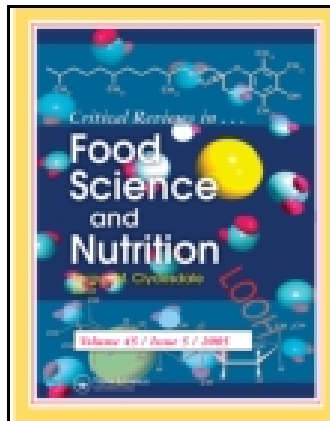


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Grape Phytochemicals and Associated Health Benefits

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The phytochemicals present in fruits and vegetables may play an important role in decreasing chronic disease risk. Grapes, one of the most popular and widely cultivated and consumed fruits in the world, are rich in phytochemicals. Epidemiological evidence has linked the consumption of grapes with reduced risk of chronic diseases, including certain types of cancer and cardiovascular disease. In vitro and in vivo studies have shown that grapes have strong antioxidant activity, inhibiting cancer cell proliferation and suppressing platelet aggregation, while also lowering cholesterol. Grapes contain a variety of phytochemicals, like phenolic acids, stilbenes, anthocyanins, and proanthocyanidins, all of which are strong antioxidants. The phytochemical composition of grapes, however, varies greatly among different varieties. While extensive research exists, a literature review of the health benefits of grapes and their phytochemicals has not been compiled to summarize this work. The aim of this paper is to critically review the most recent literature regarding the concentrations, biological activities, and mechanisms of grape phytochemicals.

Keywords Grapes, phenolics, phytochemicals, antioxidant activity, cardiovascular disease, cancer

INTRODUCTION

Cardiovascular diseases (CVD) and cancer are the leading causes of death in the United States and in most industrialized countries. According to 2007 mortality rate data, over 2,200 Americans die of CVD each day, an average of one death every 39 seconds (Roger et al., 2011). Cancer is the second most common cause of death in the United States, exceeded only by heart disease. In the United States, cancer accounts for one in every four deaths (American Cancer Society, 2012). Both diseases are thought to be the result of oxidative stress, which can damage biological macromolecules in human. However, dietary patterns may play an important role in the prevention of chronic diseases. A healthy eating plan from the 2010 Dietary Guidelines for Americans emphasizes the consumption of fruits and vegetables. Fruits and vegetables contain a wide array of phytochemicals such as phenolics, flavonoids, isoflavonoids, thiols, carotenoids, ascorbic acid, tocopherols, sulforaphane, indoles, isothiocyanates, and glucosinolates, which have positive biolog-

ical effects and may protect individuals from chronic diseases including CVD and cancer through a variety of mechanisms.

The grape (*Vitis*) is one of the popular and widely cultivated fruits in the world. There are about 60 species of *grapes*, most of which are found in the temperate zones of the Northern Hemisphere, distributed almost equally between America and Asia. Over 70% of *Vitis* species are native to North America, where two main grape species are cultivated: *V. labrusca* and *V. rotundifolia*. *V. labrusca* has been bred with various cultivated *V. vinifera* to create hybrid grapes suitable for grape juice, jelly, fresh fruit, and wine (Remaily, 1987). *Labrusca* grapes, such as the popular Concord grape, are grown mostly in the lower Great Lakes region of the United States and Canada. Due to its abundance, Concord grapes are popular in the production of juices and jellies. *V. rotundifolia*, like the muscadine grape, has a long history in the South (Lane, 1997). Grapes have the highest value in fruit crops produced in the United States, and the sixth highest value among U.S. crops overall. Grape and grape product industries in the United States contribute more than \$162 billion annually to the American economy (MKF Research, 2007).

Grape phytochemicals from extract, such as from the skin, seed, and juice, have been identified as carotenoids, melatonin, and phenolics, the latter which include stilbenes, phenolic acids, and flavonoids. These phytochemicals are not only antioxidant, anticancer, anti-inflammatory, LDL-cholesterol oxidation and

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Dr. Jun Yang is an employee of PepsiCo Inc. The views expressed in this article are those of the Dr. Jun Yang, and do not necessarily reflect the position or policy of PepsiCo, Inc.

