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Review

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Evolution of Phenolic Compounds from Color and Flavor Problems to Health Benefits

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ABSTRACT: Early studies focused on the negative effects on color and flavor of foods, followed by exploration of the antioxidant properties and the associated health benefits. The growing body of evidence suggests that plant-based polyphenols may help prevent or delay the onset of a multiplicity of diseases. Newer work suggests that a variety of polyphenols can alter the expression of genes in the inflammatory pathway. Data also show that the absorption of the polyphenols is very limited. Insulin resistance and endothelial and mitochondrial dysfunction are hallmarks of the metabolic syndrome and aging and occur at the early stages of the disease. There is limited clinical evidence that certain polyphenolic metabolites by virtue of their anti-inflammatory activities can improve insulin sensitivity and endothelial and mitochondrial function, suggesting that polyphenols are good for disease prevention. The goal of this review is to summarize the evolution and emphasize the potential benefits of polyphenols.

KEYWORDS: *polyphenol, flavonoid, anthocyanin, pigment, flavor, antioxidant, inflammation*

INTRODUCTION

Phenolic compounds, which are nearly ubiquitous in plant-based foods, include a very broad spectrum of molecules that contain an aromatic group and one or more hydroxyl groups on the aromatic ring; generally they are secondary metabolites in plants derived from phenylalanine or tyrosine.[1] The range includes simple phenolic acids, which are derivatives of benzoic acid or cinnamic acid, and extends to the complex family of flavonoids and tannins. The phenolic family includes in excess of 8000 individual compounds that have been identified.[2] Foods commonly associated with polyphenolic contents include cereals, tea, coffee, chocolate, vegetables, fruits, and nuts.[3] Polyphenolic compounds found in plants serve a variety of roles, including color, antimicrobial and antifungal action, and antioxidant protection from free radicals and phytoalexins among others.[4,5] From the food perspective, polyphenols are very important in defining the color, flavor, and texture attributes of beverages such as beer, wine, and cocoa. The number of literature citations on polyphenolic compounds has grown logarithmically in all journals and in recent years.

Many of the polyphenolic compounds have been studied as antioxidants, which have been associated with health benefits. The phenolic and polyphenolic compounds can also deliver a variety of flavor responses ranging from the sweet chalcones and some glycosylated flavonoids to bitter and astringent tannin compounds. The levels and particular compounds present in plants vary widely within plant families and cultivars. The concentrations of phenolic and polyphenolic in plants are also influenced by growing conditions, moisture, and attack by plant pathogens. Concentrations are also affected by germination, extent of ripeness, processing, and storage conditions. Historically, the interest in these molecules has evolved from their colors in flowers, fruits, and vegetables, their enzymatic browning, and the impact on flavor, particularly in wine, to the current interest in the health benefits associated with the compounds.[6−10]

Epidemiological research has demonstrated a link between a diet high in fruit and vegetable intake and decreased risks of incidence of cancer.[11] A review panel conducted by the American Institute for Cancer Research concluded that increased intake of vegetables decreases the risk of many different types of cancers, including lung, stomach, mouth, and colon, and a probable decrease on other types of cancers as well.[12] In addition, consumption of fruits decreased the risk of most of the aforementioned cancers. Also, consumption of fruits and vegetables has been associated with reduced risk of cardiovascular disease. The cardioprotection has frequently been associated with flavonoids and antioxidant polyphenols.[13] Phenolic compounds potentially could have a protective role against a wide variety of diseases, including cancer and cardiovascular disease, as well as diabetes and Alzheimer's disease.[14] Studies have shown that the mean dietary intake of all polyphenolic compounds is 780 mg/day for females and 1058 mg/day for males, with half of these composed of hydroxycinnamates, 20−25% of total flavonoids, and approximately 1% of anthocyanins.[15] There are still too few intervention studies to make any conclusive statements about their role on health.[3] Convincing evidence exists to demonstrate that polyphenols from berry fruits are absorbed in various degrees in the body and provide positive benefits to humans; however, more research does need to be conducted to determine which compounds or combinations of compounds provide the benefits. The mechanisms by which they work in vivo require much more research and understanding.[16]

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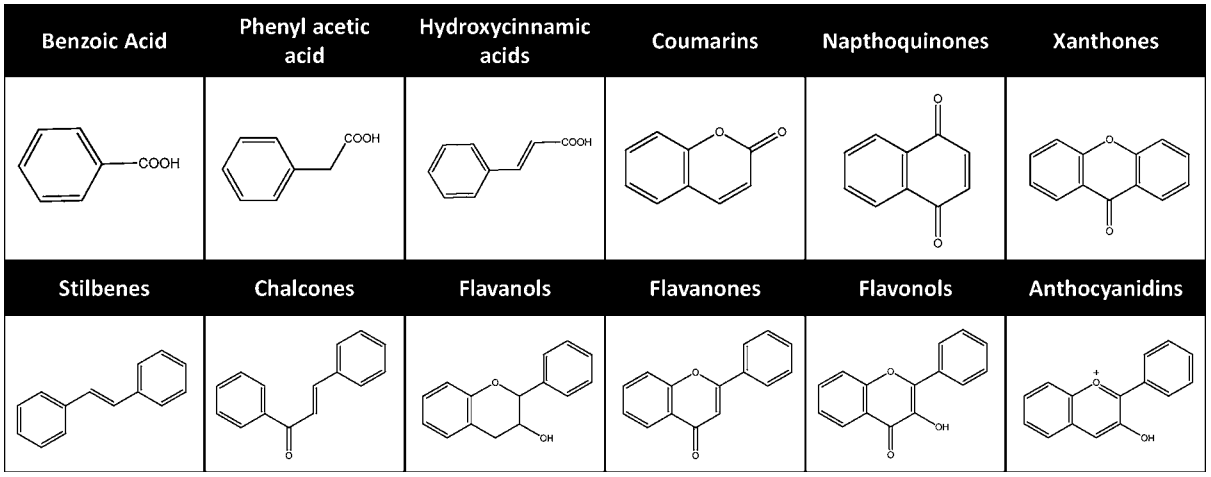

Figure 1. Polyphenolic backbones found in plants.

The purpose of this review is to summarize the evolution of the chemistry, color, flavor, quality, and emerging health benefits of phenolic and polyphenolic compounds found in the diet.

■ PHENOLIC CLASSES AND STRUCTURES

Plant polyphenols can be separated into several groups or classes of compounds. The nonflavonoid classes are primarily simpler molecules starting with benzoic acids, cinnamic acids, and stilbenes. These "simpler" structures also include more complex molecules derived from these simpler polyphenols, including stilbene oligomers, gallotannins, ellagitannins, procyanidins, and lignans.

Examples of these structures are illustrated in Figure 1. Each of these backbones can be appended with hydroxyl groups and methoxy groups as well as a wide range of glycosides. The simple monocyclic phenolics, based on benzoic acid and cinnamic acid backbones, are not essential for the growth of plants but serve as antioxidants and are part of the plant defense systems. The chemistry and occurrence of the monocyclic phenolic acids were recently reviewed by Khadem and Marles.[17] The majority of the monocyclic phenolic acids are present as conjugates. For example, gallic acid can be conjugated as a dimer and rarely as trimers (tergallic acid) or tetramers (gallagic acid). When these compounds are esterifed on glucose, they are classified as hydrolyzable tannins. Polymerized gallic acid is considered to be a hydrolyzable tannin.[18,19] Cinnamic acids provide the C6C3 building blocks for structural polymers in plant cell walls. The resulting lignins in cell walls represent a significant pool of dietary phenolic compounds.[20] Major sources of naturally occurring and added hydroxybenzoic acids were reviewed and summarized by Tomas-Barberan and Clifford.[21] The principal dietary sources are tea, red wine, caneberries, strawberries, and barley. The naturally occurring hydroxybenzoic acids are 4-hydroxybenzoic, protocatechuic, and gallic acids. Stilbenes are widely distributed in plants, particularly in red wines and peanuts. Multiple health benefits have been associated with stilbenes, particularly *trans*-resveratrol. These benefits include anti-inflammatory, anti-tumor, and antioxidant activities. Resveratrol is found in both free and glucoside forms.[22]

Flavonoids, the largest group of polyphenols, are divided into subgroups illustrated in Figure 1. Flavonoids are ubiquitous in plants and include at least 2000 naturally occurring compounds.[23] Included in the flavonoids are the highly colored anthocyanins, which are widely distributed, and berry crops are particularly rich in these compounds.[24] Six other types of flavonoids found in nature include flavones, flavanones, flavonols, flavanonols, isoflavones, and flavanols (flavan-3-ols).[23]

