Review

Occurrence and biological significance of proanthocyanidins in the American diet ♠

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Abstract

Dietary intake of proanthocyanidins (PAs) has been largely unknown because of the lack of reliable values for their content in foods. Recent development of an analytical method for PAs has allowed the quantification of individual oligomers and polymers. This method has been employed to analyze food samples collected under the USDA National Food and Nutrition Analysis Program. A database of the PA content in common foods and also infant foods has been established. It has been shown that PAs account for a major fraction of flavonoids ingested in the US diet and infants and children appear to ingest more PAs than adults on the basis of body weight. These data will provide an opportunity to examine the association between PA intake and health and disease outcomes in epidemiological studies. PA analysis and the significance of PAs in nutrition and diet are reviewed.

Keywords: Proanthocyanidins; Procyanidins; Condensed tannin; Catechin; Flavonoid; Fruits; Nuts

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1. Introduction

Oligomeric and polymeric flavan-3-ols are better known as proanthocyanidins (PAs) or condensed tannins. They are ubiquitous and present as the second most abundant group of natural phenolics after lignin (Porter, 1994). The existence of PAs in common foods including cereals, fruits, vegetables, and wines affects their texture, color, and taste (Santos-Buelga and Scalbert, 2000). PAs in foods are also of interest in nutrition and medicine because of their potent antioxidant capacity and possible protective effects on human health in reducing the risk of chronic diseases such as cardiovascular diseases and cancers (Santos-Buelga and Scalbert, 2000).

PAs have been suggested to account for a significant fraction of polyphenols ingested in a western diet because of their ubiquitous existence (Santos-Buelga and Scalbert, 2000). However, there have been no data available on the daily intake of oligomeric and polymeric flavan-3-ols, because of the lack of qualitative and quantitative information on the PAs in foods, due in large part to the lack of appropriate analytical methodology and commercially available standards for oligomers. Only recently has an appropriate analytical method been developed for the measurement of PAs (Gu et al., 2002, 2004). This method has been used to quantify PAs in foods analyzed under the USDA National Food and Nutrition Analysis Program (NFNAP). These data have been used to establish a special PA database which is posted on the USDA Nutrition Data Laboratory web site (http://www.nal.usda.gov/fnic/foodcomp). This review will focus on aspects of PA analysis and the significance of PAs in the diet as related to health and disease.

2. Development of analytical methods

PAs are highly reactive and are considered as one of the most unstable natural products. They are subject to enzymatic oxidation by polyphenol oxidases as well as spontaneous oxidation. These properties plus their structural diversity and wide molecular size range make the quantitative analysis a great challenge.

Precautions are necessary in sample preparation and storage, as the procedures used can have significant effects on the results of analysis of PAs. When analysis of fresh materials is not feasible, freeze-drying has been recommended to preserve the samples. PAs were often extracted with an aqueous organic solvent; methanol has been proven to be the best solvent for the low molecular weight components, while 70% aqueous acetone is the most potent overall extraction solvent for PAs including polymers. Acidification of the solvent has been shown to increase the extractability of PAs, since the acid helps to disassociate the bonds between PAs and polar fibrous matrices (Rohr et al., 2000).

A number of methods have been developed for the quantification of PAs. The mechanisms and limitations of these methods have been reviewed (Rohr et al., 2000; Schofield et al., 2001). Only colorimetric and chromatographic methods will be discussed here, as they are the most commonly used in quantifying PAs. Colorimetric methods include the Folin-Ciocalteu method, hydrochloric acid/butanol assay, vanillin assay and 4-(dimethylamino)-cinnamaldehyde (DMAC) assay. The Folin-Ciocalteu method is a measure of total phenolics, not specific for PAs, and suffers from severe interference from other phenols, ascorbic acid, ferrous ion and cysteine (Singleton et al., 1999). In the hydrochloric acid/butanol assay, PAs are cleaved by acid to form carbocations from their extension units which are then immediately converted to anthocyanidins that can be measured to estimate PAs. The formation of anthocyanidins from PAs has been reported to be low. The reaction is influenced greatly by PA structure, presence of transition metals and complicated by side reactions (Porter et al., 1986). The vanillin assay is largely specific for flavanols. In the presence of mineral acid, vanillin condensed with PAs to give a chromophore ($\lambda_{\text{max}} = 300 \text{ nm}$). The reaction can take place at position 6 or 8 on the A ring of any flavan-3-ol subunit (Fig. 1). The absorbance values cannot be correlated either on a weight or on a molar basis and is severely influenced by co-existing anthocyanidins ($\lambda_{\text{max}} = 515 \text{ nm}$) (Price et al., 1978). Unlike the vanillin assay, the DMAC reagent only reacts with the end unit of PAs, thus giving similar molar extinction coefficients ($\varepsilon = 16000–19000$) for monomer, oligomers and polymers at $\lambda_{\text{max}} = 640 \text{ nm}$ (McMurrough and McDowell, 1978). Therefore, the DMAC method tends to underestimate polymeric PAs. Our studies also revealed that DMAC reacts with highly polymeric PAs to cause precipitation in the solvent (Gu and Prior, unpublished observation). It should be emphasized that results obtained with colorimetric methods are highly empirical. Estimations of total PAs are often expressed as catechin equivalents, which makes...
the data difficult to interpret and compare between different samples. Qualitative data, such as subunit structure, interflavan linkage types, and proportions of oligomers with different degree of polymerization (DP) are not available with any of these methods.

Various chromatographic methods exist for the PA analysis. Reversed phase liquid chromatographic methods give good separation of flavan-3-ol monomers to trimers. However, elution is unrelated to the degree of polymerization and all of the PAs with a DP value greater than 4 were eluted towards the end of the chromatogram as a broad, unresolved peak (Guyot et al., 2001). In one report, all the PAs with DP > 4 were eluted as a distinct peak at the end of the run and quantified as polymers (Peng et al., 2001). Polymeric PAs were also found to spread throughout the whole chromatogram (Rohr et al., 2000). Gel permeation chromatography allows fractionation of monomers and oligomers in order of increasing molecular weight. However in the case of PA analysis, the chromatographic mode is adsorption rather than size-exclusion; this makes the separation of PAs according to their degree of polymerization impractical beyond the level of tetramers. A tedious derivatization procedure is usually needed to minimize the adsorption and only poor resolution and recovery can be expected. Gel permeation of the native-form of PAs on TSKgel HW-40, Sephadex LH-20, or porous polystyrene-divinylbenzene has often been used for the purpose of fractionation instead of quantification (Kennedy et al., 2003; Yanagida et al., 1999).