platelet aggregation lowering, antiplatelet, estrogenic, antiapoptotic, and antimicrobial; all functions which are beneficial to health, but they are also cardioprotective, neuroprotective, hepatoprotective, and inhibit age-related cognitive decline. In vitro and in vivo studies suggest that grape phenolics could lower the risk of cardiovascular disease by modulation of cellular redox state, prevention of LDL oxidation, improvement of endothelial function, lowering of blood pressure and inflammation, and inhibition of platelet aggregation (Pérez-Jiménez and Saura-Calixto, 2008; Dohadwala and Vita, 2009). The grape phenolic-mediated cardioprotective and vasoprotective properties are associated with its angiogenic, antihypercholesterolemic, antiatherosclerotic, antiarrhythmic, and antidiabetic actions, with mechanisms involved in reduced ventricular remodeling and increased cardiac functions (Penumathsa and Maulika, 2009). In particular, resveratrol (RSV), well known for its various biological and medicinal properties in humans, is a major active, biological component in grapes. RSV not only acts to decrease rosiglitazone-induced oxidative stress, osteoblast-like cell differentiation, and mineralization in human vascular smooth muscle cells (Bruedigam et al., 2011), but also activates the longevity protein - Sirtuin 1 (SIRT-1). It was reported that RSV decreases adipocyte number and size while increasing osteogenesis by acting on several molecular targets in adipocytes and osteoblasts (Rayalam et al., 2011). In addition, RSV, in combination with genistein and quercetin, synergistically reduces adipogenesis in murine and human adipocytes, which may lead to potential novel potent therapies for some chronic diseases. In general, the antioxidant properties of grape phenolics seem to play the largest role in the mechanism of cancer prevention; other mechanisms involved are cellular signaling and interactions, cell cycle and apoptosis, and induction of Phase II Enzymes at the genetic level.

The objectives of this paper are to discuss the accumulating evidence that grape extracts and purified bioactive components from grapes possess a diverse array of positive biological actions; and to review the current literature on grapes, especially those studies associated with grape phytochemicals, mechanisms of action, and overall health benefits.

GRAPE PHYTOCHEMICALS

Present in fruits, vegetables, grains, wine, tea, chocolate, and other plant-based foods, phytochemicals are a wide variety of bioactive compounds that have been linked to reductions in the risk of major chronic diseases. It is estimated that over 8,000 phytochemicals have been identified (Shahidi and Naczki, 2003). Due to the great structural diversity arising from various mechanisms of hydroxylation, glycosylation, methoxylation, and acylation, the phytochemical's number is constantly increasing. Generally, phytochemicals can be classified as alkaloids, carotenoids, nitrogen-containing compounds, organosulfur compounds, and phenolics, the latter constituting the largest and most ubiquitous groups of phytochemicals.

Grape (*V. vinifera*) phytochemicals are synthesized by three secondary metabolic pathways, including phenylpropanoid, isoprenoid, and alkaloid biosynthetic routes. The main phytochemicals in grape arise from acetyl-CoA and shikimic acids. Phenolic acids, flavonoids, stilbenes, and proanthocyanidins are biosynthesized through the phenylpropanoid pathway (Kurkin, 2003; Iriti and Faoro, 2009).

Phenolics

Phenolics in grape are generally classified into two groups: flavonoids and nonflavonoids. The major flavonoids include flavan-3-ols, flavonols, and anthocyanins. Flavonoids, such as anthocyanins, are principally localized in the skins, while the flavan-3-ols are present in both the skins and seeds. The non-flavonoids encompass phenolic acids and stilbenes.

Total Phenolics

In grapes, phenolics rank the third most abundant constituent after carbohydrates and acids. The distribution of total phenolics in juice, pulp, skins, and seeds is approximately 5%, 1%, 30%, and 64%, respectively (Singleton and Esau, 1969). Because red grapes can produce anthocyanins while white grapes cannot, the total phenolic level of red grape skins is higher than that of white grapes. Consequently, the phenolic content in red winemaking grapes is significantly higher than that of table grapes. Recently, the phenolic profile of different grape varieties around the world were reported (Yang et al., 2009; Katalinić et al., 2010; Baiano and Terracone, 2011; Lago-Vanzela et al., 2011; Lutz et al., 2011; Rockenbach et al., 2011). The content of total phenolics from selected grapes is summarized in Table 1, showing that the variability of phenolic content and profile is influenced largely by genetic factors, environmental conditions, and the stage of development of the plant organ (Göllücke, 2010).

The total phenolic, total flavonoid, and total anthocyanin contents in 14 selected wine grapes commonly grown in the Finger Lakes area of New York state was investigated (Yang et al., 2009). Cabernet Franc and Pinot Noir had the highest total phenolic content, while the lowest content was found in Cayuga White and Chardonnay, with over two-fold the difference between the highest and the lowest ranked varieties. The highest content of total flavonoids was measured in Pinot Noir, while the lowest content was found in Baco Noir, with over three-fold the difference. Katalinić et al. (2010) determined phenolic composition in grape skin extracts from 14 grape varieties grown in Croatia. The level of total phenols, flavonoids, catechins, flavanols, and individual phenolics, including (+)-catechin, (–)-epicatechin, epicatechin gallate, procyanidin B1 and procyanidin B2, quercetin glucoside, resveratrol monomers, piceid and astringin, was found to be variety-dependent. Using HPLC-DAD-ESIMS/MS, the phenolic composition (hydroxycinnamic acid derivatives, anthocyanins, flavonols, flavan-3-ol, stilbenes, etc.) in the skin and flesh of the new BRS Clara and BRS Morena