The type and concentration of flavanols in foods are influenced by plant source, food manufacturing and preparation processes, and food storage conditions.[25] The flavan-3-ols encompass the monomeric epicatechin and comprise the major constitutive units of condensed proanthocyanidins. Flavanols are found in many different food products, including wine, cocoa, and tea, and play an important antioxidant role and have been shown to enhance the enzymatic oxidative stress system.[26] Wine is a major source of the A- and B-type dimers and C-type proanthocyanidins, although they are found at low levels in beans. Daily intake of proanthocyanidins can reach 0.5 g per day, the majority of it being the B-1 and B-2 types and proanthocyanidins with DP > 3.[27] Berries have been shown to contain low levels of flavonols and flavan-3-ols.[16] Cocoa or cocoa-containing foods are a good source of flavanols, procyanidins,[28,29] and epicatechin, which are thought to be responsible for the positive protective effects associated with the consumption of chocolate.[25,30] The flavanol content of chocolate foods ranges from 43 mg/100 g in milk chocolate to 2500 mg/100 g in baking chocolate.[29,31] The average intake of flavanols and procyanidins in a typical Western diet ranges between 50 and 100 mg per day[31] and 58 mg in the United States.[29] Tea is another excellent source of flavanols in the diet, containing four main catechins that vary in concentration due to the type of tea preparation and are absorbed in the small intestine.[32]

Flavanones contribute colors and flavors to fruits and vegetables and have potential for antioxidant activity. Flavanones, particularly hesperetin and naringenin, commonly found in citrus fruits, act as antioxidants and play a role in anti-inflammatory response.[33] Flavanones are found both in the juice and in the tissue of citrus fruits. In citrus where the peel and albedo are easily separated from the fruit, total flavanone content is lower.[34]

Flavonols are among the most abundant and widely distributed plant flavonoids found in the diet. They can be found in most fruits and vegetables, particularly in leafy vegetables, grapes, onions, wine, and tea.[35] Common flavonols

include quercetin (most abundant), myricetin, morin, kaempferol, and fisetin.[35] Flavonols have been widely studied, demonstrating benefits on cardiovascular disease when consumed in the form of fruits and vegetables.[35]

Flavones are found in relatively small amounts in herbs, grains, and leafy vegetables.[36] Some common types of flavones include apigenin and luteolin, and increased consumption of flavones has been linked to a lower risk of cardiovascular disease.[37]

Isoflavones are found mainly in soy and products made from soy. The isoflavones are widely accepted as beneficial for menopausal symptoms and reduction of low-density lipoprotein (LDL) cholesterol.

Anthocyanins are water-soluble pigments that are responsible for the red, blue, and purple colors in many different plants.[24] They are associated with berries, red fruits, and vegetables.[38] Anthocyanins that are found in berries are conjugated anthocyanidins that are responsible for their rich and varied colors. Some fruits, such as elderberry or red currant, contain one specific type of anthocyanin, whereas other berries, such as blueberry and black currant, contain a varying number of these compounds.[16] Muscadine grapes grown in the southeastern region of the United States extending from Louisiana to North Carolina are exceptionally rich in anthocyanins.[39,40]

The six most common types of anthocyanidins found in food plants are found as O-linked conjugates with a variety of types of sugars. Malvidin, petunidin, cyanidin, peonidin, delphinidin, and pelargonidin[16] are the most common anthocyanins, and they are generally found as glycosides with glucose, galactose, and arabinose as the sugar moiety.[41] The acylated forms found in radishes, red potatoes, red cabbage, black carrots, and purple sweet potatoes tend to be more stable and therefore have application as food pigments replacing synthetic dyes.[42]

Anthocyanins degrade readily, resulting in the formation of colorless or brown compounds. In addition to their reactivity, changes in pH, oxygen, temperature, and light all have an effect on their stability.[24]

The polyphenol distributions and profiles in foods vary enormously. Two databases are now available to find specific distributions and quantities of polyphenols in foods: Phenol Explorer (www.phenol-explorer.eu/) and the USDA Database for the Flavonoid Content of Selected Foods (www.nal.usda.gov/fnic/foodcomp/Data/Flav/Flav02-1.pdf). Quantitative values for polyphenols are being continuously updated in the USDA database and in Phenol Explorer. It should be pointed out that the polyphenols occur in many crops other than fruit, including cereals, legumes, nuts, tea, coffee, wine, and beer. Pennington and Fisher have recently included polyphenolic data as part of the food component profiles, which was part of a program to use component profiles to establish fruit and vegetable subgroups.[43,44] Pérez-Jiménez[45] have published a report summarizing the composition of the 100 foods that are the richest sources of polyphenols.

QUANTITATIVE DETERMINATION OF PHENOLIC COMPOUNDS

The total phenol contents of foods, ingredients, and supplements are based on the Folin−Ciocalteu reaction. The phenolic compounds form blue complexes with the phosphomolybdic−phosphotungstic reagent at high pH.[41] The analysis is simple, highly reproducible under carefully controlled conditions, and, therefore, widely used over a broad spectrum of applications. Several papers report strong correlation with more complex assays such as DPPH, FRAP, TEAC, and ORAC.[46−52] Unfortunately, the method needs a greater degree of standardization using an agreed upon reference. Different groups have used different standards, which are arguably appropriate to the matrix being tested but makes comparisons between methods very difficult.[50,53−55] The total phenolic assay measures a broad spectrum of phenolics but does not account for polymerization or other reactions that could alter effects in living systems. The total phenolic assay is also not specific to phenolic compounds; thus, other reducing agents in the system can interfere.[47,48]

The Folin method represents a classic approach to estimate total phenolic compounds in a variety of matrices. Although the method is nonspecific, it is frequently applied as a measure of total phenolics in biochemical, animal, and clinical trials. Because phenolics encompass a broad spectrum of classes of compounds, it is desirable to identify the classes of phenolics present such as flavonoids, chalcones, anthocyanins, and procyanidins. Spectrophotometric techniques can be applied to further differentiate the phenolics present in a food. The differences in ultraviolet spectra are an important tool in determining which wavelengths to monitor for detection and quantification by HPLC. HPLC combined with UV detection and mass spectrometric (ESI, MS, MS/MS) measurement provides the most useful techniques currently available to identify specific classes and structures of food phenolics.[56] Procyanidins from matrices such as chocolate have been analyzed by ESI and tandem mass spectrometry after separation by reversed phase HPLC. Procyanidins and catechins can be measured and correlated with physiological effects using these techniques.[57]

EFFECT OF pH ON ANTHOCYANIN COLOR

Historically, some of the pioneering work on food and flower color was the work of Willstätter and the Robinsons, who isolated anthocyanins and confirmed their structures synthetically.[58−61] In 1947 Blank[62] published a thorough review of the anthocyanin pigments in plants. The distribution of anthocyanins and the various glycosides in a range of foods were reviewed by Mercadante and Bibbio in 2008.[63] They reviewed the influence of pH, ascorbic acid, temperature, structure, and glycosides on the stability of the anthocyanin pigments. Detailed data on the distribution of anthocyanins as pigments in a broad spectrum of foods have been reviewed in detail elsewhere.[64,65]

The primary function of flavonoids in plants is to provide protection against ultraviolet light. Flavonoids absorb the UV-B range of light, protecting tissue against damage[66] while not interfering with photosynthesis.[67] The anthocyanins/anthocyanidins are responsible for much of the nonchlorophyll color in fruits and vegetables. The most frequent forms are glycosides such as cyanidin-3-rutinoside. The glycosides can produce colors ranging from bright red to deep purple depending on the particular substitution and pH of the environment. Willstätter, in a series of papers, worked out the structure of the anthocyanin cations that are responsible for color in flowers and fruits.[68−71] The Robinsons were able to elucidate the influence of pH and the interaction with other tannins to control flower color.[58−61] Bate-Smith and Harborne were the first to apply both chromatographic and spectral methods to identify anthocyanins.[72−76] In the later work Harborne was able to separate pigments on the basis of their glycosylation patterns. This established work made it possible to characterize