Good separation of PAs based on molecular size was achieved on silica phase using Thin Layer Chromatography (Lea, 1978). This method has been adapted to normal phase HPLC to separate procyanidins in cocoa beans up to pentamers (Rigaud et al., 1993). Optimization of this method led to the separation of procyanidins according to the degree of polymerization up to decamers (Hammerstone et al., 1999). A major hindrance for PA analysis has been the lack of commercially available standards. Procyanidin monomer through decamers have been purified on preparative normal phase HPLC from cocoa. A composite standard was made using these purified oligomers and commercially available (−)-epicatechin (4). A method to quantify the oligomeric procyanidins has been developed using normal phase HPLC using fluorescence detection. Quantitative data obtained by four laboratories on the same cocoa and chocolate sample demonstrated close agreement, indicating that this method is reliable and reproducible (Adamson et al., 1999).

Plants contain PAs with increasing degree of polymerization. It has been reported that the lower molecular weight procyanidins are usually present in plant tissue in relatively low concentrations compared to that of larger oligomers and polymers (Czochanska et al., 1980; Foo and Porter, 1980). Although the normal phase HPLC method is clearly superior to previous methods in quantifying procyanidins, a clear drawback of normal phase HPLC is that with current technology, procyanidins beyond decamers cannot be analyzed. Further experiments indicated that polymeric procyanidins with DP > 10 could not be resolved by normal phase HPLC, but were eluted as one single peak at the end of the run. Based on this, the original method employed by Adamson et al. (1999) has been modified and optimized (Gu et al., 2002). A procyanidin fraction (DP = 36.1) purified from lowbush blueberries was used as an external polymer standard to quantify all procyanidins with DP > 10. A longer gradient was used to improve the separation of hexamers to decamers which also provided for a sharper and higher peak of polymers. It was also found that peak overlapping led to the upward baseline shift. Using a valley-to-valley integration method greatly underestimated the procyanidin content. A flat base line integration method was used in its place. The oligomeric PAs with the same DP eluted as a cluster of adjacent peaks, which were integrated from chromatograms using fluorescence detection for quantification. Monomers and oligomers (DP = 2–10) were quantified individually. All of the polymeric PAs with DP > 10, which elute as a distinct single peak in the chromatograms, were quantified collectively against the polymeric procyanidin standard (Gu et al., 2002).

The method has been extensively validated using multiple approaches including PA recovery tests, UV spectra analysis, thiolyis, and ESI mass spectra of the polymers, in an attempt to answer questions concerning the quantitative analysis of PA polymers (Gu et al., 2002). Typical questions that arise are: (1) ‘Are the polymers fully extracted from the samples?’; (2) ‘Are the polymers fully eluted from the HPLC column?’; and (3) ‘Are the polymers contaminated with non-proanthocyanidin compounds?’ Studies of overall recovery rates of standards spiked into various food matrices (rice, nuts, and tomato) were found to be similar. They ranged

Fig. 1. Flavan-3-ol monomeric units in proanthocyanidins.
from 99.5% to 81.2% for monomers through polymers, indeed showing a tendency for the extraction efficiency to decrease with the increase of molecular weight. Recovery rates appear to be satisfactory for quantitative analysis, but obviously not all matrices have been tested. The polymers that were used in these studies were those that were purified by elution from a Sephadex LH20 column which may not be the polymers that are most retained. It is possible that some polymers may coelute with ellagitannins in the case of strawberries. However, in testing the fluorescent response of various phenolic compounds including gallic acid, it was found that fluorescent detection is largely specific for flavan-3-ols. Thus, responses of contaminants should be minimized. In addition, the UV spectra of the polymeric peaks obtained on the diode array detector superimposed with the UV spectra of the monomers and dimers. The polymers that were used in these studies were those that were purified by elution from a Sephadex LH20 column, but obviously not all matrices have been tested.

### Table 1

<table>
<thead>
<tr>
<th>Constituents</th>
<th>Relative response factors of fluorescence detection</th>
<th>Detection limit of fluorescence detection (ng)</th>
<th>Relative response factors of 280 nm UV detection</th>
<th>Detection limit at 280 nm UV (ng)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monomers</td>
<td>1.00</td>
<td>0.023</td>
<td>1.00</td>
<td>9.0</td>
</tr>
<tr>
<td>Dimers</td>
<td>0.65</td>
<td>0.036</td>
<td>0.96</td>
<td>9.0</td>
</tr>
<tr>
<td>Trimmers</td>
<td>0.69</td>
<td>0.033</td>
<td>1.04</td>
<td>8.0</td>
</tr>
<tr>
<td>Tetralters</td>
<td>0.61</td>
<td>0.038</td>
<td>0.95</td>
<td>10.0</td>
</tr>
<tr>
<td>Pentamers</td>
<td>0.58</td>
<td>0.041</td>
<td>0.96</td>
<td>9.0</td>
</tr>
<tr>
<td>Hexamers</td>
<td>0.45</td>
<td>0.052</td>
<td>0.87</td>
<td>12.0</td>
</tr>
<tr>
<td>Heptamers</td>
<td>0.62</td>
<td>0.038</td>
<td>0.94</td>
<td>9.0</td>
</tr>
<tr>
<td>Octamers</td>
<td>0.52</td>
<td>0.045</td>
<td>0.98</td>
<td>10.0</td>
</tr>
<tr>
<td>Nonamers</td>
<td>0.36</td>
<td>0.064</td>
<td>0.74</td>
<td>11.0</td>
</tr>
<tr>
<td>Decamers</td>
<td>0.56</td>
<td>0.041</td>
<td>0.95</td>
<td>9.0</td>
</tr>
<tr>
<td>Polymers</td>
<td>0.45</td>
<td>0.058</td>
<td>0.90</td>
<td>9.0</td>
</tr>
</tbody>
</table>

All the data were based on the composite standard purified from cacao and the polymer standard purified from lowbush blueberry.

- **Response factor (area/ug)** were relative to monomers (epicatechin) in the composite standard.
- **Detection limit** was defined as amount of PAs resulting in peak area of three times of the standard deviation of the baseline noise.