Table 1 Total phenolic content of different parts in grape variety

Grape	Total phenolics			Expressed as	Location	Reference
	Skin	Seed				
Red grape (<i>Vitis vinifera</i> & <i>Vitis labrusca</i>)						
Pinot Noir	660 ± 5		16, 518 ± 98	Catechin equivalents in mg/100 g dry weight	Santa Catarina, Brazil	Rockenbach et al., 2011
Isabel	1839 ± 11		2128 ± 19			
Sangiovese	750 ± 12		7682 ± 29			
Negro Amaro	686 ± 8		7237 ± 96			
Cabernet Sauvignon	1065 ± 17		8249 ± 125			
Primitivo	1328 ± 1		8963 ± 33			
	Pulp	Skin	Seed			
Noble & Carols muscadine grapes (<i>Vitis rotundifloia</i>)						
Seed mix of Noble & Carols			591.4 ± 2.0	Gallic acid equivalents in mg/100 g fresh weight	Wray, GA, USA	You et al., 2012
Noble skin		513.6 ± 5.7				
Carols skin		447.4 ± 3.7				
Noble fruit	396.0 ± 4.9					
Carols fruit	332.9 ± 3.9					
	Pulp	Skin	Seed			
Red & White grapes						
Vranec	2.17 ± 0.01	48.3 ± 0.08	139 ± 0.48	Gallic acid equivalents in mg/g fresh weight	Skopje, R. Macedonia	Ivanova et al., 2011
Merlot	2.32 ± 0.02	33.3 ± 0.09	124 ± 0.13			
Smederevka	1.46 ± 0.02	29.9 ± 0.14	108 ± 0.05			
Chardonnay	1.92 ± 0.014	8.71 ± 0.03	190 ± 0.20			
	Pulp	Skin				
Brazilian seedless table grape						
BRS Clara	135.5 ± 0.1	441.2 ± 15.3		Gallic acid equivalents in mg/kg	Brazil	Lago-Vanzela et al., 2011
BRS Morena	138.9 ± 0.2	869.2 ± 16.4				
		Skin				
Table grape (<i>Vitis vinifera</i> L.)						
Autumn Royal		129.0 ± 0.1		Gallic acid equivalents in mg/g	Chile	Lutz et al., 2011
Crimson seedless		64.3 ± 0.6				
Red Globe		63.2 ± 0.4				
Ribier		125.1 ± 1.0				
		Skin				
Red & White grapes <i>Vitis vinifera</i> L.						
Kujundžuša		1121 ± 23.5		Gallic acid equivalents in mg/kg	Croatia	Katalinić et al., 2010
Rkaciteli		539 ± 12.8				
Zlatica		1232 ± 3.52				
Medna		435 ± 1.69				
Kuč		545 ± 3.66				
Maraština		956 ± 7.05				
Debit		1294 ± 21.0				
Vranac		2252 ± 10.9				
Trnjak		3486 ± 54.7				
Rudežuša		2972 ± 18.2				
Merlot		1666 ± 21.1				
Babić		1031 ± 16.0				
Lasin		731 ± 9.06				
Plavina		820 ± 8.61				
		Skin				
Wine grape (<i>Vitis vinifera</i> & hybrid)						
Cabernet Franc	424.6 ± 3.8			Gallic acid equivalents in mg/100 g fresh weight	New York, USA	Yang et al., 2009
Chardonnay	201.1 ± 4.9					
Pinot Noir	396.8 ± 12.4					
Riesling	255.8 ± 8.8					
Baco Noir	217.0 ± 14.1					
Catawba	311.7 ± 9.1b					
Cayuga white	206.3 ± 8.2					
Chancellor	325.8 ± 21.7					
Concord	334.0 ± 13.6					
DeChaunac	293.5 ± 21.6					

(Continued on next page)

Table 1 Total phenolic content of different parts in grape variety (*Continued*)

