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In association with well-known health benefits related to the consumption of fruit- and vegetable-rich diets, research on the protective effects of plant-derived phenolic compounds (polyphenols) has developed notably in recent years. In particular, their antioxidant properties have been the objective of extensive research. However these phenolics are the target of an array of chemical reactions that, if confirmed to occur in vivo, would contribute to their health promoting effects. It is now emerging that both parent compounds and their metabolites produced after ingestion can regulate cell and tissue functions by both antioxidant and nonantioxidant mechanisms. This volume provides the latest evidence supporting these concepts.

The strategy behind the selection of the themes was to provide a comprehensive overview of the basic and applied research on phenolic compounds and their potential protective effects on health. The first chapters are on the identification, metabolism, and basic mechanisms affecting phenolic actions in biological systems. The book then develops in a series of pivotal chapters addressing the effects of flavonoids, stilbenes, and curcuminoids on cardiovascular disease, cancer, and neurodegeneration. The final chapter is on the complex functions that phenolics perform in plants, as a model that can help to better understand their effects on animal physiology. Explanations are essentially centered in applying basic biochemical mechanisms to improve nutrition and/or developing pharmacological strategies.

As being part of a series launched under the umbrella of the IUBMB, the volume was planned to tackle not only the cutting edge research, but also to provide a source for basic, educational information. The target audience includes not only scientists and health professionals but also educators and students, policymakers, food and pharmaceutical developers, and many others interested in understanding how plant-derived phenolic compounds can affect human health and so, in part, explains how fruit and vegetables play a key role in enhancing human health.


I want to especially thank the group of outstanding scientist that provided chapters of the highest quality and readability. Particular appreciation is due to prof. Angelo Azzi who was central in the planning and concretion of the book.

I dedicate this volume to my four children, Maggie, Martín, Joaquín, and Ignacio.
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1 Dietary Flavonoids and Phenolic Compounds

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INTRODUCTION

Plants synthesize a vast range of secondary metabolites with a significant portion consisting of phenolic compounds and flavonoid compounds [Crozier et al., 2006a]. These phytochemicals are structurally diverse, and many are distributed among a very limited number of species within the plant kingdom. This character allows them to act as biodiagnostic markers in chemotaxonomic studies. Phenolic compounds and flavonoids accumulate in relatively high amounts in plants and appear to have a myriad of supplemental functions in a plant’s life cycle. These include structural roles in different supporting or protective tissues, involvement in defense strategies, as attractants for pollinators and seed-dispersing animals, and as allelopathic agents, ultra violet (UV) protectants and signal molecules in the interactions between plants and their environment. One of the most versatile classes of flavonoids, the anthocyanins, protect chloroplasts from photodegradation by absorbing high-energy quanta, while scavenging free radicals and reactive oxygen species (ROS) [Gould, 2004]. Flavonols, as well as providing protection against the damaging effects of UV-B light, are also involved in promoting the growth of pollen tubes down the style to facilitate fertilization. In addition, isoflavonoids play important defense roles against pathogen and insect attack and are key signal molecules in the formation of nitrogen-fixing root nodules in legumes. After the death of plants, phenolic compounds may persist for weeks or months and affect decomposer organisms and decomposition processes in soils. Therefore, their effects are not restricted to only the plant itself but may extend to the functioning of whole ecosystems [Horner et al., 1988].

Secondary metabolites, other than providing plants with unique survival or adaptive strategies, are of commercial significance to humankind. They have been used as dyes, fibers, glues, oils, waxes, flavoring agents, drugs, and perfumes and are viewed as potential sources of new natural drugs, antibiotics, insecticides, and herbicides [Croteau et al., 2000; Dewick, 2002]. In recent years the role of phenolic compounds and flavonoids as protective dietary constituents has become an increasingly important area of human nutrition research. Unlike the traditional vitamins, they are not essential for short-term well-being, but there is increasing evidence that modest long-term intakes may exhibit a potential for modulating human metabolism in a manner favorable for the prevention or reduction in the risk of degenerative diseases such as cardiovascular diseases, diabetes, obesity, and cancer [Anderson et al., 1999].