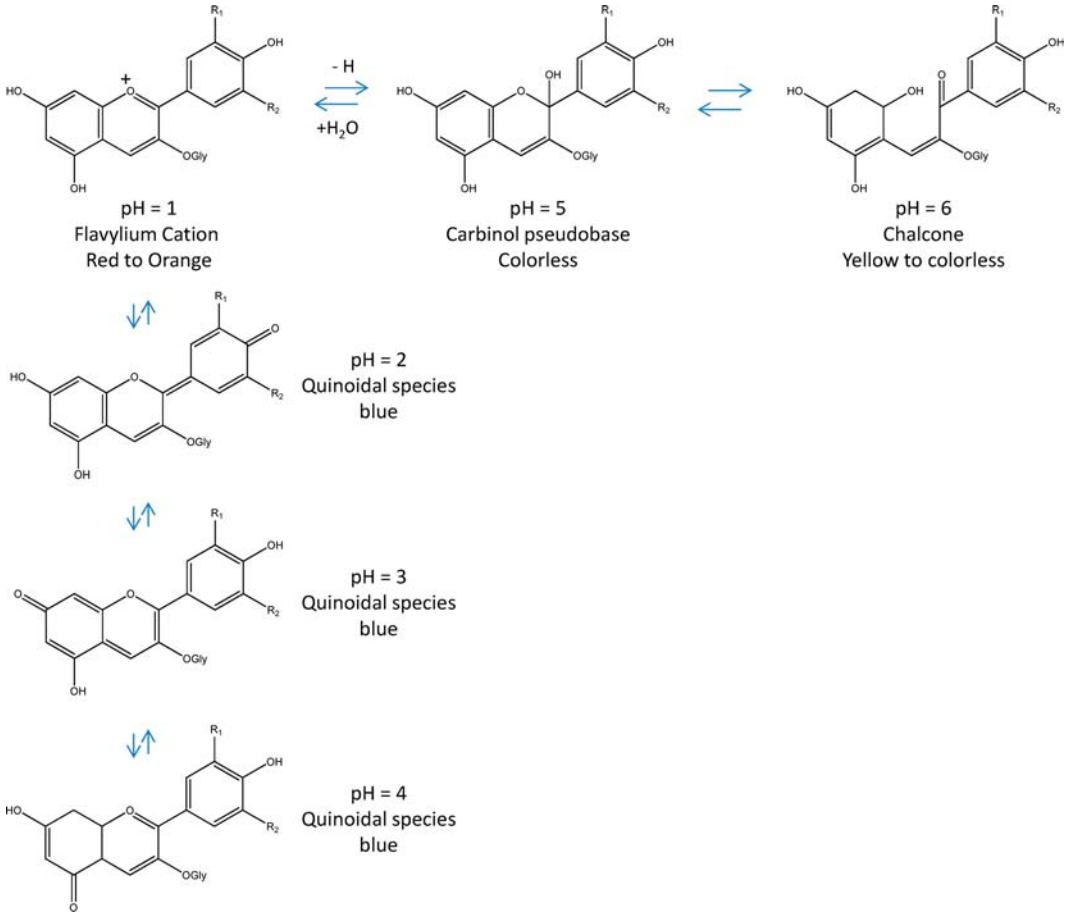

Figure 2. Structures of anthocyanins present at various pH levels. R_1 and R_2 are either −OH or $-OCH_3$. Adapted from Castañeda-Ovando.[123]

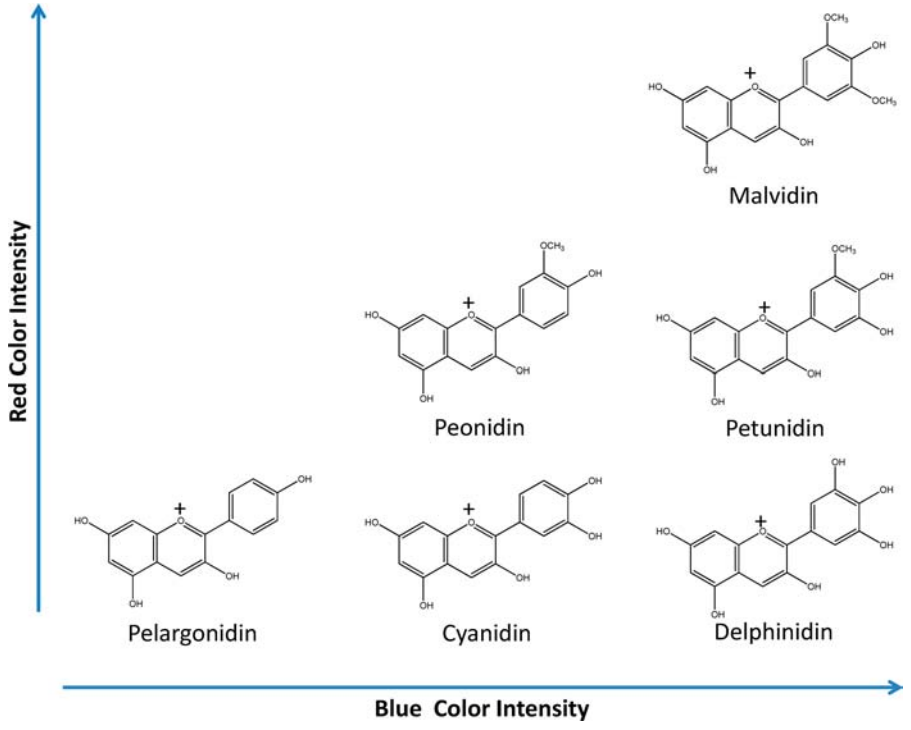

Figure 3. Structural differences influence red and blue colors of anthocyanins.

anthocyanins on a microscale. Next, Harborne demonstrated that the carbohydrate residues on anthocyanins can be acylated with hydroxybenzoic acids, cinnamic acids, and dicarboxylic acids.[75−84] On the basis of the earlier works of Willstätter and

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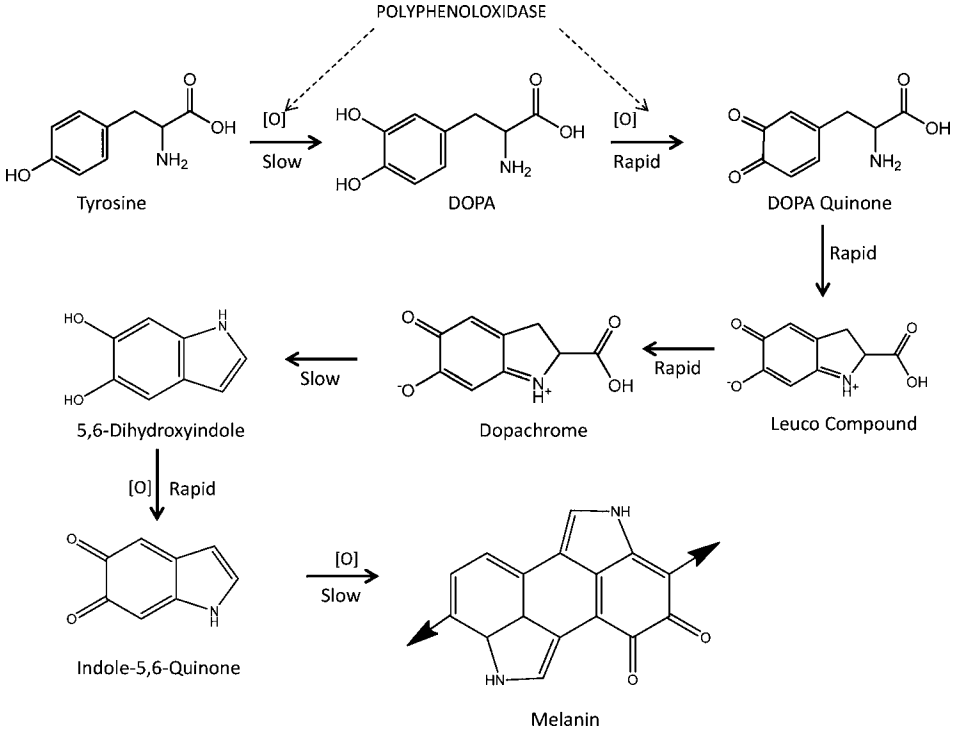


Figure 4. Polyphenol oxidase initiated melanin formation. Adapted from Marshall et al.[264].

Zollinger[85] and Robinson and Robinson,[58] Harborne's work demonstrated why structurally identical anthocyanins can result in widely different colors.[83,86] Haslam demonstrated that between pH 4 and 6, four distinct anthocyanin forms exist in equilibrium.[87,88] The influence of pH on the color of anthocyanins is demonstrated in Figure 2.

One of the important roles of anthocyanins in plants is to facilitate the pollination of the plant.[89,90] The work demonstrated that color was critical to the pollinators in a particular environment.

The color and appearance of food is the first sensory response to a food. Color is therefore critical in our response to a food. Processing can influence the color properties of foods and affect their appeal. The color of the anthocyanins in foods is influenced by a number of factors including heat, pH, ascorbic acid, sugars, metal ions, and copigments such as tannins. Small structural differences in anthocyanins result in differences in color under physiological conditions. Figure 3 illustrates the influence of structure on the color of common anthocyanins. There are several reviews that cover these effects in greater detail.[91−99]

The quantity of anthocyanins present in crops displays enormous variability, which accounts for differences in color intensity and hue. Early work by the Robinsons[61] reported qualitative and quantitative variation of anthocyanins on flower color. Blank[62] provides an extensive review of the historical work on anthocyanins including the classic chemistry and occurrence in plants, and more recently there are multiple reports of variation of total polyphenol anthocyanins in fruits and berries. Andersen and Jordheim[64] published an updated literature review of the anthocyanins focusing on the chemistry, including discussion of some of the less common compounds and the glycosidic linkages.