Grape	Total phenolics			Expressed as	Location	Reference
		Skin				
Marechal Foch		312.5 ± 10.9				
Niagara		229.6 ± 3.9				
Sheridan		331.4 ± 8.2				
Vidal Blanc		228.0 ± 5.5				
	Pulp juices	Skin	Seed			
Table grape						
Baresana	0.395 ± 0.025	39.6 ± 6.7	116 ± 23	Gallic acid equivalents in g/kg of dry skins or seeds; Gallic acid equivalents in g/L of pulp juices	Italy	Baiano and Terracone, 2011
Italia	0.745 ± 0.102	49.3 ± 10.3	183 ± 20			
Pizzutello	0.503 ± 0.059	29.4 ± 4.2	154 ± 21			
Thompson seedless	0.823 ± 0.080	—	22.7 ± 4.6			
Crimson seedless	0.617 ± 0.057	—	62.9 ± 13.6			
Michele Palieri	0.449 ± 0.036	44.6 ± 6.7	189 ± 38			
Red Globe	0.349 ± 0.049	33.1 ± 6.9	111 ± 12			

seedless table grapes was found (Lago-Vanzela et al., 2011). The BRS Clara and BRS Morena grape varieties contained total phenolic contents of 577 and 1,008 mg of GAE/kg of fresh weight, respectively. The distribution of phenolic content for both grapes was concentrated in the skin with 86.2% for the BRS Morena grape and 76.5% in the BRS Clara grape, respectively; these grapes contained 13.8% and 23.5% phenolic content in the flesh. Rockenbach et al. (2011) quantified the phenolic content in seed and skin extracts of red grape (*Vitis vinifera* and *Vitis labrusca*) pomace from Brazil. The study found a higher level of phenolics in the seeds than in the skins. The skin of Cabernet Sauvignon and Primitivo varieties contained the highest contents of anthocyanins with 935 and 832 mg/100 g, respectively. When four varieties of grape juice and skin fractions of table grapes grown in Chile were studied in order to determine and compare total phenolics, anthocyanins, and specific compounds such as caffeic acid, gallic acid, resveratrol, and catechin content, higher amounts of total phenolics were observed in the skin fractions ($P < 0.05$) (Lutz et al., 2011). A study of seven table grape cultivars grown in Apulia region examining phenolic content found, in decreasing order, the greatest amount in seeds, skins, and pulps (Baiano and Terracone, 2011). The highest phenolic content was discovered in the white and the red/black table grapes of Italia and Michele Palieri cv., respectively. However, the experimental data from this study showed that the phenolic content of different grapes depended mainly on varietal differences, not on grape-skin color, which confirms the results from previous reports (Yang et al., 2009). You et al. (2012) have recently identified and compared the phytochemicals of the whole fruit and different plant parts of the Noble and Carols muscadine (*V. rotundifolia*) grapes by using HPLC-UV-MS and HPLC-ELSD methods. The results showed that 24 phenolics, including five anthocyanins in the muscadine grapes Gallic acid, (–)-epicatechin, and ellagic acid were found as major phenolics in Carols muscadine grapes and seed portion, while anthocyanins were the major phenolics in Noble muscadine and skin portion. To track phenolic content change during ripening, HPLC-DAD-MS and MS/MS techniques were used at veraison, physiological ripeness, and the late harvest phase of the grapes

of Vranec, Merlot, Smederevka, and Chardonnay varieties in their skin, seed, and pulp extract (Ivanova et al., 2011). Thirty-one phenolic compounds, including phenolic acids derivatives, anthocyanins, flavonols, and flavan-3-ols, were identified in the extracts prepared from the grapes at physiological maturity. Compared to Merlot, Vranec contained a higher total phenolic and flavonoid content in the skins and seeds, as well as a higher content of flavan-3-ols and anthocyanins in the skins. In addition, the level of anthocyanin monoglucosides and *p*-coumaroylglucosides in Vranec grapes was relatively high, as verified by HPLC-ESI-IT MS analysis. As the major component in the grape seeds, flavan-3-ols found in Vranec, Merlot, Smederevka, and Chardonnay at veraison phase were 16.7 ± 0.51 , 18.4 ± 0.16 , 24.5 ± 0.01 , and 12.4 ± 0.14 mg/g, respectively.

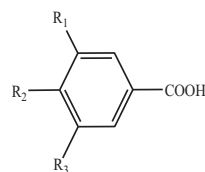
Phenolic Acids

The most common phenolic acids occurring in *Vitis* are usually comprised of benzoic acid derivatives, containing seven carbon atoms (C6-C1), and cinnamic acid derivatives, containing nine carbon atoms (C6-C3) (Fig. 1). Natural phenolic acids in grapes, occurring either in the free or conjugated forms, generally appear as esters or amides. Benzoic acid derivatives are a minor component in new wines. Hydroxycinnamic acid derivatives are the major phenolics present in grape juice and white wine. Three common hydroxycinnamic acid derivatives in grapes and wine are caffeic acid (caffeic acid), coumaric acid (coumaric acid), and ferulic acid (ferulic acid). In red grapes, larcitrin and syringetin derivatives were also documented (Mattivi et al., 2006). Some phenolic acid content was present in the grapes is displayed in Table 2.