HEALTH BENEFITS AND MODE OF ACTION OF FLAVONOIDS AND PHENOLIC COMPOUNDS

The rapid rise of degenerative diseases worldwide is threatening economic and social development as well as the lives and health of millions of people. It represents a major health challenge to global development in the coming century.
It is estimated that up to 80% of cardiovascular disease, 90% of Type II diabetes, and one third of cancers can be avoided by changing lifestyle, including diet [WHO, 2003]. Diet-related high cholesterol, high blood pressure, obesity, and insufficient consumption of fruits and vegetables have been cited as significant interlinking risk factors that cause the majority of these diseases. There is, therefore, increasing interest in the role of nutrition and specific dietary constituents in the prevention of such diseases. Flavonoids and phenolic compounds are prominent among dietary constituents that are the focus of such interest.

Since the 1990s a number of epidemiological studies have been carried out attempting to correlate high dietary phenolic compounds and flavonoid intake, through the consumption of fruits and vegetables, with reduced risk of degenerative diseases. Many, but not all, of these studies have indicated some degree of inverse associations between high dietary phenolic/flavonoid intake and reduction of degenerative diseases [Steinmetz and Potter, 1996; Law and Morris, 1998; Riboli and Norat, 2003]. Since oxidative stress imposed by ROS is known to play a crucial role in the pathophysiology associated with neoplasia, atherosclerosis, and neurodegenerative diseases, the potential mechanism of the protective effects of phenolic compounds and flavonoids were thought to be due to direct scavenging of free radicals [see Heim et al., 2002].

Accumulating evidence now indicates the importance of interactions between various phytochemicals in reducing the risk of various degenerative diseases [Chan et al., 2000; Mouria et al., 2002; Mertens-Talcott et al., 2003]. The combination of antioxidative agents with different modes of action is thought to increase efficacy and minimize toxicity. In a recent review by Lee and Lee [2006], the abilities of phenolic-based antioxidant therapies to decrease ROS levels was shown to produce the best health benefits through a diet rich in multiple antioxidants rather than a high dosage of a single supplement. Evidence of the potential benefits of food synergy was provided by Liu et al. [2000] when they demonstrated that a combination of fruits, such as orange, apple, grape, and blueberry, displayed a synergistic effect on antioxidant activity in vitro. The median effective dose (EC_{50}) of each fruit in combination was five times lower than the EC_{50} of each fruit alone, suggesting synergistic effects due to the combination of the four fruits. In another study, Sakamoto [2000] emphasized the importance of consuming black tea together with soybean products as commonly occurs in a typical Japanese diet. In this study, thearubigen in black tea did not alter the in vitro growth of human prostate cancer cells. However, a small amount of thearubigen (0.5 μg mL^{-1}) administered with genistein (20 μg mL^{-1}), the major isoflavone in soybean, synergistically inhibited cell growth and increased the DNA distribution at the G2 M phase of the cell division cycle by 34% compared with genistein alone [Sakamoto, 2000]. Similar conclusions were reached by Temple and Gladwin [2003] when they reviewed 200 cohort and case–control studies that provided risk ratios concerning intake of fruits
and vegetables and risk of cancer. Their studies showed that the cancer-preventing action of fruits and vegetables is most probably due to the many bioactive compounds that act in concert to prevent cancer rather than being due to one or two potent anticarcinogens.

Nutrients generally have very specific functions such as being an enzyme cofactor. In contrast, in addition to their additive and synergistic effects, phenolic compounds and flavonoids, often exhibit pleiotropic effects that in combination may reduce the risk of chronic disease. For instance, curcumin, the active constituent of turmeric (*Curcuma longa*), a root vegetable, has been shown to be beneficial in all three stages of carcinogenesis [Thangapazham et al., 2006]. Isoflavones, the bioactive ingredient in leguminous vegetables, not only cause a small reduction in blood cholesterol but also reduce blood pressure, arterial dimensions, and oxidative stress [Anderson et al., 1999]. This combined effect may cause a reduction in the risk of coronary heart disease [Kris-Etherton et al., 2004].

In addition to the complexity mentioned above, the health implications of dietary phenolic compounds and flavonoids are also dependent on the composition of the components of the diet and the bioavailability of the individual compounds under study. Accumulating evidence on the absorption and bioavailability of phenolic compounds and flavonoids in humans reveals that most of these phytochemicals are modified during absorption from the small intestine, through conjugation and metabolism, and by the large intestine, mainly through the actions of the colonic microflora, and by subsequent hepatic metabolism [Graefe et al., 2001; Manach et al., 2004; Mullen et al., 2004, 2006, 2008; Jaganath et al., 2006]. Thus, metabolites that reach the cells and tissues are chemically, and, in many instances, functionally distinct from the dietary form, and such features underlie their bioactivity [Kroon et al., 2004]. This, in addition to the fact that in most instances very low levels of dietary phenolic compounds and flavonoids are actually absorbed and appear in the bloodstream (<10 μM), implies that the concept of these compounds functioning as hydrogen-donating antioxidants in vivo appear to be an oversimplified view of their mode of action [Williams et al., 2004; Williamson and Manach, 2005; Fraga, 2007].