■ ENZYMATIC OXIDATION OF POLYPHENOLS

Polyphenolic compounds are enzymatically oxidized by polyphenol oxidase (PPO), which results in undesirable color changes particularly in fruits, vegetables, and shrimp. Polyphenol oxidases are enzymes with copper at the active site, which inserts an oxygen ortho to an aromatic hydroxyl group, converting the phenol to a quinone. The activity is almost universal in plants, animals, bacteria, and fungi. In plants, the activity occurs in tissues damaged by insect attack or in food processing such as peeling, grinding, or cutting.[100] In enzyme nomenclature there are two different oxidases, a tyrosinase (EC1.14.18.1) and catechol oxidase (EC1.10.3.2).[101] The typical substrates for the enzyme are the polyphenols catechol, 4-methylcatechol, DOPA, caffeic acid, chlorogenic acid, and catechin.[102] Figure 4 illustrates the initial stages of enzymatic browning with tyrosine as a substrate.

Enzymatic degradation of phenolic compounds is caused by PPO. In Figure 4 the primary mechanism of PPO activity leading to browning of fruits is illustrated. The topic of enzymatic browning is of continuing interest because of the negative impact of the reaction on the quality of shrimp, fruits, and vegetables.[102] Many fruits can undergo severe color changes as a result of polyphenol oxidation and anthocyanin degradation.[103] The variations in reactions among individual fruits were reviewed by Adams.[104] In the same review the degradation of the anthocyanin pigments in grapes, blueberries, and strawberries was reviewed. Tea processing and "fermentation" represents an instance when the enzymatic oxidation process is beneficial for production of black tea. Anthocyanins during aging, processing, and pH changes can undergo a number of transformations that affect color.

■ EFFECTS OF PHENOLIC COMPOUNDS ON FLAVOR

Polyphenolic compounds can have a profound effect on the flavor of foods. They are particularly important in the flavor of

beer and wine. Polyphenols contribute bitter and astringent flavors to a variety of foods including beer, wine, tree nuts, chocolate, coffee, tea, fruit-based products, and soy products. Astringency, a tactile response, and bitterness, a taste response, are caused by flavonoid polymers such as the anthocyanidins or condensed tannins. Variations in composition, polymer size, and degree of galloylation all affect the bitter and astringent responses. The responses are also influenced by pH, sweetness, viscosity, and ethanol concentration.[105] The simpler phenolics found in wine are hydroxybenzoates, hydroxycinnamates, and stilbenes.[106] Wine also contains flavanols and anthocyanins. The majority of the phenolics in wine exist as condensed tannins.[106] In wine production the primary sources of phenolic compounds are the skin and seeds of the grape. The wine industry applies major effort to control the exposure of the wine must to skins and seeds to control the bitter and astringent notes in the wine. There is enormous variation in these compounds based on the variety and growing conditions of the grapes.

In beer, the phenolic compounds, which come from barley, other adjuncts, and hops, affect flavor, astringency, haze, body, and fullness.[107] The phenolic compounds in beer are critical to the flavor and stability of the product. Callemien and Collin published an extensive review of the phenolic compounds found in beer as well as the impact on product stability.[108]

The predominant phenolic compounds in tea and coffee are phenolic acids and flavonoids. The processing of tea and coffee causes significant changes in the phenolics in the final products. Catechins account for 30−42% of the water-soluble solids in tea.[109] The major tea catechins are (−)-epicatechin, (−)-epicatechin gallate, and (−)-epigallocatechin. Black tea is the most widely consumed form of tea. During the fermentation process PPO and peroxidase catalyze the oxidation of flavanols, pyrogallol, and catechol to their respective *o*-quinones. The quinones react further to form a variety of products. It is during the same fermentation that theaflavins and thearubigins are generated. The extensive chemistry and historical perspective on the chemistry of tea have been summarized by Wang and Ho.[110] Secondary phenols are formed in the processing of tea, whiskey, cinnamon, and persimmon fruits.[111]

Whiskey barrels are toasted or charred; during the process the ellagitannins in the wood are decomposed, and during the aging process the tannins are further oxidized, resulting in a complex mixture including castalagin and whiskey tannins.[111−113]

EFFECTS OF PROCESSING ON ANTHOCYANIN QUALITY

The potential health benefits of blueberries have resulted in intense research on the antioxidant potential and the purported health benefits of the berries. Blueberries (*Vaccinium corymbosum* L.) contain a wide array of polyphenols including anthocyanins, flavan-3-ols, proanthocyanidins, and flavonols.[114−116] The complement of phenolic compounds in blueberries is responsible for the free radical scavenging capability of the fruit.[115−118] The question becomes, what is the stability of these antioxidant benefits during processing of the fruit? Brownmiller et al. evaluated the effects of processing and storage on blueberry characteristics.[119] Berries were blanched, pressed filtered, and clarified. Treated materials were stored for up to 6 months. They observed losses of 28−59% of the anthocyanins, with greatest losses in clarified juices. The ORAC values did not change substantially, indicating that the polymerized anthocyanins provided antioxidant activity. It is unlikely that these polymers will be absorbed, and the authors concluded that methods are required to stabilize the anthocyanins during heating and storage. A possible mechanism for the thermal breakdown of anthocyanins and the kinetics of breakdown have added new insight to the decomposition of anthocyanins and may lead to stabilization strategies in the future.[120] The stability of anthocyanins is dependent on their specific structures and the matrix in which they are being held.[66,121,122]

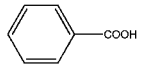
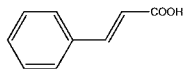
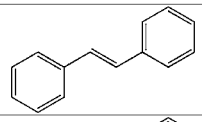
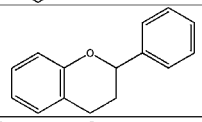
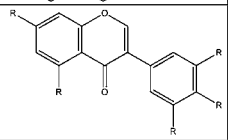
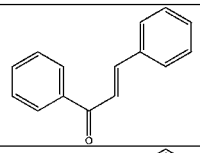
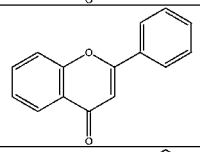
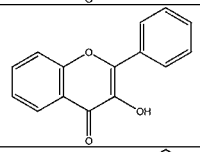
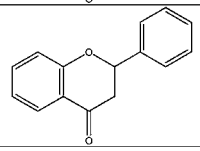
Anthocyanins are very reactive and therefore readily degraded, resulting in the formation of colorless or brown compounds. Their reactivity is influenced by pH, oxygen, temperature, and light.[123] The changes in processing may also change the composition of these foods, which in turn will affect the absorption, bioactivity, and fate of the compounds in the digestive tract.

The ortho hydroxyl groups on the A and B aromatic rings of phenolics promote oxidation, whereas the meta hydroxyl groups increase the likelihood of electrophilic substitution. When the central C ring is positively charged, it is susceptible to nucleophilic additions. These reactions can occur in the production and aging of wine.[124]

Postharvest processing and storage influence the stability of phenolic acids and flavonoids in foods in a broad spectrum of reactions. In an extensive review, Amarowicz et al.[125] concluded that finding homogeneous tendencies of reactions in the diverse family of compounds is very difficult. Variations in phenolic distribution, other components such as ascorbic acid, and other components in food further complicate the potential chemistry of reaction and side reactions. The influence of processing on the phytochemicals in cranberries serves as an excellent example of the complexities of processing-related changes. Whereas intact cranberries are relatively stable, processing to produce juice causes a variety of reactions. Pappas and Schaich[126] reviewed the processing-related changes in cranberry juice production, which has both positive and negative effects on the juice. Freezing and thawing destabilized cell walls, resulting in release of more phenolic compounds, and storage at 15 °C resulted in increases in anthocyanin content. Heat, increasing pH, light, dissolved oxygen, and added ascorbic acid destabilized cranberry color and anthocyanin content. The degradation of anthocyanins as a result of thermal processing was carefully studied by Patras et al.,[120] and they established kinetic models relating to anthocyanin breakdown to protocatechuic acid, phloroglucinaldehyde, and 4-hydroxybenzoic acid.