Flavonoids

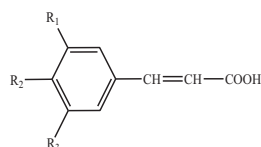
The generic structure of flavonoids consists of two aromatic rings (A and B rings) linked by three carbons that are usually in an oxygenated heterocycle ring called a C ring (Fig. 2). Based on

1) Benzoic Acid



Benzoic acid Derivatives	Substitutions		
	R ₁	R ₂	R ₃
<i>p</i> -Hydroxybenzoic acid	H	OH	H
Protocatechuic acid	H	OH	OH
Vanillic acid	OCH ₃	OH	H
Syringic acid	OCH ₃	OH	OCH ₃
Gallic acid	OH	OH	OH

2) Cinnamic Acid



Cinnamic acid Derivatives	Substitutions		
	R ₁	R ₂	R ₃
<i>p</i> -Coumaric acid	H	OH	H
Caffeic acid	OH	OH	H
Ferulic acid	OCH ₃	OH	H
Sinapic acid	OCH ₃	OH	OCH ₃

Figure 1 Structures of common phenolic acids: (1) benzoic acid derivatives; (2) cinnamic acid derivatives.

differences in the heterocycle C ring, flavonoids are categorized as flavonols (quercetin, kaempferol, and myricetin), flavones (luteolin and apigenin), flavanols (catechins, epicatechin, epigallocatechin, and epicatechin gallate), flavanones (naringenin), anthocyanidins, or isoflavonoids (genistein, daidzein, dihydrodaidzein, and equol). Naturally occurring flavonoids are mostly conjugated in glycosylated or esterified forms, but can also occur as aglycones, especially as a result of the effects of food processing (Hollman and Arts, 2000). Grape flavonoids are primarily categorized into flavonols, flavones, flavanols (flavan-3-ols), flavanones, and anthocyanidins (Fig. 3). Flavonoids (dihydroflavonoids), flavonols, and tannins (polymeric flavan-3-ols) are three classes of flavonoids commonly detected in grapes (Adams, 2006). A total of 16 flavonoids (five dihydroflavonols, seven quercetin derivatives, and four kaempferol derivatives) have been identified and quantified by HPLC-GC in the Albari'n blanco, a white *V. vinifera* L. cultivar native to the Asturias (North of Spain). Dihydroflavonols were detected to be abundant flavonoids in Albari'n blanco grapes, though this class of phenolic compounds was usually found to be scarce in grape skins (Masa and Vilanova, 2008). The total flavonoid content with different grape varieties is summarized in Table 3.

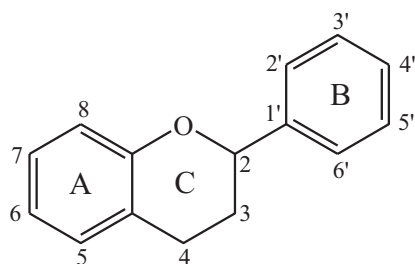
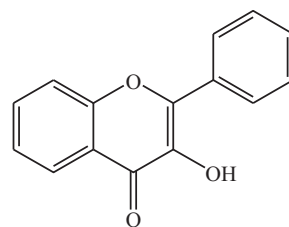
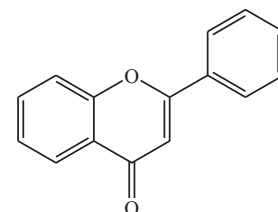


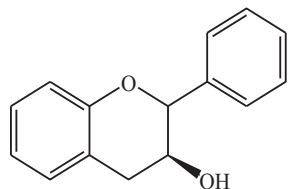
Figure 2 Generic structure of flavonoids.



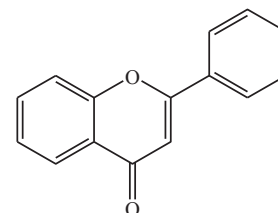
Flavonols



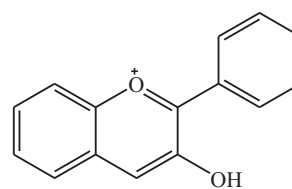
Flavones



Flavan-3-ols



Flavanones

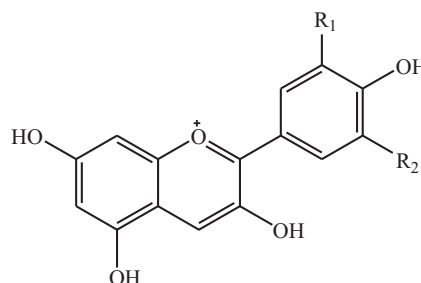


Anthocyanidins

Figure 3 Structure of main classes of grape flavonoids.