The standard curves for monomers through decamers and polymers showed good linearity \( R > 0.98 \) and an intercept close to zero. The final data were corrected using the recovery rates obtained on rice to overcome the low extractability of these compounds. The relative standard deviation of quantification was 4.2% \( (n = 38) \) for the total PAs in the control blueberry sample. The relative standard deviation for individual oligomers was 7.9 ± 3.4% (Gu et al., 2002, 2004). The relative response factors, detection limit of monomer to decamers and polymers with fluorescence and UV detection are listed in Table 1 and can be used for purposes of cross-laboratory correction and comparison.

### 3. Occurrence and structural diversity of proanthocyanidins in foods

PAs are mixtures of oligomers and polymers composed of flavan-3-ol units linked mainly through C4 → C8 and/or C4 → C6 bonds (B type). The flavan-3-ol units can also be doubly linked by an additional ether bond between C2 → O7 (A type). The size of the PA molecule can be described by degree of polymerization. The three rings of flavan-3-ols are denoted as A, B, and C (Fig. 1). They differ structurally according to the number of hydroxyl groups on both aromatic rings and the stereochemistry of the asymmetric carbons of the heterocycle. The three carbons C2, C3, C4 of the flavanol heterocycle are asymmetric and may occur in different configurations. With some rare exceptions, the configuration of C2 is R. Flavan-3-ols with 2S configuration are distinguished by the prefix enantiomer (ent). The stereochemistry of the C2–C3 linkage may be either trans (2R, 3S) or cis (2R, 3R) as in (+)-catechin and (-)-epicatechin. The interflavan linkages can be α or β. The PAs consisting of (epi)catechin (4)3 are procyanidins. PAs containing (epi)afzelechin (2)1 or (epi)gallocatechin (6)5 as sub-units are propelargonidins or prodelphinidins, respectively (Table 2).

Structural studies of PAs have relied on tedious chromatographic isolation and spectroscopic analysis. Technical difficulties have confined these studies to the level of dimers and trimers. \(^1\)H and \(^13\)C NMR spectroscopy have also been used to characterize the PAs. Recent advances have seen more application of mass spectrometry coupled with HPLC as a quick and sensitive method to analyze the PAs. The mean degree of polymerization
and proportion of the constituent units can be obtained by depolymerization of the PAs in the presence of phloroglucinol or toluene-α-thiol. Procyanidins are the predominant form of PAs in foods. An early study using $^{13}$C NMR spectroscopy demonstrated that cranberry, apple, and hawthorn con-
tain exclusively procyanidins ( Foo and Porter, 1981). Thiolyis studies demonstrated that sorghum contained procyanidins with (+)-catechin (3) as the terminal unit and (−)-epicatechin (4) as the extension units ( Gupta and Haslam, 1978; Gu et al., 2002). Procyanidin oligomers isolated from apple were found to consist of homogeneous epicathchin (4) (Foo and Lu, 1999). Procyanidins extracted and fractionated from cider apples had a DP which ranged from 7 to 190. Constitutive units were found to be mainly (−)-epicatechin (4) with a proportion above 95% (Guyot et al., 2001). Procyanidins with DP 3–15 have been detected in unripe apples (Prieur et al., 1999). PAs were found to consist of homogeous epicathchin (3) (Ferreira et al., 2002). PAs in almands were found to be of the procyanidin type, not galloylated and containing epicathchin (4) as the major extension unit. Dimers, trimers, and tetramers were isolated. Procyanidins with DP > 5 were found to account for 47% of the total amount (de Pascual-Teresa et al., 1998). The PAs in brown or black soybean coat were detected as minor components in unprocessed cocoa (Gu et al., 2002). Chocolate and cocoa liquor are typically made by fermentation and roasting of the cocoa beans. Epimerization of the epicathchin (4) to catechin (3) in cocoa procyanidins has been as observed as an increased number of isomer peaks on the chromatograms obtained using normal phase HPLC (Gu and Prior, unpublished data). In addition, an O-glycoside of a dimer and two O-glycosides of A-type procyanidins have been detected in isolated cocoa liquor (Hatano et al., 2002). A-type procyanidin dimers were also detected as minor components in blueberries, where B-type procyanidins are the predominant components. Direct evidence has been obtained that B-type procyanidin dimers convert to A-type dimers by oxidative reaction under mild conditions (Burger et al., 1990; Kondo et al., 2000). It is possible that these low levels of A-type oligomers were artifacts of B-type procyanidins after oxidation.

Until recently, foods that have been studied relative to their PA content have been restricted to a few kinds of foods; the structural features of PAs in a majority of foods have been unknown. The recently developed normal phase HPLC coupled with tandem mass spectrometry has been employed to screen for the existence of PAs in 102 types of foods collected in the US. As a result, the constituent flavan-3-ols, type of interflavan linkages, and the range and average DP of PAs in these foods are listed in Table 2. A list of foods containing no detectable levels of PAs can be found in a previous publication (Gu et al., 2004). PAs were found in 43 foods, which included 23 kinds of fruits, 7 nuts, 8 cereals/beans, 2 beverages, 2 spices, and 1 vegetable (Table 2) (Gu et al., 2003a,b). Fruits were found to be the major source of PAs in the diet. Twenty-three out of the 32 fruits tested were found to contain PAs. In general, vegetables are not an important source of PAs. Of the 19 different vegetables tested, PAs were detected only in Indian squash. Pinto beans, red kidney beans, and other minor cereals such as sorghum and barley contain PAs, whereas they are not detected in the staple crops such as corn, rice, and wheat. Most nuts contain PAs. Wine, beer, and some commonly consumed fruit juices are
good sources of PAs, while coffee is not. A survey on infant foods also indicated that 25% of infant cereals, 90% of infant juices, and 85% of fruit-based infant foods contain PAs (Gu et al., 2004).

Most of the foods in Table 2 contain exclusively homogeneous B-type procyanidins. These foods include the most important dietary sources of PAs, such as apples, chocolate, peaches, and bananas. Procyanidins in walnuts were partially galloylated. Heterogeneous PAs were also detected in many foods. According to the structural features of the PAs, these foods could be classified into three categories: the propelargonidin group, the prodelphinidin group, and the A-type PA group. Some foods contained very heterogeneous PAs, like cinnamon, which can fit into two categories. Propelargonidins were considered to be rare in foods. Two unique propelargonidin dimers were isolated as minor compounds in green tea (Lakenbrink et al., 1999). Propelargonidins were detected in raspberry, strawberry, pinto bean, small red bean, red kidney bean, almond, and cinnamon. The prodelphinidins were detected in 10 foods (Table 2). The proportion of constituent flavan-3-ols and mean DP has also been determined by thiolyis. The connection sequence of heterogeneous PA oligomers was identified on tandem mass spectrometry. Differences have been seen in various foods (Gu et al., 2002, 2003a,b).