In processed berry products the formation of polymeric anthocyanins is a major concern. Storage of blackberry products at 25 °C can result in as much as 75% losses in anthocyanins, primarily as a result of polymerization.[127] In blueberry products there was minimal loss in monomeric anthocyanins, but a 25% loss in ORAC after blanching. Monomeric anthocyanins continued to decrease during storage of the juice and other processed products, whereas ORAC values remained stable.[119] In cranberry juice the flavonols and procyanidins are more stable than anthocyanins during processing. Increases in flavonol aglycones were observed as a result of hydrolysis of the glycosides during juice processing.[128] The concern is that the higher molecular weight polymers are less likely to be absorbed. However, these materials will reach the colon, where they have the potential to be altered by the

Table 1. Occurrence and Flavor of Phenolic Compounds in Foods

Class	Basic Structure	Examples	Occurrence	Flavor
Benzoic Acid		Hydroxybenzoic Protocatechuic Vanillic Syringic	Beer Raspberries Acai Acai	Bitter Astringent Astringent Bitter
Hydroxy-cinnamic acid		Synapic Ferulic Cinnamic	Cereals Apple, Coffee Cinnamon	Bitter-Sweet Astringent Cinnamon
Stilbenes		Resveratrol	Grapes Peanut	Bitter, Astringent
Flavan-3-ols		(+)- Catechin (-)-Epicatechin	Tea, Chocolate Tea, Chocolate	Bitter, Astringent Bitter, Astringent
Isoflavones		Genistein Glycitein Daidzein	Soy	Bitter
Chalcone		Neohesperidin	Citrus	Bitter Sweet when hydrogentated to dihydrochalcone
Flavone		Tangeritin Nobiletin	Orange Orange	Bitter Bitter
Flavonol		Quercetin	Wine, Tea, Endive	Bitter
Flavanone		Naringin	Orange Juice Grapefruit Juice Citrus peel	Bitter

microbiome, which may result in bioactive compounds that are absorbed.

Although major interest has focused on fruit and particularly berry products, the flavonoids in processed vegetables are also influenced by processing conditions. In onions, green beans, and peas, quercetin and kaempferol are the major flavonoids. In onions, peeling resulted in 50% losses of quercetin and 66% losses of kaempferol; however, only minimal losses were observed during heat processing. Peas and green beans showed very low losses, although the concentrations were low.[129] In contrast, berry processing resulted in major anthocyanin losses. Production of highbush blueberry juice after concentration resulted in the recovery of only 32% of the berry anthocyanins, with major changes in profile.[130] Blackberry and black raspberry canning and thermal processing of purees also resulted in significant losses of anthocyanins, up to 27 and 51%, respectively, and the degree of polymerization also increased with thermal processing.[127,131] It can therefore be concluded that anthocyanins are susceptible to damage during processing, but some of the other phenolics are relatively stable. It should be emphasized that there are few data on the bioavailability of the reaction products or phenolics from processing.

IMPACT ON FLAVOR AND AROMA

Historically, much of the interest in polyphenolic compounds has been focused on flavor issues. As a general group they can provide bitter or astringent flavors (Table 1). The flavors of phenolics are critical in many foods, ranging from beer and wine, to vegetables, and to isolated proteins. The flavors can add essential positive attributes as well as unpleasant attributes. These benefits/negatives are also highly concentration-dependent. The intensity and duration of the bitter or taste response of phenolic compounds are altered by the degree of polymerization.[132]

Simple molecules such as vanillin and eugenol have strong and characteristic aromas. Generally, however, the polyphenolic compounds have historically been associated with bitter and astringent flavors. The impact of phenolic compounds in beer was extensively reviewed by Callemien and Collin.[108] Several papers discuss the importance of phenolics in the flavor of wine.[106,133,134]

Table 2. Comparison of Antioxidant Methods Used for Polyphenolic Antioxidant Analysis

method	basis		chemistry	advantages/disadvantages
ORAC	HAT	measures antioxidant inhibition of peroxy radical induced oxidations; chain-breaking activity by HAT; peroxy radical reacts with fluorescent probe to form non-fluorescent product; measure decreased rate and product formed over time	R—N═N—R + O_2 → N_2 + ROO* ROO* + probe → ROOH + ox/ probe ROO* + AH → ROOH + A* ROO* + A* → ROOA	models reaction of antioxidants in food and physiological systems; can be used in hydrophobic and hydrophilic systems;[4,34,35,53,265] readily automated; compares wide spectrum of products; relation to in vivo activity is questioned
TRAP	HAT	measures interference in the reaction between generated peroxy radicals and a target probe[12,16,27,53]	ROO* + A* → ROOA	models the antioxidant compounds ability to interfere with reaction between water-soluble peroxy radicals and a probe; long lag time for accumulation of colored radical reagents
DPPH	stable radical	measures the decay of DPPH free radical reacted with antioxidants	DPPH + H_2O → DPPH* DPPH* + AH → A* ROO* + A* → ROOA	models the antioxidant compound's ability to scavenge free radicals in the reaction system − simplicity, reproducibility; as methanol is used as reaction medium, water-soluble and polar lipid antioxidants can be used in the model; however, it may be interfered with by red or purple pigments in the sample because the absorbance is measured at 517 nm
TEAC	SET	measures the production of Mn(II)	X* + AH → X^- + AH^{*+} AH^* + H_2O → A* + H_3O^+ X^- + H_3O^+ → XH + H_2O M(III) + AH → AH^+ +M(II)	models the antioxidant compound's ability to donate electron—simplicity, reproducibility, more diversity than other method because methanol can be used as reaction medium; the method can be applied to polar lipophilic antioxidants; some inorganic compounds could also interfere with the reaction
FRAP	SET	measures the production of Fe(II) from Fe(III) at 593 nm	Fe(III) in TPTZ (ferric tripyridyltriazine) → Fe(II) at lower pH	models the antioxidant compounds ability to donate electron—simple but the measurement at wavelength 593 nm may be interfered with by the blue, green, or purple colorants in the sample; also, the reaction is nonspecific; some inorganic compounds could also reduce Fe(III) to Fe(II)
CUPRAC	SET	measures the production of Cu(I) from Cu(II) at 450 nm	Cu(II) in bio(neocuproine) copper chelate → Cu (I) at pH 7	models the antioxidant compounds ability to donate electron—simple but the measurement at wavelength 450 nm may be interfered with by the yellow colorants in the sample; also, the reaction is nonspecific; some inorganic compounds could also reduce Fe(III) to Fe(II)

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Table 3. Antioxidant Activities of 20 Flavonoids and Cinnamic Acid Derivatives Analyzed in the FRAP, DPPH* (ARP Values), ORAC, CUPRAC, and ESR Assays

	μmol TE/ μmol				
phenolic compound	$FRAP_{60}$[a]	$DPPH_{120}$[b]	ORAC[c]	CUPRAC	ESR
Flavonols					
quercetin	4.0 ± 0.0	3.8 ± 0.1	2.7 ± 0.1	4.38	16.0
quercetin-3-rutinoside	2.4 ± 0.0	3.3 ± 0.1	3.6 ± 0.3		5.1
quercetin-3-glucoside	2.3 ± 0.0	3.1 ± 0.0	3.2 ± 0.2		
quercetin-3-galactoside	2.0 ± 0.1	3.1 ± 0.4	3.2 ± 0.1		
quercetin-3-rhamnoside	2.3 ± 0.0	3.4 ± 0.1	3.7 ± 0.2		
myricetin	2.9 ± 0.1	3.0 ± 0.1	2.6 ± 0.2		47.1
kaempferol	1.8 ± 0.0	1.2 ± 0.0	2.1 ± 0.1	1.87	2.7
kaempferol-7-neohesperidoside	1.8 ± 0.1	1.3 ± 0.1	2.1 ± 0.3		
kaempferol-7-rutinoside	0.1 ± 0.0	ND[d]	2.2 ± 0.2		
Flavan-3-ols					
(+)-catechin	1.8 ± 0.0	3.5 ± 0.2	3.9 ± 0.2	3.09	15.3
(−)-epicatechin	1.7 ± 0.1	3.4 ± 0.1	4.0 ± 0.2	5.32	11.5
Anthocyanins					
cyanidin-3-glucoside	3.9 ± 0.0	2.8 ± 0.2	2.8 ± 0.3		2.6
cyanidin-3-galactoside	3.7 ± 0.2	2.9 ± 0.1	2.7 ± 0.2		17.4
petunidin-3-glucoside	3.5 ± 0.1	2.5 ± 0.2	2.6 ± 0.1		
delphinidin-3-glucoside	3.1 ± 0.0	1.9 ± 0.1	2.4 ± 0.3		61.4
malvidin-3-glucoside	2.4 ± 0.0	1.6 ± 0.1	2.3 ± 0.2		
peonidin-3-glucoside	1.8 ± 0.0	1.6 ± 0.0	2.3 ± 0.3		
Cinnamic Acid Derivatives					
caffeic acid	1.5 ± 0.0	1.5 ± 0.0	2.1 ± 0.1	2.89	
chlorogenic acid	1.5 ± 0.0	1.9 ± 0.1	2.0 ± 0.1	2.47	18.4
p-coumaric acid	0.3 ± 0.0	0.01 ± 0.00	1.6 ± 0.2	0.55	