Anthocyanins

Anthocyanins, widely distributed throughout the plant kingdom, are natural, nontoxic, and water-soluble flavonoid pigments. They confer the red and blue colors found in the skins of blue, red, or black grapes (Shi et al., 2003). Approximately 10,000 tons of anthocyanins from black grapes are annually



Anthocyanidin Derivatives	Substitutions		Color
	R ₁	R ₂	
Cyanidin	OH	H	Orange red
Delphinidin	OH	OH	Bluish red
Malvidin	OCH ₃	OCH ₃	Bluish red
Pelargonidin	H	H	Orange
Peonidin	OCH ₃	OH	Red
Petunidin	OCH ₃	OH	Bluish red

Figure 4 Structures of anthocyanidins in grapes.

Table 2 Phenolic acid content of different parts in grape variety

Grape	Phenolic acids	Grape part		Expressed as	Location	Reference
		Skin	Seed			
Red grape (<i>Vitis vinifera</i> & <i>Vitis labrusca</i>)						
Pinot Noir	Chlorogenic acid	5.30 ± 0.09	3.50 ± 0.16	mg/100 g dry weight	Santa Catarina, Brazil	Rockenbach et al., 2011
Isabel		23.11 ± 0.51	4.62 ± 0.02			
Sangiovese		4.05 ± 0.72	4.29 ± 0.06			
Negro Amaro		8.37 ± 0.02	4.71 ± 0.13			
Cabernet Sauvignon		nd	2.87 ± 0.01			
Primitivo		15.15 ± 0.88	6.80 ± 0.05			
Skin						
Red grape <i>Vitis vinifera</i>	Hydroxycinnamic acid	172.48 ± 49.37		μmol/kg(grape) for grape skins	Spain	Gómez-Alonso et al., 2007
Cencibel						
		Flesh	Skin			
Brazilian seedless table grape	Total Hydroxycinnamic acid derivatives	34.5 ± 2.7	85.1 ± 8.8	μmol/kg	Brazil	Lago-Vanzela et al., 2011
BRS Clara		8.0 ± 1.0	101.1 ± 12.5			
BRS Morena						
Skin						
Red & White grapes <i>Vitis vinifera</i>						
Chardonnay	Total hydroxycinnamates	33 ± 21.9		mg/kg of fresh grape	Spain	Rodríguez Montealegre et al., 2006
Sauvignon		13 ± 4.7				
Moscatel		38 ± 6.6				
Gewürztraminer		22 ± 5.8				
Riesling		45 ± 16.9				
Viogner		5.8 ± 1.89				
Cencibel		19 ± 4.9				
Cabernet Sauvignon		18 ± 4.2				
Merlot		12 ± 4.3				
Shiraz		13 ± 2.0				
Skin						
White & Red grapes <i>Vitis vinifera</i> L.						
Sercial Maturity ripening stage	Hydroxybenzoic acids	369.8		mg/kg dried skin	Portugal	Perestrelo et al., 2012
	Hydroxycinnamic acids	810.0				
Tinta Negra Maturity ripening stage	Hydroxybenzoic acids	90.4				
	Hydroxycinnamic acids	221.7				
Pulp juices						
Table grape	Hydroxycinnamoyl tartaric acid			Caffeic acid equivalents in g/L of pulp juice	Italy	Baiano and Terracone, 2011
Baresana		0.013 ± 0.001				
Italia		0.022 ± 0.003				
Pizzutello		0.016 ± 0.002				
Thompson Seedless		0.019 ± 0.001				
Crimson Seedless		0.023 ± 0.003				
Michele Palieri		0.040 ± 0.003				
Red Globe	0.011 ± 0.001					

nd = not detected.

consumed (Walford, 1980). Anthocyanins, characterized by their flavylum nucleus, are subdivided into the sugar-free anthocyanidin aglycons and the anthocyanin glycosides. There are six commonly occurring anthocyanidin structures in grapes (Fig. 4). The anthocyanin molecule itself consists of two or three portions: the aglycone base on the flavylum nucleus,

a group of sugars, and a group of acyl acids. *V. vinifera* may contain up to 17 pigments (Riberau-Gayon, 1982). They are the three-monoglucosides of cyanidin, peonidin, malvidin, petunidin, and delphinidin, and the same compounds acylated with acetic, coumaric, or caffeic acid. The anthocyanins in *V. Labrusca* contain the monoglucosides and diglucosides