Few foods were found to contain the A-type PAs. A dimeric and three trimeric A-type procyanidins were isolated from cranberry (Foo et al., 2000a,b). A-type PA dimers to pentamers have been observed in cinnamon (Anderson et al., 2004). Among other foods, procyanidins A1 and A2 were isolated from peanut (Karchesy and Hemingway, 1986). Three novel A-type dimers were isolated from peanut skin, including epicatechin-(4β→6, 2β→O7)-catechin, epicatechin-(4β→6, 2β→O7)-ent-catechin, and epicatechin-(4β→6, 2β→O7)-ent-epicatechin (Lou et al., 1999). A-type procyanidin dimers were also detected in plum using HPLC-ESI-MS (Tomas-Barberan et al., 2001). A survey of foods has shown that cranberry, peanut, plum, avocado, and curry contain A-type PAs. The position of an A-type linkage in the PA oligomers has been identified according to their product ion spectra. It was found that A-type linkages are present as a terminal unit in plum or between the extension units in curry, cinnamon, and avocado, whereas A-type linkages exist at both positions in cranberry and peanut. Thiolyis analysis also provided the same conclusion (Gu et al., 2003a,b). Some A-type PAs with novel structures were identified in cinnamon. It is not clear whether differences in the structures of A-type PAs produce differences in their biological effects, like in cranberry and cinnamon. Besides the structure, the proportion of A-type PA was also markedly different. Based upon the peak area, over 84–90% of procyanidins in curry and cinnamon were A-type procyanidins, while cranberry and peanut contained less (51–65%). About 17–29% of prodelphinidins in plums were A-type procyanidins, and avocado contained the least A-type procyanidins (<12%) (Gu et al., 2003a,b).

Understanding the structural difference of PAs in various foods is important because the difference in molecular size, interflavan linkages, and hydroxyl pattern on the constituent flavan-3-ols has been shown to affect their metabolism and biological effects (Foo et al., 2000a,b; Tebib et al., 1994; Rice-Evans et al., 1996; Mao et al., 1999).

4. Proanthocyanidin content in foods

Quantitative information on the PA content of foods has been limited and scattered in the literature. The level in pecans was found to be in a range of 699–1710 mg/100 g using the vanillin assay (Polles, 1981). Using HPLC and a diode array detector, the total amount of monomeric and dimeric PA in ripe fresh nectarines, peaches, and plums were 2.3–43.4 mg/100 g, 9.3–69.6 mg/100 g, and 13.9–61.8 mg/100 g (Tomas-Barberan et al., 2001). The level of catechin (3), epicatechin (4), five procyanidin dimers (including B1, B2, B3, and B4), and one trimer have been analyzed in 160 French wines using a reversed phase HPLC and post-column derivatization by DMAC. The average total concentrations of dimers and trimers in Red wines was found to be 285.8 mg/L. Red wine contained a higher level of total flavan-3-ols than White and Rosé wines (Carando et al., 1999). A recent study measured the levels of oligomeric PA (including catechins, dimers, trimers and tetramers) in wine, and also found that PAs in Red wine were substantially higher (177 ± 96 mg/L) than those in white wines (8.8 ± 4.5 mg/L) (Sanchez-Moreno et al., 2003). In one report, 56 different kinds of Spanish foods were analyzed for flavan-3-ols using a reversed phase HPLC and post-column derivatization. The level of 7 monomers, 7 dimers, and one trimer were measured. Total flavanol contents were found to vary from undetectable in most of the vegetables to substantial amounts (up to 184 mg/100 g) in some cereals, fruits, as well as in tea and red wine. Epicatechin was the most abundant flavan-3-ol, followed by catechin and procyanidin B2 (de Pascual-Teresa et al., 2000).

Measured PA content for a given food from different laboratories has been quite different. These discrepancies can be explained in part by the nature of the sample analyzed (sample origin, stage of ripeness, post-harvesting conservation and processing), but the differences likely arise due in part to the different assay methods used. The PAs in a brown sorghum were determined to be 1.2% catechin equivalents using vanillin assay and 1.6% using a protein precipitation assay (Price et al., 1980). The PAs in barley of different varieties varied
from 385 to 494 mg/100 g as catechin equivalents using the vanillin-HCl method (Yadav et al., 2000). The level obtained on reversed phase HPLC was 64–126 mg/100 g (Jerumanis, 1985). Measured by the Vanillin assay, the content of procyanidins in apples was found to be 17–50 mg/100 g. An assay based on thiolytic and HPLC showed the contents of procyanidins in four cider apples were 2.9–16.2 mg/100 g (Guyot et al., 2003). Procyanidin levels (monomers through decamers) were reported in the range of 49–104 mg/100 g in fresh fruits using normal phase HPLC (Hammerstone et al., 2000).

In the USDA PA database project, food samples were collected systematically from four regions within the US in two separate seasons in order to reflect the foods available in the marketplace that are consumed in the US. Multiple sampling locations and times were used in order to obtain an estimate of the variation in PA concentrations that might result from varying growing conditions (i.e. moisture, disease and predator load, temperatures and other stress factors). These foods have been analyzed for PAs using normal phase HPLC with procyanidins as external standards (Gu et al., 2004). The PA content in some of the common foods and in some infant foods is depicted in Fig. 2. The standard deviation of the total PA concentration (Table 2) in most cases represents 8 separate samples and reflects the variation that might be expected in the market due to environmental, etc. factors. In some cases this can be fairly high (i.e. raspberry, 77%; blackberry, 65%; and nectarine, 64%).

Cultivars or genetic background were found to be a major factor affecting PA content and profile in the same foods. PA content in wild lowbush blueberries (332 mg/100 g) was markedly higher than in cultivated highbush blueberries (180 mg/100 g). Sumac grain sorghum contains high concentrations of PAs (1920 mg/100 g), whereas white sorghum is devoid of any PAs. PAs tend to concentrate in the peel of fruits or the bran of the grains. For example, the concentrations of PAs in apples with peel are higher than those without peel (Fig. 2). The concentration of PAs in Sumac sorghum bran (3965 mg/100 g) is twice as high as the PAs in the whole grain (Gu et al., 2004).