[a]FRAP of antioxidants (250 μM) after 60 min of reaction time, expressed as μmol TE/μmol of antioxidant ± SE (n = 3). [b]ARP as μmol of DPPH* reduced after 120 min by the amount (μmol) of antioxidant necessary for 50% reduction of DPPH*, expressed as μmol of TE/μmol of antioxidant ± SE (n = 6). [c]ORAC expressed as μmol of TE/μmol of antioxidant ± SE (n = 6). [d]No detectable reaction with DPPH*.[55,184−186]

Phenolic antioxidants have been used to protect foods from lipid oxidation for many years. The synthetic phenolic-based antioxidants butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), *tert*-butylhydroquinone (TBHQ), and propyl gallate effectively inhibit lipid oxidation by quenching free radicals or interrupting the propagation of lipid peroxidation. In the mid-1990s the safety of these compounds came under scrutiny.[135−139] These concerns resulted in consumer desires for clean labels and the need for antioxidants from natural sources.[138,139] Plant tissues live under constant stress from reactive oxygen species (ROS), free radicals, peroxides, and other pro-oxidants. As a result, many plants have evolved protective mechanisms to help control these stress factors.[140−142] Natural phenolic compounds are frequently found in herbs and spices, which have traditionally been used for flavor but earlier were used as preservatives for food. The antioxidant capabilities of the herbs and spices were intensely investigated and found to provide strong antioxidant activity.[139,143] Spices become attractive sources of antioxidants because they are typically rich in polyphenolic compounds, which either scavenge free radicals, quench singlet oxygen, or, in some cases, chelate pro-oxidant metal ions. Many of the common spices used can serve as sources of radical-scavenging antioxidants.[144] Frequently, the polyphenolic antioxidants have been extracted from the parent spice source to produce antioxidant mixtures with lower flavor intensity. The antioxidants in common spices are summarized in a review by Suhaj, and more extensive data can be found in the USDA database.[145,146] The interest in natural antioxidants in foods and food ingredients has resulted in investigation regarding the identification of phenolic antioxidants in a wide range of foods and food ingredients including tea and coffee,[109,110,147−149] cereals and grains,[150−153] cocoa,[149,154−161] fruits and vegetables,[11,65,162−167] and legume seeds.[168] The phenolic antioxidants extracted from various sources can be used to stabilize lipid-containing foods,[169] and endogenous phenolics protect oils such as olive oils.[170]

ESTIMATION OF ANTIOXIDATIVE ACTIVITIES OF PHENOLIC COMPOUNDS

In recent years the emphasis in the literature concerning phenolic and polyphenolic compounds is their antioxidant activity and its potential impact on health and wellness. There are a number of in-depth reviews on the benefits and concerns around phenolic antioxidant activity related to health benefits. Many of the studies are cell culture based and fail to have sufficient clinical support to provide proof of benefits.[171−182] The interest in the antioxidant activity of phenolics evolved into measuring the antioxidant activity of food plants, herbals, and traditional medicine plants. The establishment of cell culture assays then allowed measurement of the impact of the phenolic antioxidants on antioxidant activity in cultured cells. This has resulted in extensive work attempting to correlate the antioxidant activity in cultured cells with risk reduction for many chronic diseases.

A number of methods have been applied to estimate the antioxidant activity of phenolic and polyphenolic compounds in plant tissue, in cultured cell systems, and in vivo. Cell culture assays for antioxidant activity often relate to oxidative DNA damage, as this is considered to be relevant to carcinogenesis,

Table 4. Correlations of Analytical Methods for Antioxidants[a]

					FRAP		DPPH
		TP	TEAC	ORAC	FE	TE	VCE
Fruits[117,187,193,194]							
TEAC		**0.9075**					
ORAC		0.8908	0.8145				
FRAP	FE	0.8957	0.7753	0.7920			
	TE	0.0267	0.0001	NA	NA		
DPPH	TE	0.6492	0.7295	0.2871	0.5430	0.0304	
	VCE	NA	NA	0.2469	NA	NA	
ABTS		NA	NA	0.4149	NA	NA	0.7352
TRAP		NA	0.8535	NA	0.8493	NA	NA
Vegetables[117,187,193,195]							
TEAC		0.7177					
ORAC		0.4932	**0.9841**				
FRAP	FE	0.4120	0.6483	**0.9335**			
	TE	0.4160	0.6860	NA	NA		
DPPH	TE	0.2055	0.3062	0.6928	0.8521	**0.9821**	
ABTS		NA	NA	0.0104	NA	NA	0.8873
TRAP		NA	0.4309	NA	0.5542	NA	NA
Beverages[117,156,193,196]							
TEAC		0.5181					
ORAC		0.8440	0.5549				
FRAP	FE	0.8482	0.0271	0.7327			
	TE	**0.9365**	0.2079	NA	NA		
DPPH	TE	**0.9275**	**0.9155**	NA	NA	**0.9629**	
	VCE	NA	NA	0.5162	NA	NA	
	% inhib	0.6210	0.8262	0.3379	0.7280	NA	NA
ABTS		NA	NA	0.4959	NA	NA	**0.9693**
TRAP		NA	**0.9868**	NA	**0.9812**	**0.9854**	NA

Herbs[197]			FRAP	DPPH
		TP	TE	TE
FRAP	TE	0.0001		
DPPH	TE	0.0022	0.1704	
ABTS		0.0003	0.7874	0.1949

Plant Extracts[198]				FRAP	DPPH	
		TP	ORAC	FE	% inhib	ABTS
ORAC		0.7368				
FRAP	FE	0.8131	0.4151			
DPPH	% inhib	**0.9003**	0.7685	0.6836		
ABTS		**0.9442**	0.6397	0.8764	0.8486	
SOD		0.7649	0.6108	0.7605	0.7764	0.8089

[a]Abbreviations: TP, total phenolics; FE, Fe^{2+} equivalents; TE, trolox equivalents; VCE, vitamin C equivalents; % inhib, % inhibition.

and generally evaluate the effect of phenolics on 12-*O*-tetradecanoylphorbol 13-acetate (TPA)-inducing ROS generation, H_20_2 scavenging, H_2O_2-induced apoptosis, xanthine oxidase activity, and lipopolysaccharide (LPS)-inducing NO generation.[183]

The methods that evaluate the capacity of antioxidants to deactivate radicals are based on either single-electron transfer (SET) or hydrogen atom transfer (HAT). In HAT-based methods the antioxidant donates a hydrogen to quench the free radical. The activity of the hydrogen donor is determined by the bond-dissociating energy of the donor group.[184] HAT reactions are influenced by the presence of other reducing agents, metals, pH, and solvent. Reaction times are from seconds to minutes.[53]

$$X^* + AH \rightarrow XH + A^* \quad (AH = \text{any H donor})$$

The SET reaction is based on the transfer of a single electron to reduce a compound. This single electron can be transferred to metals, carbonyls, or radicals.[184] The SET reactions are generally slower.

$$X^* + AH \rightarrow X^- + AH^{*+}$$

$$AH^{*+} + H_2O \rightarrow A^* + H_3O^+$$

$$X^- + H_3O^+ \rightarrow XH + H_2O$$

Because SET reactions are dependent on ionization potential, they tend to slow with increasing pH.[53,185] In cell culture and plasma samples the SET reactions are sensitive to

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uric acid and ascorbic acid, which are important to maintaining plasma redox balance. Trace metals cause major interference problems with SET methods and can cause high variability in results.[53]

The SET and HAT methods invariably react together depending on the pH and the particular antioxidant being tested. Briefly, the methods are described in Table 2.

Table 3 summarizes data from refs 186−189 comparing FRAP, DPPH, ORAC, CUPRAC, and ESR values for some pure phenolics. The data shows that there is great variation with pure phenolics between assays and that when similar assays are conducted in different laboratories, these results can also show high levels of variation. Wolfe and Liu[190] developed a cellular antioxidant assay designed for use on foods and dietary supplements. This was an attempt to establish an assay that would have greater correlation with in vivo effects. There is a clear need for a rapid assay that estimates the health benefits of polyphenols in foods. The antioxidant activity measured by chemical methods has been an area of intense research, and two international symposia that were sponsored by the *Journal of Agricultural and Food Chemistry* discussed and debated the merits of various assays and how they related to health and disease.

There are several studies that compare antioxidant methods of a variety of foods.[148,156,191,192] The antioxidant capacity of several foods and plant extracts was obtained from the literature.[117,187,192−198] The assays included were total phenolics (TP), TEAC, FRAP, DPPH, ABTS, ORAC, and TRAP. Foods were separated into five categories, namely, fruits, vegetables, beverages, herbs, and plant extracts. For each of the five categories of foods, *R*-squared values were calculated to achieve a comparison of the different methods reported. The analysis was performed with Microsoft Excel 2010. Table 4 summarizes the correlations of the various methods, between methods, and total phenolic content of the various groups of foods tested. Generally, there are agreements within the methods within groups. The variation in polyphenolic content of foods makes it difficult to have one analysis fit all. When one considers the variations of results measuring antioxidant activity for different phenolics and combines it with plant diversity, it is not surprising that comparison between plants or types of plants is more challenging. Hossain et al.[144] attempted to resolve this question through application of hierarchical component clustering using different antioxidant methods and analyzing for individual polyphenol compounds in spices. Most antioxidant methods correlate well with the total Folin phenolic assay.