Table 3 Total flavonoid content of different parts in grape variety

Grape	Total flavonoids			Expressed as	Location	Reference
	Pulp	Skin	Seed			
Red & White grapes						
Vranec	0.40 ± 0.01	10.2 ± 0.04	52.0 ± 0.16	Catechin equivalents in mg/g fresh weight	Skopje, R. Macedonia	Ivanova et al., 2011
Merlot	0.41 ± 0.01	8.80 ± 0.03	48.6 ± 0.34			
Smederevka	0.18 ± 0.01	10.8 ± 0.05	49.4 ± 0.24			
Chardonnay	0.23 ± 0.01	3.12 ± 0.12	69.6 ± 0.11			
		Skin				
Red & White grapes <i>Vitis vinifera</i>						
Kujundžuša		872 ± 23.9		Gallic acid equivalents in mg/kg	Croatia	Katalinić et al., 2010
Rkaciteli		478 ± 27.3				
Zlatica		1182 ± 3.78				
Medna		389 ± 2.23				
Kuč		456 ± 4.00				
Maraština		768 ± 8.77				
Debit		654 ± 10.9				
Vranac		1396 ± 21.1				
Trnjak		2556 ± 44.0				
Rudežuša		2594 ± 21.7				
Merlot		1068 ± 22.4				
Babić		756 ± 17.6				
Lasin		400 ± 9.60				
Plavina		554 ± 4.23				
		Pulp + Skin				
Grape (<i>Vitis vinifera</i> & Hybrid)						
Cabernet Franc		180.9 ± 15.3		Catechin equivalents in mg/100 g fresh weight	New York, USA	Yang et al., 2009
Chardonnay		166.4 ± 20.4				
Pinot Noir		301.8 ± 6.2				
Riesling		133.5 ± 13.7				
Baco Noir		97.8 ± 9.8				
Catawba		180.9 ± 5.4				
Cayuga White		176.1 ± 10.7				
Chancellor		140.0 ± 18.8				
Concord		168.2 ± 6.0				
DeChaunac		113.9 ± 12.0				
Marechal Foch		127.0 ± 14.2				
Niagara		173.1 ± 11.3				
Sheridan		166.8 ± 1.38				
Vidal Blanc		100.7 ± 9.4				
		Skin	Seed			
Table grape						
Baresana		25.9 ± 3.1	55.7 ± 12.5	(+) -catechin equivalents in g/kg of dry matter	Italy	Baiano and Terracone, 2011
Italia		24.9 ± 2.2	110 ± 11			
Pizzutello		19.3 ± 1.9	62.3 ± 3.9			
Thompson Seedless		15.8 ± 2.9	—			
Crimson Seedless		37.2 ± 5.5	—			
Michele Palieri		35.6 ± 1.6	37.9 ± 5.1			
Red Globe		25.7 ± 4.5	26.3 ± 1.9			

acylated with the above acids in different proportions depending on the cultivar. Anthocyanins in grape skins are predominately the 3-*O*-glucosides of malvidin, cyanidin, delphinidin, peonidin, and petunidin (Wrolstad, 2000). Concord grapes may contain up to 20 pigments with the major aglycones being cyanidin 3-monoglucoside and delphinidin 3-monoglucoside. Grape anthocyanins play a crucial role in the color quality of red wines, and have been increasingly used as food colorants and nutraceuticals. The total anthocyanin content in grapes is presented in Table 4.

Flavonols

Quercetin is a flavonol, which is always found in glycoside form in grape skins. Two other simple flavonoid aglycones, myricetin (3',4',5'-trihydroxy) and kaempferol (4'-hydroxy), also exist in grapes (Fig. 5). The red skin variety of *V. vinifera* possesses different derivatives of flavonol aglycones, including quercetin, kaempferol, myricetin, and isorhamnetin (Makris et al., 2006). The major flavonol glycosides in the skins of white grapes were quercetin and kaempferol derivatives, but