It has been hypothesized that cells respond to phytochemicals through direct interactions with receptors or enzymes involved in signal transduction, or through modifying gene expressions that may result in alteration of the redox status of the cell that may trigger a series of redox-dependent reactions [Williams et al., 2004]. There is now emerging evidence that flavonoids may play an important role in molecular processes especially as modulators of intracellular signaling cascades, which are vital to cellular function [Williams et al., 2004]. For example, in a recent study carried out by Mackenzie and associates (2008), a naturally occurring phenolic compound, curcumin [1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione,1] was found to deregulate signaling cascades, such as NF-κB, leading to a decreased expression of proteins involved in cell proliferation and apoptosis. In another study on Caco-2 cells, hexameric
procyanidins was found to inhibit TNFα-induced NF-κB activation, which is believed to play a central role in inflammation including human intestinal bowel disease [Erlejman et al., 2008].

There is growing evidence from human feeding studies that the absorption and bioavailability and thus bioactivity of phenolic compounds and flavonoids are very much dependent on the nature of their chemical structure. Their chemical classification and dietary occurrence is briefly discussed in the following section.

**FLAVONOIDS—STRUCTURE AND THEIR DIETARY OCCURRENCE**

To date, more than 6000 different flavonoids have been described and the number continues to increase [Harborne and Williams, 2000]. Flavonoids are polyphenolic compounds comprising of 15 carbons, with 2 aromatic rings connected by a 3-carbon bridge. According to the modifications of the central C-ring, they can be divided into different structural classes including flavonols, flavones, flavan-3-ols, flavanones, isoflavones, and anthocyanidins (Fig. 1.1). In a few cases, the 6-membered heterocyclic ring C occurs in an isomeric open form or is replaced by a 5-membered ring as in the case of chalcone. Other flavonoid groups, which quantitatively are relatively minor dietary components, are dihydroflavones, flavan-3,4-diols, coumarins, and aurones.

**Flavonols**

The flavonols are the most widespread of the flavonoids in plant food. They vary in color from white to yellow and are closely related in structure to the flavones. They are represented mainly by quercetin, kaempferol, and myricetin while the methylated derivative isorhamnetin is also quite common (Fig. 1.2). Of the various flavonols found in the diet, quercetin is the most ubiquitous. It is present in various fruits and vegetables, with especially high concentrations, 200–1000 μg g⁻¹ fresh weight, occurring in onions (Allium cepa) [Hertog et al., 1992; Crozier et al. 1997]. In a recent study by Sultana and Anwar [2008], flavonol levels were determined in 22 plant materials (9 vegetables, 5 fruits, and 8 medicinal plants). The highest concentrations were detected in the medicinal plant, moringa (Moringa oleifera) (68 μg g⁻¹ fresh weight), followed by strawberry (Fragaria spp.) (40 μg g⁻¹), peepal (Ficus religiosa) (12 μg g⁻¹), spinach (Spinacea oleraceae) (19 μg g⁻¹), and cauliflower (Brassica oleraceae) (18 μg g⁻¹).

Flavonols that accumulate in plant tissues are almost always in the form of glycosylated conjugates. The main flavonols in onions are quercetin-4’-O-glucoside and quercetin-3,4’-O-diglucoside with smaller amounts of isorhamnetin-4’-O-glucoside (Fig. 1.3) [Mullen et al., 2004].
A whole range of other quercetin conjugates such as quercetin-3-O-galactoside, quercetin-3-O-rhamnoside, quercetin-3-O-xyloside, quercetin-3-O-rutinoside, quercetin-3-O-arabinopyranoside, and quercetin-3-O-arabinofuranoside are found in apples (*Malus x domestica*) (Fig. 1.4) [Marks et al., 2008].
Figure 1.3 Main flavonol glucosides in onion.