A major advantage of the ORAC assay is that it can be altered to use with either hydrophilic or hydrophobic systems.[199] USDA workers[200,201] have extended the ORAC for use in assessing the antioxidant capacity of human serum, which provides a useful tool for assessing the impact of antioxidant consumption on human serum status.

In recent years the ORAC analysis has occasionally been misused in the promotion of supplements. If one performs a search on an engine such as Google and enters ORAC, a number of commercial promotions can be found claiming high ORAC values. These frequently include unfair comparisons, for example, comparing a dry plant extract to hydrated products such as blueberry or acai juices.

Recent literature is suggesting that the in vivo role of polyphenolic compounds goes far beyond antioxidant activity. Many of the polyphenols have been demonstrated to act as anti-inflammatory agents through interference with inflammatory pathways.[202−212] It has been shown[202] that anthocyanins and other phenolic compounds interfere with the tumor necrosis factor α pathway in macrophages. Many studies have been focused on cell culture models, and as a result there remains a need for animal models and clinical trials to substantiate the anti-inflammatory effects.

HEALTH BENEFITS

Because antioxidative activities are the hallmark of phenolics that have been described in numerous publications, we will not describe them here. Similarly, the ability to chelate metals will not be discussed. Rather, we will focus on the mechanisms by which phenolics may exert beneficial health effects when consumed by discussing the bioavailability and metabolism of phenolics and their effects on endothelial and mitochondrial dysfunction. Both the endothelial and mitochondrial dysfunctions are discussed because they represent common features of all chronic diseases for which the health benefits of phenolics are very much needed.

Bioavailability of Phenolic Compounds. There is considerable work on absorption of phenolic and polyphenolic compounds. Generally, there is limited absorption despite the epidemiological observations that show significant health benefits associated with polyphenolic consumption. There is currently growing interest in understanding how the polyphenols are altered by the microbiome.

Phenolic compounds are diverse, and their bioavailability in the human gastrointestinal tract differs from one class of phenolics to another and is multifactorial owing to their diversity. Phenolic acids, flavonoids, stilbenes, coumarins, quinones, and lignans do not necessarily absorb in a similar way. In general, phenolics are known to be poorly bioavailable. This poor bioavailability is multifactorial and starts as soon as the phenolic compounds enter the mouth. The process of bioavailability involves the ingestion of the phenolics, which encounter their first interaction with salivary proteins. Two groups of salivary proteins, proline-rich and histidine-rich proteins or histatins, interact with and precipitate tannins and act as a first line of defense against tannin absorption.[213] Astringency or the puckering sensation in the mouth is associated with the ability of proline-rich salivary proteins to sequester polyphenols from foods or beverages.[214] This implies that some ingested phenolics do not reach the stomach unaffected. Proline-rich and especially histidine-rich protein histatins in the submandibular/sublingual saliva also protect salivary amylase from inhibition by tannins.[215] This protective mechanism allows carbohydrate digestion by salivary amylase to proceed unaffected. Except for tannins, there is no literature on the interactions of phenolics and salivary proteins.

Following the mouth, ingested phenolics enter the small intestine, where the first potential absorption takes place. However, before phenolics enter the circulation, several scenarios may occur: (1) Phenolics have been shown to inhibit pathogens bound to the epithelial cells in the small intestine, suggesting that the interacting phenolics may have a reduced or delayed bioavailability.[216] (2) Phenolics, especially ellagitannins from cranberry, cloudberry, raspberry, strawberry, and bilberry, are antimicrobial and prevent the growth of *Salmonella* and *Staphylococcus* in epithelial cells.[216] The fate of the phenolics after complexing with bacteria is not known. (3) Others have shown that phenolics in the small intestine can also bind to minerals, specifically iron, forming iron-chelating complexes.[217]

(4) Phenolics are hydrolyzed by glucosidase from the brush-border of the small intestine epithelial cells into aglycones.[218] Two hydrolytic enzymes have been identified in the epithelial cell, including lactase phloridizin hydrolase (LPH) and cytosolic β-glucosidase (CBG).[218] (5) The metabolite can either enter the circulation or be effluxed back into the lumen of the small intestine by the ATP-binding cassette family of transporters including multidrug resistance protein (MRP) and P-glycoprotein (P-gp). The absorption and bioavailability of phenolic compounds are also a function of the structure of the molecule, including its molecular size, and the presence of glycosyl or ester groups.[219]

The absorption of phenolic compounds in humans is a complex and highly variable phenomenon that manifests rapid absorption and sometimes no absorption at all, with or without phenolic compound structure modification.[164] For instance, gallic acid, free or bound as found in black tea or wine, was shown to be absorbed as is, methylated, or glucuronidated.[220] Malvidin-3-glucoside, the major anthocyanin in most blueberries and red grape juice, has been detected intact in the plasma and urine of human volunteers.[221] Resveratrol, a model stilbene, has a very low bioavailability in humans due in part to its susceptibility to first-pass glucuronidation in the gastrointestinal tract and liver.[222] Phenolics or phenolic metabolites that reach the bloodstream can be subject to phase II metabolism involving, among others, cytochrome P450 enzymes with potential conversion in the liver, where enterohepatic transport in the bile may return some of the metabolites to the small intestine.[218] Onion quercetin-*O*-glucosides are the best example of phenolic compounds that are hydrolyzed in the small intestine by LPH and CBG lactase, and the resultant aglycone is transported into the enterocyte and is subject to sulfation, glucuronidation, and methylation; metabolites such as quercetin-3′-*O*-sulfate, quercetin-3-*O*-glucuronide, and quercetin-*O*-diglucuronide are detected in circulation.[218] Green tea flavan-3-ols including (−)-epicatechin-3-*O*-gallate and (−)-epigallocatechin-3-*O*-gallate are also absorbed as glucuronide, methyl glucuronide, and methyl sulfate metabolites.[218] Whereas lower oligomers of procyanidins are absorbed, particularly from wine and cocoa, larger polymeric procyanidins are not absorbed in the small intestine. Anthocyanins are diverse and enter the circulation as sulfate, glucuronides, or methyl glucosides. Isoflavones from soybean also enter the circulation in different forms such as equol, glucoside, sulfate, and glucuronide.[218] Ellagitannin metabolites in circulation include ellagic acid, glucuronides, and methyl glucuronides of ellagic acid and urolithin, and urine excretions contain urolithin, glucuronides, and methyl glucuronides. The concentrations of the metabolites in circulation are often on the order of nanomoles or submicromoles.

Recent studies suggest that the bioavailability of phenolics should be investigated and discussed taking into consideration the gut microbiota. Phenolic compounds that are not absorbed or transformed in the small intestine travel to the large intestine, where they are metabolized into phenolic acids by the gut microflora including *Bacteroidetes*, *Clostridium*, *Eubacterium*, *Ruminococcus*, *Eggertbella*, *Lactobacillus*, and *Bifidobacteria*.[223] In individuals with altered gut microflora, including those with inflammatory bowel disease, the profile of phenolic metabolites is altered and different from the phenolic metabolites in comparable healthy individuals.[224] In the large intestine, bacteria-mediated deglycosylation along with glucuronidation and sulfation lead to ring fission, catabolism, and the generation of phenolic acids, some of which are found in circulation and some of which are excreted. Orange flavanones including rutinosides are absorbed from the large intestine, where they are metabolized into glucuronides or phenolic acids after probably undergoing phase II metabolism. Similar metabolism and formation of phenolic acids occur when tomato juice quercetin-3-*O*-rutinosides are ingested.[225]

Inhibition of Endothelium Dysfunction. Healthy vascular endothelium exerts a fine control of cardiovascular homeostasis by preventing access to molecules susceptible to stimulate inflammation including LDL.[226] To maintain vascular tone and integrity of the barrier, vascular endothelial cells produce vasodilators such as nitric oxide (NO) from L-arginine by the action of nitric oxide synthase or prostacyclin and vasoconstrictors such as endothelin-1. NO is a vasodilator that also suppresses the expression of endothelial adhesion molecules and prevents platelet aggregation.[225] However, oxidative stress conditions such as hyperglycemia, diabetes, hypertension, dyslipidemia, smoking, or oxidized LDLs generate ROS, which in turn rapidly inactivate NO.[226] Rapid inactivation of NO contributes to endothelial barrier dysfunction, leading to increased permeability of the endothelial cells. As a result, small and dense molecules such as LDL enter and accumulate in the arterial intima, the adhesiveness of leukocytes increases, and more leukocytes enter the endothelial cells and initiate inflammation.[227] Endothelial dysfunction is an early and independent predictor of poor prognosis in cardiovascular disease and characterized by impaired endothelium-dependent vasodilation, a reduced NO production and bioavailability, and a prothrombic and pro-inflammatory state of endothelial cells.[36] Endothelial dysfunction is a hallmark of hypertension, atherosclerosis, coronary heart disease, hyperglycemia, diabetes, dyslipidemia, and aging.