Processing or cooking can also affect PA content in foods. PA levels are high in fresh plums and grapes; however, they are not detectable in prune (dried plum) and raisin (dried grape), which suggests that the PAs were degraded during the drying processing (Gu et al., unpublished data). Extrusion of a hi-tannin sorghum produced an increase in the concentration of monomers through trimers while the concentration of PAs with DP > 6 decreased markedly (Awika et al., 2003). Simmering pinto beans in water for 2 h also lead to a dramatic loss of PAs, especially the polymers (Fig. 2). PAs with DP > 10 are the predominant components in pears, while in the infant food, which were labeled as being produced from 100% pears, no PAs with DP > 7 were detected (Fig. 3). The total content of procyanidins in the pear infant food (13.4 mg/100 g) was markedly lower than in the fresh pear fruit (31.9 mg/100 g). Similar observations were made for all other infant foods. Both the degradation of the overall PAs and the depolymerization of the higher oligomers and polymers appear to occur during food processing. Additional work is needed on effects of processing of foods on PA concentrations in foods.

5. Consumption and significance in the diet

Epidemiological studies have suggested association between ingestion of polyphenols, especially flavonoids, and the prevention of diseases. A number of authors have estimated the daily intake of flavonoids based on
food composition and consumption survey data. Estimated data from several countries are largely consistent. The overall flavonoid (flavonols and flavones) intake in a population of women in the US has recently been estimated to be $24.6 \pm 18.5$ mg/day, of which quercetin is the major contributor (70.2%) (Sesso et al., 2003). The mean intake of flavonoids (including flavonols, flavones, and flavanones) was estimated to be $24.2 \pm 26.7$, $28.6 \pm 12.3$, and $25.9$ mg/day in the populations of Finland, Denmark, and the Netherlands, respectively (Gelijse et al., 2002; Hertog et al., 1993; Knekt et al., 2002). The intake of isoflavones has been estimated to be high in Asian countries and less than 1 mg/day in the US (de Kleijn et al., 2001).

Consumption of flavan-3-ol monomers have been studied previously. Arts et al. estimated that the mean intake of flavan-3-ol monomers in the Netherlands was $50 \pm 56$ mg/day, with tea being the major contributor (65.2–87.3%) followed by chocolate and apple. He also pointed out that the average daily intake of flavan-3-ol monomers in United States should be lower than that in Denmark because of the lower tea consumption (Arts et al., 2001). We estimated the daily intake of flavan-3-ol monomers from tea to be in the range of 12.7–34.2 mg/day/person for adults in the United States based on the data of Lakenbrink et al. (2000). Although, tea is a major source of flavan-3-ol monomers (and oxidative derivatives), it is not an important source of PAs. Few PAs have been detected in green leaves (Lakenbrink et al., 1999).

The lack of reliable concentration data for PAs in foods has made it impossible to accurately evaluate their dietary intake. Intake was roughly estimated to range from several tens to several hundreds of milligrams per day (Santos-Buelga and Scalbert, 2000). Based on the PA content and the daily food intake data from USDA studies (USDA Continuing Survey of Food Intakes by Individuals (CSFII) for 1994–1996), consumption by individuals in the US was calculated for the first time. The mean intake for all ages (>2 yr old) was estimated at $53.6$ mg/day/person for all PAs of DP $\geq 2$ (Fig. 4). Detailed examination of intakes for age/sex groups indicated a bimodal high intake phenomenon for children (2–5 and 6–11 yr) and older males (40–59 and >60 yr) each of whom consumed 59 mg/day or more. The average daily intake of oligomeric and polymeric PAs are much higher than that of monomeric flavan-3-ols, and is twice as high as the combined overall intake of other flavonoids, which includes flavonols, flavones, flavanones, and isoflavones (Gu et al., 2004; Gelijse

![Fig. 4. Estimated ingestion of proanthocyanidins in different gender and age groups in the US.](image-url)
et al., 2002; Hertog et al., 1993; Knekt et al., 2002). It is clear that PAs are the major flavonoids ingested in the Western diet. Variations in PA intake among individuals were not determined, but are expected to be large due to different eating habits. No data is yet available concerning the PA content in dietary supplements. People who take dietary supplements, such as Pycnogenol™ or GSPE, can ingest several hundred milligrams of PAs per day.

The intake of PAs for 6–10-month old infants increases markedly with the addition of fruits to the diet. The daily intake for 10–24-month old infants has not been estimated due to lack of consumption data; however, it is expected to be even higher, because serving sizes are larger and fresh fruits are introduced. The average daily intake of PAs on the basis of body weight are similar for all age groups >12 yr. However, PA intake of infants 6–10 months and 2–5-year old children are four to five fold higher than the average intake in adults (Fig. 4). Knowledge concerning the influence of such high intake of PAs or other phytochemicals on the health and growth of infants is very scarce. Studies have shown that the bioavailability of isoflavones in infants is higher than in adults (Badger et al., 2002). Increasing evidence suggests that nutrition and nutrient exposure during gestation or in early infancy may have long-term effects (Lucas, 1998; Wu et al., 2004); whether the effects are positive or negative remains to be determined. However, Maynard et al (Maynard et al., 2003) have shown that exposure to fruits during early childhood provides protection against the development of cancer in later adulthood.

6. PA metabolism and potential health effects

6.1. Gut metabolism of proanthocyanidins

Very little is known about the metabolic fate of PAs. Because PAs in general are very high molecular weight molecules, it is unlikely that most are absorbed intact. Thus, gut metabolism may have a major role in their physiological effects in vivo. In human subjects given 733 mg of PA polymers and 351 mg of monomers from a cocoa beverage, no change in the HPLC profile of PAs was observed during the 50–60 min in which the PAs were in the stomach suggesting that ingested PAs reach the small intestine intact and are available for absorption or metabolism (Rios et al., 2002). Gonthier et al. (2003) compared the metabolism of procyanidin dimer B3 [catechin-(4x–8)-catechin], trimer C2 [catechin-(4x–8)-catechin-(4x–8)-catechin], and polymer isolated from the willow tree to the metabolism of catechin monomer in rats. Following the feeding of willow tree PAs (0.1%, w/w for 5 days), neither the parent compound nor catechin derivatives could be detected in the urine in contrast to animals fed catechin monomer, which excreted large amounts of catechin and its 3'-O-methylated form (25.7%). On the other hand, 16 metabolites of microbial origin were detected and identified as derivatives of phenylvaleric, phenylpropionic, phenylacetic, and benzoic acid. Their total yields significantly decreased from the catechin monomer (10.6%) to the procyanidin dimer (6.5%), trimer (0.7), and polymer (0.5%). Therefore, the degree of PA polymerization had a major impact on their fate in the body. Increased polymerization is characterized by a poor absorption through the gut barrier and a limited metabolism by the intestinal microflora as compared to catechin (Gonthier et al., 2003). However, in another in vitro study, polymeric PAs were almost totally degraded after 48 h of incubation with human colonic microflora under anaerobic conditions. Some similar metabolites to those seen by Gonthier et al., 2003 were observed which included phenylacetic, phenylpropionic and phenylvaleric acids, monohydroxylated mainly in the meta or para position. These data are some of the first observations of degradation of dietary phenolic polymers into low-molecular-weight aromatic compounds (Deprez et al., 2000). Intake of 80 g of chocolate containing 439 mg PAs and 147 mg catechin monomers in human subjects increased urinary excretion of 3-hydroxyphenylpropionic acid, ferulic acid, 3,4-dihydroxyphenylacetic acid, 3-hydroxyphenylacetic acid, vanillic acid, and 3-hydroxybenzoic acid (Rios et al., 2003). Following intake of 960 mg of a procyanidin fraction of French maritime pine bark extract in humans, two metabolites were identified as delta-(3,4-dihydroxy-phenyl)-gammavalerolactone and delta-(3-methoxy-4-hydroxyphenyl)-gamma-valerolactone conjugated with glucuronic acid/sulphate. Maximal urinary excretion of these metabolites was 8–12 h after intake (Duweler and Rohdewald, 2000).