Figure 1.4 Principal flavonol glucosides in apples.
Quercetin-3-\(O\)-rutinoside, on the other hand, is the main flavonol in tomatoes (Lycopersicon esculentum), asparagus (Asparagus officinalis), peaches (Prunus persica), and nectarines (Prunus persica var. nectarina) [Makris and Rossiter, 2001; Crozier et al., 2006c]. Quercetin-3-\(O\)-glycoside, quercetin-3-galactoside, and aquercetin arabinoside has also been detected in mangos (Mangifera indica) [Schieber et al., 2000]. Other flavonols in the diet include kaempferol-3-\(O\)-rutinoside in kiwi fruit (Actinidia deliciosa) and conjugates of myricetin in berries (Fig. 1.5) (Peterson and Dwyer, 1998).

Grapes of Vitis vinifera, grape products, and wines contain a wide range of flavonols such as quercetin, myricetin, kaempferol, isorhamnetin, quercetin-3-\(O\)-glucoside, quercetin-3-\(O\)-glucuronide, quercetin-3-\(O\)-glucoside, quercetin-3-\(O\)-galactoside, kaempferol-3-\(O\)-glucoside, and kaempferol-3-\(O\)-galactoside [Makris et al., 2006]. Tea (Camellia sinensis) infusions also contain a diverse spectrum of flavonols linked to mono-, di- and tri-saccharides [Del Rio et al., 2004].

Flavones

Flavones are structurally very similar to flavonols and differ only in the absence of hydroxylation at the 3-position on the C-ring. Flavones are mainly represented in the diet by apigenin and luteolin. Unlike flavonols, they are not widely distributed with significant concentrations being reported in only celery (Apium graveolens), parsley (Petroselinum crispum), and artichoke (Cynara scolymus) [Crozier et al., 2006a]. As a consequence their dietary intake...
is very low. Flavone conjugates such as the 7-O-(2‴-O-apiosyl)glucosides of apigenin, luteolin, and chrysoeriol (Fig. 1.6) are found in celery [Herrmann, 1976], while artichoke contains luteolin-7-O-glucoside, luteolin-7-O-rutinoside, and apigenin-7-O-rutinoside (Fig. 1.7) [Wang et al., 2003].

Substantial quantities of luteolin-7-O-glucuronide, luteolin-7-O-glucoside, and luteolin-7-O-rutinoside occur in Red Oak Leaf and Lollo Rosso, two red-leaved varieties of lettuce (*Lactuca sativa*) [Llorach et al., 2008]. Polymethoxylated flavones such as nobiletin, scutellarein, sinensetin, and tangeretin (Fig. 1.8) are found exclusively in citrus species [Crozier et al., 2006c], while diosmetin-7-O-glucuronide has been isolated from the fruits of a Chinese herb, *Luffa cylindrical*.

![Flavone conjugates occurring in celery.](image1.png)

**Figure 1.6** Flavone conjugates occurring in celery.

![Flavone conjugates found in artichoke.](image2.png)

**Figure 1.7** Flavone conjugates found in artichoke.
Red bush or rooibos tea, made from infusions of young leaves and shoots of the South African shrub *Aspalathus linearis*, and popularized by the *The No. 1 Ladies’ Detective Agency* novels of the Edinburgh University Emeritus Professor of Medical Law, Alexander McColl Smith [1999, 2000], contains a number of compounds including C-flavone glycosides in the form of isoorientin (luteolin-6-C-glucoside) and orientin (luteolin-8-C-glucoside) [Bramati et al., 2003]. Orientin and isoorientin also occur in lemongrass (*Cymbopogon citrata*) along with two other flavone C-glucosides, chrysoeriol-6-C-glucoside (isoscoparin) and 7-O-methyl-luteolin-6-C-glucoside (swertiajaponin) (Fig. 1.9) [Cheel et al., 2005].

Recent observations reveal that when flavones are methoxylated, metabolic stability and membrane transport in the intestine/liver dramatically increases,
thus improving oral bioavailability. In addition, methoxyflavones also show increased cancer chemopreventive properties when compared to the more common unmethylated flavones [Walle, 2007].

**Flavan-3-ols**

Flavan-3-ols represent the most common flavonoid consumed in the American and, most probably, the Western diet and are regarded as functional ingredients in various beverages, whole and processed foods, herbal remedies, and supplements. Their presence in food affects quality parameters such as astringency, bitterness, sourness, sweetness, salivary viscosity, aroma, and color formation [Aron and Kennedy, 2007]. Flavan-3-ols are structurally the most complex subclass of flavonoids ranging from the simple monomers (+)-catechin and its isomer (−)-epicatechin to the oligomeric and polymeric proanthocyanidins (Fig. 1.10), which are also known as condensed tannins [Crozier et al., 2006b].

