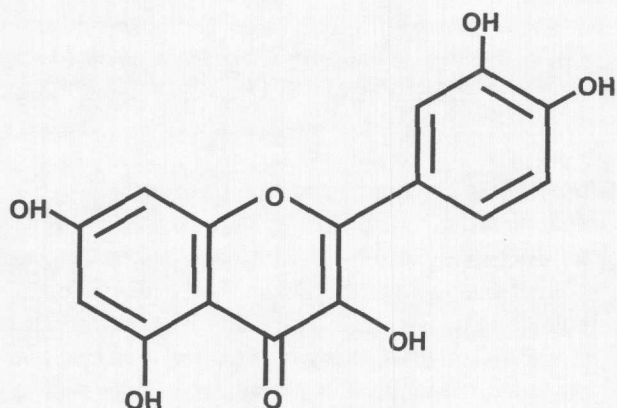


Figure 3. Structure of quercetin showing the structural characteristics related to its antioxidant capacity.

and peroxy radicals, although their efficiency as scavengers of the superoxide anion is not yet clear.<sup>129</sup> As mentioned previously, polyphenols are chelators of metals and inhibit the Fenton and Haber-Weiss reactions, which are important sources of active oxygen radicals.<sup>126</sup> In addition, flavonoids retain their free radical-scavenging capacity after forming complexes with metal ions.<sup>131</sup>

Although antioxidant activity traditionally has been attributed only to soluble phenolic compounds (extractable polyphenols), a recent report suggests that nonextractable polyphenols (polymeric proanthocyanidins and high-molecular-weight hydrolyzable tannins) are 15 to 30 times more effective at quenching peroxy radicals than are simple phenols.<sup>132</sup> Because these compounds are not absorbed, they could exert their antioxidant activity within the digestive tract and protect lipids, proteins, and carbohydrates from oxidative damage during digestion, and spare soluble antioxidants.

Most studies have shown the antioxidant activity of polyphenols using different *in vitro* models,<sup>130-140</sup> and subsequently, phenolic compounds are classified according to their antioxidant capacity or antiradical efficiency.<sup>128,141,142</sup> The role of polyphenols *in vivo* is not clear. The antioxidant efficiency of polyphenols depends on the extent of absorption and metabolism of these compounds, as well as the activity of methoxylated and conjugated forms circulating in plasma. As mentioned before, only partial amounts of food polyphenols are absorbed *in vivo*,<sup>60-63</sup> and only very low levels of tea catechins were detected in plasma after tea ingestion.<sup>61,62</sup> Nevertheless, these low concentrations seem sufficient to exert a potent antioxidant action *in vivo*, as observed in human studies<sup>143,144</sup> and as suggested by epidemiologic data.<sup>121-124</sup>

Antioxidant polyphenols, mainly flavonoids, are potent inhibitors of LDL oxidation.<sup>126,136,140,143</sup> Several mechanisms by which flavonoids exert their protective effect have been proposed: (1) reduction of free radical formation, (2) protection of  $\alpha$ -tocopherol in LDL from oxidation, (3) regeneration of oxidized  $\alpha$ -tocopherol, and (4) chela-

tion of metal ions (for a review see reference 145). Through these antioxidant actions, polyphenols exert their protective effect against cardiovascular disease. In addition, flavonoids have antithrombotic and vasoprotective effects as well as hypolipidemic effects, as discussed previously.

Different types of polyphenols (phenolic acids, hydrolyzable tannins, and flavonoids) also have been shown to have anticarcinogenic effects.<sup>146-148</sup> Polyphenols might interfere in several of the steps that lead to the development of malignant tumors, thereby protecting DNA from oxidative damage, inactivating carcinogens, inhibiting the expression of mutant genes and the activity of enzymes involved in the activation of procarcinogens, and activating enzymatic systems involved in the detoxification of xenobiotics (for a review see reference 129). Some polyphenols, however, also have been shown to have mutagenic activity in microbial assays, although contradictory results, depending on the type of assay used and type of phenolic studied, have been reported, as reviewed by Brown.<sup>149</sup>

### Conclusion

Although the number and variability of food phenolics make the study of this immense group of metabolites difficult, their nutritional significance as well as their potentially beneficial health effects call for detailed studies. Polyphenols may have important applications in the prevention and treatment of highly prevalent human diseases, such as cardiovascular disease and cancer, as well as gastric and duodenal ulcer, allergy, vascular fragility, viral and bacterial infections, etc. To fully understand the actual significance of food phenolics, it is necessary to investigate not only their bioavailability but also their mechanisms of action and their possible synergism with other constituents either in the diet or within the human body, as well as the polyphenolic content and composition of foods. These factors constitute the body of future research.

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