In a randomized, double-blind placebo-controlled trial, 69 volunteers received GSPE (1000 mg/day total polyphenols) or placebo for 6 weeks (Ward et al., 2004). Supplementation with grape seed polyphenols resulted in a consistent increase in the excretion of 3-hydroxyphenylpropionic acid and 4-O-methylgallic acid and a less consistent increase in the excretion of 3-hydroxyphenylacetic acid. These observations suggest that these compounds, in particular 3-hydroxyphenylpropionic acid, are major breakdown products of proanthocyanidin metabolism in vivo (Ward et al., 2004).

Intestinal bacteria that can degrade PAs and their monomeric units, flavan-3-ols, have not been described. Bacteria which are resistant or insensitive to PAs have been isolated in recent years from the gastrointestinal tract ecosystem (Smith and Mackie, 2004). The mechanism of action of tannin-resistant bacteria in animals is not known, but their presence may have a protective effect. Smith and Mackie (Smith and Mackie, 2004) observed that PAs altered the fecal bacterial populations in
the rat gastrointestinal tract, resulting in a shift in the predominant bacteria towards tannin-resistant gram-negative Enterobacteriaceae and Bacteroides species. After 3 weeks of PA diets, the proportion of tannin-resistant bacteria increased significantly from 0.3% to 25.3% with a 0.7% tannin diet and to 47.2% with a 2% tannin diet. The proportion of tannin-resistant bacteria returned to pre-exposure levels in the absence of dietary PAs (Smith and Mackie, 2004).

6.2. PA absorption and metabolites in blood and urine

In Caco-2 cells, Deprez et al. (2001) observed that (+)-catechin and PA dimer and trimer had similar permeability coefficients, close to that of mannitol, a marker of paracellular transport. In contrast, permeability of a PA polymer with an average degree of polymerization of 6 (MW = 1740) was approximately 10 times lower. These results suggest that PA dimers and trimers could be absorbed in vivo and that polymer bioavailability is limited in the gut lumen (Deprez et al., 2001).

Results from perfusion of the isolated small intestine of the rat with the procyanidin dimers B2 [epicatechin-(4β→8)-epicatechin] and B5 [epicatechin-(4β→6)-epicatechin] extracted from cocoa indicated that both forms of dimer were transferred to the serosal side of enterocytes but only to a very small extent (<1% of the total transferred flavanol-like compounds) (Spencer et al., 2001). However, perfusion of dimer resulted in large amounts of unmetabolised/unconjugated epicatechin monomer being detected on the serosal side (95.8%). The cleavage of dimer during transfer seemed to be energy-dependent, requiring an intact cell system, as incubation with jejunal homogenates failed to yield epicatechin. Low levels of methylated dimer were also detected (3.2%), but no conjugates or metabolites of epicatechin were detected indicating that metabolism of monomer and dimer is limited during the cleavage/translocation of dimer. The methylation of dimer may be by catechol-O-methyltransferase, however, at high concentrations of dimer, catechol-O-methyltransferase activity was reduced leading to an inhibition of both monomer and dimer O-methylation (Spencer et al., 2001).

Tanaka et al. (2003) were able to measure the absorption of orally administered procyanidin B-2 and procyanidin B-3 in rat plasma. Baba et al. (2002) also were able to observe the absorption and excretion in the urine of procyanidin B2 in rats. A portion of the procyanidin B2 was degraded internally to (−)-epicatechin and to the conjugated and/or methylated (−)-epicatechin metabolite.

In other studies (Donovan et al., 2002), catechin, the procyanidin dimer B3 and a GSPE containing catechin, epicatechin and a mixture of procyanidins were fed to rats in a single meal. After the meal, catechin and epicatechin were present in conjugated forms in both plasma and urine. In contrast, no oligomeric PAs or conjugates were detected in the plasma or urine of any rats. PAs were not cleaved into bioavailable monomers and had no significant effects on the plasma levels or urinary excretion of the monomers when supplied together in the GSPE (Donovan et al., 2002).

To confirm the absorption of PAs into the human body, Sano et al. (2003) gave four healthy adults 2.0 g of PA-rich GSPE. Procyanidin B1 [epicatechin-(4β→8)-catechin] was detected in human serum at a concentration of 10.6 nM 2 h after consumption (Sano et al., 2003). Dimeric PAs were detected in human plasma (~16 nM) as early as 30 min after the consumption of flavanol-rich cocoa (0.375 g cocoa/kg body wt) and reached maximal concentrations by 2 h (Holt et al., 2002). Rein et al. (2000) observed a 12-fold increase in plasma epicatechin (from 22 to 257 nM) at 2 h after consumption of an 80-g semisweet chocolate (procyanidin-rich) bolus.

Antioxidant and other potential biological effects of chocolate and other PA rich sources may not be explained solely by the absorption of catechin monomers but perhaps also by the absorption of microbial phenolic acid metabolites (Rios et al., 2003). Additional research is needed on other procyanidin metabolites such as phenolic acids and on the effects of the unab sorbed oligomers and polymers on the human gastrointestinal tract (Donovan et al., 2002).