The most abundant type of proanthocyanidins in plants are the procyandinids, which consist exclusively of (epi)catechin units. The less common proanthocyanidins containing (epi)afzelechin (Fig. 1.11) and (epi)gallocatechin (Fig. 1.10) subunits are called propelargonidins and prodelphinidins, respectively [Balentine et al., 1997].

Flavan-3-ols are found abundantly in fruits such as apricots (*Prunus armeniaca*), sour cherries (*Prunus cerasus*), grapes and blackberries (*Rubus* spp.) [Porter, 1988]. The seeds of grapes contain substantial quantities of (+)-catechin, (−)-epicatechin, procyanidin oligomers, and polymers [Gu et al., 2004]. Apples, on the other hand, are a good source of (−)-epicatechin and procyanidin dimers B1 and B2 (Fig. 1.12), while peaches and nectarines contain (+)-catechin, (−)-epicatechin, and proanthocyanidins including procyanidin B1 [Hong et al., 2004]. Barley, seemingly, is the only common cereal with a significant proanthocyanidin content (0.6–1.3 g kg⁻¹) [Santos-Buelga and Scalbert, 2000].

(+)-Catechin and the proanthocyanidin prodelphinidin B3 are, respectively, the major monomeric and dimeric flavan-3-ols found in barley and malt where prodelphinidin B3 is the main contributor for the radical scavenging activity [Dvoráková et al., 2007]. Proanthocyanidins have also been detected in nuts. Hazelnuts (*Corylus avellana*) and pecans (*Carya illinoensis*) are particularly rich in proanthocyanidins containing ca. 5 g kg⁻¹, whereas almonds (*Prunus dulcis*) and pistachios (*Pistachio vera*) contain 1.8–2.4 mg kg⁻¹, walnuts (*Juglans* spp.) ca. 0.67 g kg⁻¹, roasted peanuts (*Arachis hypogaea*) 0.16 g kg⁻¹, and cashews (*Anacardium occidentale*) 0.09 g kg⁻¹ [Crozier et al., 2006c]. Dark chocolate derived from the roasted seeds of cocoa (*Theobroma cacao*) is also a rich source of procyanidins [Gu et al., 2004]. Monomeric flavan-3-ols and the proanthocyanidin B2, B5 dimers, and C1 trimer are found in fresh cocoa beans (Fig. 1.13). Flavan-3-ols have also been detected in mint
Figure 1.10 Flavan-3-ol structures.
(Mentha rotundifolia), basil (Ocimum basilicum), rosemary (Rosemarinus officinalis), sage (Salvia officinalis), and dill (Anethum graveolens) [Shan et al., 2005].

Flavan-3-ols can undergo esterification with gallic acid to form catechin gallates, and hydroxylation reactions to form gallocatechins (Fig. 1.10). Gallocatechins such as \((-\)-epigallocatechin, \((-\)-epigallocatechin gallate, and \((-\)-epicatechin gallate are abundant in green tea infusions [Stewart et al., 2005]. During fermentation to produce black tea, these compounds polymerize, giving rise to theaflavins and high-molecular-weight thearubigins (Fig. 1.14) [Crozier et al., 2006c]. Other beverages such as red wine and beer are also rich in flavan-3-ols. Red wines contain oligomeric procyanidins and prodelphinidins, originating mainly from the seeds of red grapes [Auger et al., 2004]. Flavan-3-ols such as \((+\)-catechin and \((-\)-epicatechin, and the dimers prodelphinidin B3 and procyanidin B3 have been detected in beer [Crozier et al., 2006c].

**Flavanones and Chalcones**

Flavanones are mainly represented by naringenin, hesperetin, and eriodictyol, while a number of minor compounds, including sakuranetin and isosakuranetin, also occur (Fig. 1.15). Two structural features—the absence of a \(\Delta^{2,3}\) double bond
bond and the presence of a chiral center at the carbon-2—characterize flavanones [Iwashina, 2000]. In the majority of naturally occurring flavanones, the C-ring is attached to the B-ring at C2 in the α configuration.

The flavanone structure is highly reactive and has been reported to undergo hydroxylation, glycosylation, and O-methylation reactions. Flavanones are

**Figure 1.13** Monomeric flavan-3-ols and proanthocyanidin B2, B3 dimers, and C1 trimer found in fresh cocoa beans.

**Figure 1.14** Theaflavins and thearubigins present in black tea.