The mechanism by which polyphenolic compounds may improve endothelium function is not well established. Mechanistic evidence suggests that specific classes of phenolic compounds or their metabolites may prevent endothelial dysfunction by reducing multiple risk factors associated with endothelial malfunctioning including decreasing blood pressure, dyslipidemia, and LDL oxidation.[226] Flavonoids or anthocyanins do not directly induce NO production or increased bioavailability. Rather, these molecules, by virtue of their antioxidative and anti-inflammatory activities, can augment nitric oxide status through distinct pathways, thereby improving endothelial function. For instance, flavonoids can modify protein kinase mediated signal transduction and induce antioxidant and anti-inflammatory gene expression.[228,229] By the same token flavonoids can down-regulate inflammatory gene expression. Flavonoids can improve blood pressure, a well-established risk factor for endothelium dysfunction.[230] Flavonoids are reducing agents and chelators of metal-catalyzed oxidation of LDL.[231,232]

Soy isoflavones genistein, daidzein, and glycitein activate endothelial nitric oxide synthase and increase the capacity of serum to stimulate prostacyclin release in human endothelial cells.[233,234] Oral supplementation of soy isoflavones to postmenopausal women significantly increased flow-mediated vascular dilation (FMD) of the brachial artery in women with low baseline FMD but did improve endothelial function in women with high FMD.[235] Similar improvement in endothelial dysfunction has been observed following oral supplementation of soy isoflavones to patients with ischemic stroke.[236] Consumption of an isoflavone-enriched low-fat meal containing

80 mg of isoflavones acutely increases endothelium-dependent vasodilation in postmenopausal women.[237] Similar results have been obtained with purified isoflavone genistein in postmenopausal women.[238] In some studies, soy protein has been shown to enhance the bioactivity of isoflavones on endothelial cells.[239]

Cocoa bean (*Theobroma cacao*) is the source of cocoa, and the latter is a rich source of polyphenolic compounds including catechins, flavonol glycosides, anthocyanins, and procyanidins. Oligomers and polymers of procyanidins have been isolated in cocoa.[240] Cocoa polyphenols are bioavailable in nanomolar concentrations.[180] Hundreds of human clinical trials have been conducted on the benefits of cocoa, and the majority of these trials have shown that flavonoid-rich cocoa products improve endothelial function. Cocoa drinks and cocoa dark chocolate, but not white chocolate, induced vasodilation via increased endothelial NO production and bioavailability, inhibited the activity of matrix metalloproteinases, inhibited angiotensin converting enzyme activity, improved insulin-mediated vasodilation in hypertensive patients, activated the eNOS system, and lowered blood pressure in healthy people.[180,238] However, because most commercial cocoa products contain high amounts of sugars, it has been suggested that sugar may mask the health benefits of cocoa products on the market.[241]

The vascular action of pomegranate phenolics has been positive for endothelial function. One serving or 240 mL of homemade pomegranate juice with no sugar added given to 30 adolescents aged 12−15 years with metabolic syndrome once a day for 1 month showed significant improvement in basal brachial artery dimension and FMD as an index of endothelial function.[242] However, the same 240 mL pomegranate juice consumption for 18 months had no significant effect on overall carotid intima-media thickness (CIMT) progression rates in men and women at moderate risk for coronary heart disease, but the authors suggested that the juice may have slowed CIMT progression in subjects with increased oxidative stress and disturbances in the TG-rich lipoprotein/HDL axis.[243] There are countless in vitro positive effects of pomegranate juice on vascular health in the literature.

Green and black tea consumption improves endothelial function and ameliorates endothelial dysfunction in humans. The mechanism of improved endothelial function has been ascribed to the plasma level of epigallocatechin gallate (EGCG) and catechins in green tea and theaflavin in black tea that inhibit matrix metalloproteinases, increase eNOS activity, and improve FMD.[244−247] Green tea also improved flow-mediated endothelium dependent vasodilation (FMD) of the brachial artery in smokers.[248] Theaflavins and thearubigins are bioactive compounds in black tea responsible for the contribution of black tea consumption in the prevention of cardiovascular diseases.[180,238,249]

The effect of grape and red wine polyphenols on vascular health has been very controversial. Some studies have shown improved endothelial function in healthy individuals as well as smokers, whereas others have shown no improvement at all.[239] No positive clinical effect of resveratrol on NO in humans has been reported to date.[239] The mechanism of activity of grape skins or red wine has been ascribed to resveratrol. However, the resveratrol level in wines is very low; the plasma level of resveratrol or its metabolite is also so low that is unlikely to achieve any meaningful result.

High levels of virgin olive oil in meals improved ischemic reactive hyperemia during the postprandial state possibly via reduction of oxidative stress and increase of nitric oxide metabolites.[250] Mechanistically, the protective effect of the oil may be ascribed to its content of hydroxytyrosol and oleuropein aglycone, both of which, at concentrations that are physiologically relevant, significantly reduce the endothelial cell surface expression of intercellular and vascular cell adhesion molecules (ICAM-1 and VCAM-1) and E-selectin and their mRNA expression.[251]

Inhibition of Mitochondrial Dysfunction. Mitochondrial dysfunction results from the damage to complex I, the first and most complex protein in the electron transport chain, during which elevated levels of ROS are produced in the mitochondria and target DNA, lipids, membranes, and proteins, leading to alterations of signaling pathways; the latter leads to mitochondrial dysfunction.[252] The pathology of several chronic diseases is considered to be associated with mitochondrial dysfunction at the early stages of many diseases. Insulin resistance, which is the centerpiece of the pathological mechanism of metabolic syndrome, is closely related to mitochondrial dysfunction.[253] Excessive production of ROS has been reported as the underlying mechanism for the etiology of several chronic diseases. For instance, activation of Ras, Myc, and p53 cause mitochondrial dysfunction, resulting in mitochondrial ROS production and downstream signaling (e.g., NF-κB, STAT3, etc.) that promote inflammation-associated cancer.[254] Alzheimer's disease (AD) is considered to be associated with mitochondrial dysfunction at the early stage of AD before the onset of clinical symptoms.[255,256] Mitochondrial dysfunction has been implicated in the loss of cardiomyocytes in various cardiac pathologies including congestive heart failure, cardiomyopathy, and ischemia-reperfusion.[257] Parkinson's disease (PD) is characterized by a combination of inflammation, mitochondrial dysfunction, iron accumulation, and oxidative stress. Mitochondrial complex I impairment and subsequent oxidative stress have been identified as modulators of cell death in experimental models of PD.[258] Recent studies show that polyphenols including resveratrol, green tea EGCG, and citrus luteolin significantly inhibit the activation of caspase-3 and modulate mitogen-activated protein kinases, which play an important role in neuronal apoptosis.[259] Cinnamon polyphenol extract (CPE) reduced oxygen-glucose deprivation (OGD)-induced cell swelling as well as the decline in DeltaPsi(m) in cultures through inhibition of membrane permeability transition.[260] Phenolic compounds such as quercetin, resveratrol, and rutin, which can enter and accumulate in the mitochondria, may protect them from dysfunction associated with accumulation of NADH that leads to overproduction of mitochondrial oxygen radical species.[261] Protocatechuic acid, the metabolite of cyanidin-3-glucoside, inhibits hydrogen peroxide-induced ROS formation and mitochondrial functioning loss and DNA fragmentation in human neuronal cell lines SH-SY5Y.[262] Chronic administration of moderate amounts of grape seed proanthocyanidin extract (GSPE) at 25 and 50 mg GSPE/kg body weight improved the mitochondrial function and thermogenic capacity of the brown adipose tissue of obese Wistar rats.[263]

The emphasis of polyphenols has changed significantly over the past century. It has evolved from the elucidation of anthocyanin colors to ongoing studies on the positive and negative impacts on flavor to current studies on health benefits. The polyphenols have been documented to provide multiple health benefits, although the mechanisms of action are yet to be

determined in many cases. The antioxidant activity of the compounds evolved to research suggesting that the in vivo modes of action may be related to gene expression and regulation, which influence inflammatory pathways. There are clearly many remaining questions to be answered on the multiple benefits of polyphenols, their metabolites, and the impact of foods containing this extensive family of compounds.

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Notes

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NOTE ADDED AFTER ASAP PUBLICATION

Author Ashley Gutierrez was inadvertently omitted from the original ASAP posting of May 16, 2012. This has been corrected with the posting of June 1, 2012.