6.3. In vivo health effects

Acute studies in rats have demonstrated that GSPE is safe with an LD50 of 5000 mg/kg or greater and no detrimental effects in vivo were observed under the conditions investigated (Ray et al., 2001). Administration of 0.5%, 1.0%, or 2.0% GSPE for 90-days in the diet of rats did not induce any significant toxicological effects (Wren et al., 2002).

6.3.1. Urinary tract health

One of the major health benefits attributed to the ingestion of cranberry juice is the maintenance of urinary tract health. Traditionally, cranberry juice was thought to cause acidification of the urine resulting in a bacteriostatic effect. However, recent research has demonstrated that a bacterial anti-adhesion mechanism may be responsible for effects observed in the urinary tract. PAs with unique molecular structures (A-type) have been isolated from cranberry fruit that exhibit potent bacterial anti-adhesion activity (Foo et al., 2000a,b; Howell, 2002). These A-type PAs can inhibit adherence of uropathogenic isolates of P-fimbriated Escherichia coli bacteria to cellular surfaces containing α-Gal(1→4)β-Gal receptor sequences similar to those on epithelial cells in the urinary tract (Foo et al., 2000a,b). PA molecules exhibiting this activity consisted...
predominantly of epicatechin units with mainly a DP of 4 and 5 containing at least one A-type linkage. Procyanidin A2 was the most common terminating unit occurring about four times as frequently as the epicatechin monomer (Foo et al., 2000a,b). Three PA trimers possessing A-type interflavanoid linkages, epicatechin-(4β→6)-epicatechin-(4β→8, 2β→O→7)-epicatechin, epicatechin-(4β→8, 2β→O→7)-epicatechin-(4β→8)-epicatechin, and epicatechin-(4β→8)-epicatechin-(4β→8, 2β→O→7)-epicatechin, were isolated from cranberries that exhibited anti-adhesion activity (Foo et al., 2000a,b).

### 6.3.2. Antioxidant and cardioprotective properties

GSPE was administered orally (100 mg/kg/d) in the regular diet for 3 weeks to a group of rats while the other group was given only the regular diet for the same period of time (Sato et al., 2001). After 3 weeks, rats were sacrificed, hearts excised, and perfused via the Langendorff mode. After stabilization, hearts were perfused in the working mode for baseline measurement of contractile function. Hearts were then made globally ischemic for 30 min followed by 2 h of reperfusion. The results indicated significant induction of JNK-1 and c-fos proteins in the ischemic/reperfused myocardium, which was inhibited by GSPE. In concert, GSPE significantly reduced the appearance of apoptotic cardiomyocytes in the ischemic/reperfused hearts and reduced the appearance of the reactive oxygen species in the hearts. Improved postischemic contractile recovery was achieved with GSPE suggesting its cardioprotective action (Sato et al., 2001). Facino et al. (1999) also observed that GSPE supplementation in the rat (young and aged) made the heart less susceptible to ischemia/reperfusion damage and this was positively associated with an increase in plasma antioxidant activity. Red GSPE also improved the recovery of postischemic function in isolated rat hearts (Pataki et al., 2002), due to the ability of GSPE to reduce or remove, directly or indirectly, free radicals in myocardium that is reperfused after ischemia (Pataki et al., 2002).

In a human clinical study (Natella et al., 2002), 8 healthy volunteers consumed a test meal rich in oxidized and oxidizable lipids without (control) or with 300 mg of GSPE. The content of lipid hydroperoxides in chylomicrons was 1.5-fold higher after the control meal than after the GSPE-supplemented meal. Plasma lipid hydroperoxides increased only after consumption of the control meal. Plasma antioxidant capacity increased in the postprandial phase only following the GSPE-supplemented meal. The supplementation of a meal with GSPE appeared to minimize the postprandial oxidative stress by decreasing the oxidants and increasing the antioxidant levels in plasma, and, as a consequence, enhancing the resistance to oxidative modification of LDL (Natella et al., 2002).

In human subjects that received 110 mg of PAs from grapes for 30 days, levels of α-tocopherol in red blood cell membranes increased significantly and lymphocyte oxidized DNA [8-oxo-7,8-dihydro-2′-deoxyguanosine/2′-deoxyguanosine ratio] was reduced, and the red blood cell membrane fatty acid composition shifted to a higher level of polyunsaturated fatty acids. These results suggested that dietary PAs may spare vitamin E and reduce DNA oxidative damage (Simonetti et al., 2002). In a study in which male Sprague–Dawley rats were fed diets containing 0%, 0.5%, 1%, or 2% cocoa rich in flavanols for 2 weeks, cocoa supplementation was associated with a 50% lower than normal concentration of 8OH2′dGuanosine (8OH2′dG) in the testes. Liver and heart 8OH2′dG levels were unaffected by dietary treatment (Orozco et al., 2003).

In a randomized double-blind crossover design (20 subjects), dietary flavanols from a flavanol-rich cocoa beverage (187 mg flavan-3-ols/100 ml) lowered the plasma level of F-2-isoprostanes, indicators of in vivo lipid peroxidation, relative to a low-flavanol cocoa drink (14 mg/100 ml). The difference in F2-isoprostanes 2 and 4 h after intake was statistically significant when the intake was combined with physical exercise (Wiswedel et al., 2004).

Cardioprotective effects including antioxidant properties, inhibition of platelet activity, and activation of endothelial nitric oxide synthase have all been ascribed to the cocoa flavonoids. In a randomized, double-blind, placebo-controlled study conducted over a 2 week period with 21 healthy adult subjects, consumption of flavonoid-rich dark chocolate (213 mg procyanidins, 46 mg epicatechin) improved endothelial function and was associated with an increase in plasma epicatechin concentrations in healthy adults relative to intake of a low-flavanoid dark chocolate bar (46 g). However, no changes in oxidative stress measures, lipid profiles, blood pressure, body weight or BMI were observed (Engler et al., 2004). Wan et al. (2001) have also suggested that cocoa powder and dark chocolate may favorably affect cardiovascular disease risk status in human subjects by modestly reducing LDL oxidation susceptibility, increasing serum total antioxidant capacity and HDL-cholesterol concentrations, and not adversely affecting prostaglandins. Cocoa flavanol and PA supplementation (234 mg) for 28 d significantly increased plasma epicatechin and catechin concentrations and significantly decreased ADP and collagen induced platelet aggregation and P selectin expression. However, plasma oxidation markers and antioxidant status did not change (Murphy et al., 2003).

### 6.3.3. Cancer

Early studies (Santos-Buelga and Scalbert, 2000) actually suggested the PAs might be carcinogenic. However, considering all of the available literature...
and more recent studies, the indication is that PAs are more likely anticarcinogenic in humans and many animal models. There was no effect of feeding 0.1–1.0% GSPE on 7,12-dimethylbenz[a]anthracene-induced rat mammary tumorigenesis (Singletary and Meline, 2001). However, GSPE was chemopreventive in an animal model of breast cancer when fed a Teklad diet at 4% of the diet but not when fed at 1.5% or 5% in the AIN-76A diet suggesting that whether or not a compound is chemopreventive may depend upon the diet in which the agent is administered (Kim et al., 2004). Feeding female rats diets containing 0.10–1.0% GSPE was associated with a significant (72–88%) inhibition of azoxymethane (AOM)-induced aberrant crypt foci (ACF) formation and a 20–56% inhibition of ornithine decarboxylase activity in the distal third of the colon (Singletary and Meline, 2001). Balb/c mice given by gavage a hydrolyzable tannin, gallotannin (GT), or a condensed tannin extracted from red alder (RA) bark had a significant reduction in multiplicity, size, and distribution of ACF and tumors induced by 1,2-dimethylhydrazine (DMH) (Gali-Muhtasib et al., 2001) supporting a potential role for PAs as chemopreventive agents against colon cancer (Gali-Muhtasib et al., 2001).

Feeding of GSPE (0.2% and 0.5%, w/w) in an AIN76 control diet to SKH-1 hairless mice resulted in prevention of photocarcinogenesis in terms of tumor incidence (20–95%), tumor multiplicity (46–95%) and tumor size (29–94%) against UVB-induced initiation and promotion stages of photocarcinogenesis. Feeding of GSPE (0.5%, w/w) also resulted in prevention of malignant transformation of UVB-induced papillomas to carcinomas in terms of carcinoma incidence (45%), carcinoma multiplicity (61%) and carcinoma size (75%) compared with non-GSPE treated mice at the end of 30 weeks (Mittal et al., 2003).

Cacao liquor PAs exerted chemopreventive effects in the lungs of male F344 rats using a multi-organ carcinogenesis model without any promoting influence in other major organs (Yamagishi et al., 2003). However, no significant modification in the small intestine, colon or kidney was evident.

6.3.4. Other in vivo health effects

Ramirez and Roa (2003) demonstrated that rats given a dose of 20.0 g PAs/kg had significantly lower stomach free radical concentrations following induction of gastric damage with an HCl/ethanol solution suggesting that PAs can have gastroprotective and antiulcerogenic effects. Robert et al. (2001) reported that per os administration of oligomeric PAs to rats greatly increased the resistance of brain capillaries to bacterial collagenase, as shown by the inhibition of the diffusion of fluorescein-isothiocyanate-marked dextran particles from the blood-stream into the brain.

PAs derived from cacao (0.5% cacao liquor in diet) inhibited diabetes-induced cataract formation in rats (Osakabe et al., 2004). In another study, PAs and/or their metabolites prevented the progression of cataract formation in hereditary cataractous rats fed 0.082% PAs in the diet for 27 days (Yamakoshi et al., 2002). These inhibitory effects on cataract formation are likely due to antioxidiant capacity effects of PAs.

Kamitani et al. (2004) observed that GSPE treatment caused an increase in both bone formation and bone strength in rat mandibles. Following 3 weeks of a calcium-restricted diet, rats given 3 mg of GSPE as supplement in 100 g of a standard diet for the next 3 weeks had significantly higher trabecular bone density, and trabecular bone mineral content, cortical bone density, cortical bone cross-sectional area, and cortical bone mineral content than the control rats. PAs from grape seeds given orally (400 mg/kg for 3 days) possessed in vivo urate-lowering activities in a model of hyperuricaemic mice pretreated with oxonate (Wang et al., 2004). Normal adult female rats fed 5% GSPE in the diet had 13 proteins in the brain that were altered in amount and/or charge (Deshane et al., 2004). Because many of these changes were quantitatively in the opposite direction from previous findings for the same protein in either Alzheimer’s disease or in mouse models of neurodegeneration, the data suggest that these identified protein may mediate the neuroprotective actions of GSPE (Deshane et al., 2004). What remains to be determined is whether the effects are due to polyphenols or their metabolites or whether the GSPE in the gut is altering a signaling process between the gut and the brain.

Consumption of 6 g of cinnamon per day improved the glucose and lipid profiles of human subjects with type 2 diabetes (Khan et al., 2003). A-type PA polymers have been isolated from cinnamon that exhibit insulin-like activity (Anderson et al., 2004).

7. Conclusions and perspective for future studies

Many foods contain substantial amounts of PAs with various structures. PAs account for a major fraction of the flavonoids ingested in the Western diet. The availability of data on the PA content in foods provides the first opportunity to examine the epidemiological association between PA intake and health and diseases. Further research is needed in several aspects concerning the nutritional significance of PAs in foods. Although the bioavailability and metabolism of PAs is still poorly understood and controversial, it seems clear that dimers are the only PAs that can be absorbed and then they are present at quite low concentrations in the plasma. Oligomeric and polymeric PAs have been shown to be degraded into simple phenolic acids by the gut microbial flora which are absorbed. Because hydroxycinnamic
acid and other polyphenols can also be degraded into these compounds (Rios et al., 2003; Olthof et al., 2003), the contribution of PAs is not yet clear. A portion of PAs may remain unabsorbed. They were speculated to exert local activity in the gastrointestinal tract which may be particularly important when the intestine is exposed to oxidizing agents. Because vitamins C and E are absorbed in the upper segments of the intestine and low molecule flavonoids are partially absorbed, PAs may constitute a dominant dietary antioxidant present in the colon.

A large number of the animal studies with PAs have been with GSPE and protective effects have been seen with colon cancer and ischemia/reperfusion damage in the heart. A critical question is whether these effects are specific to grape seed PAs since they contain appreciable gallated extension units in their structure. Based upon the animal studies and the recent double blinded clinical studies in humans, it is becoming clear that components are being absorbed that have beneficial health effects in terms of antioxidant, cardio-vascular and cancer, but it is not clear the mechanism whereby these effects are mediated. Until more is understood about the biologically active component(s), in vitro studies using PAs in cell culture may have limited value. More studies are warranted that correlate bioavailability and other biological effects of PAs to their structures. The influence of ingested PAs to the mental and physical development of infants and children constitute another important aspect for future study.

References


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