Table 4 Total anthocyanin content of different parts in grape variety

Grape	Anthocyanins			Expressed as	Location	Reference
	Skin	Seed				
Red grape (<i>Vitis vinifera</i> & <i>Vitis labrusca</i>)						
Pinot Noir	385.93 ± 5.67	nd		Cyanidin-3-rutinoside equivalents in mg/100 g dry weight	Santa Catarina, Brazil	Rockenbach et al., 2011
Isabel	456.52 ± 1.31	nd				
Sangiovese	301.57 ± 0.23	nd				
Negro Amaro	289.46 ± 7.05	nd				
Cabernet Sauvignon	934.67 ± 10.1	nd				
Primitivo	831.92 ± 2.77	nd				
		Skin				
Red grape <i>Vitis vinifera</i>						
Cencibel		924.2 ± 173.1		Malvidin-3-glucoside equivalents in mg/kg grape skins	Spain	Gómez-Alonso et al., 2007
	Pulp	Skin	Seed			
Noble & Carols muscadine grapes (<i>Vitis rotundifloia</i>)						
Seed mix of Noble & Carols			5.68 ± 0.55	Cyanidin-3,5-diglucoside equivalents in mg/100 g fresh weight	Wray, GA, USA	You et al., 2012
Noble skin		416.9 ± 5.7				
Carols skin		3.68 ± 0.71				
Noble fruit	111.9 ± 2.0					
Carols fruit	1.77 ± 0.18					
	Pulp	Skin	Seed			
Red & White grapes						
Vranec	0.19 ± 0.01	8.40 ± 1.13	nd	Malvidin-3-glucoside equivalents in mg/g fresh mass	Skopje, R. Macedonia	Ivanova et al., 2011
Merlot	0.07 ± 0.01	7.21 ± 0.04	nd			
Smederevka	nd	nd	nd			
Chardonnay	nd	nd	nd			
	pulp	skin				
Brazilian seedless table grape						
BRS Morena	16.18 ± 4.29	526.36 ± 67.14		Malvidin 3-glucoside equivalents in mg/kg	Brazil	Lago-Vanzela et al., 2011
		Skin				
White & Red grapes <i>Vitis vinifera</i> L.						
Sercial (Maturity)		nd		Malvidin-3-glucoside equivalents in mg/kg dried skin	Portugal	Perestrelo et al., 2012
Tinta Negra (Maturity)		7014.8				
		Skin				
Table grape <i>Vitis vinifera</i> L.						
Autumn Royal		1.16 ± 0.018		Cyanidin 3-glucoside equivalents in mg/g	Chile	Lutz et al., 2011
Crimson seedless		0.25 ± 0.001				
Red Globe		0.20 ± 0.004				
Ribier		1.73 ± 0.023				
		Skin				
Red & White grapes <i>Vitis vinifera</i> L.						
Kujundžuša		nd		Malvidin-3-glucoside equivalents in mg/kg	Croatia	Katalinić et al., 2010
Rkaciteli		nd				
Zlatarica		nd				
Medna		nd				
Kuč		nd				
Maraština		nd				
Debit		nd				
Vranac		739 ± 39.0				
Trnjak		1286 ± 32.8				
Rudežuša		1848 ± 60.0				
Merlot		739 ± 18.8				
Babić		336 ± 12.4				
Lasin		158 ± 4.53				
Plavina		238 ± 6.25				

Table 4 Total anthocyanin content of different parts in grape variety (*Continued*)

Grape	Anthocyanins Pulp + Skin	Expressed as	Location	Reference
Wine grape (<i>Vitis vinifera</i> & hybrid)				
Cabernet Franc	58.7 ± 4.4	Cyanidin 3-glucoside equivalents in mg/100 g fresh weight	New York, USA	Yang et al., 2009
Chardonnay	nd			
Pinot Noir	49.8 ± 4.3			
Riesling	nd			
Baco Noir	101.6 ± 2.5			
Catawba	8.1 ± 0.8			
Cayuga White	nd			
Chancellor	198.7 ± 4.8			
Concord	80.6 ± 2.4			
DeChaunac	239.6 ± 25.4			
Marechal Foch	174.1 ± 15.3			
Niagara	nd			
Sheridan	54.4 ± 7.7			
Vidal Blanc	nd			
	Skin			
Table grape				
Baresana	nd	Gallic acid equivalents in g/kg of dry skin	Italy	Baiano and Terracone, 2011
Italia	nd			
Pizzutello	nd			
Thompson Seedless	nd			
Crimson Seedless	8.3 ± 1.88			
Michele Palieri	13.3 ± 1.8			
Red Globe	10.1 ± 1.1			

nd = not detected.

isorhamnetin glucoside was also found in smaller amounts (Mattioli et al., 2006; Rodríguez Montealegre et al., 2006). Recently, the flavonol profiles of *V. vinifera* white grape cultivars were determined by HPLC-DAD-ESI-MSn (Castillo-Muñoz et al., 2010). The results indicated that flavonol profiles of white grapes are dominated by quercetin-type flavonols. Isorhamnetin-type flavonols were identified in white grape cultivars including Pedro Ximenez, Gewu rztraminer, Verdejo, Albillo, and Riesling. The 3-*O*-glucosides and 3-*O*-galactosides of kaempferol, quercetin, and isorhamnetin, and the 3-*O*-glucuronides of kaempferol and quercetin were detected in all the grape varieties tested. The total flavonol content in grapes is shown in Table 5.

Flavanols (Flavan-3-ols)

Flavonols, found in the seed and skin, are the most abundant class of flavonoids in grapes. These are often specifically called the flavan-3-ols to identify the location of the hydroxy group on the C ring. The five common flavan-3-ol monomers found in grape skins are (+)-catechin (C), (–)-gallocatechin (GC), (–)-epicatechin (EC), (–)-epigallocatechin (EGC), and (–)-epicatechin 3-gallate (ECG). Common dimers, such as procyanidin B1 (PB1) and procyanidin B2 (PB2), are also present in grape skins. Colorless flavanols include C and EC, the monomeric units of proanthocyanidins. Proanthocyanidins, also known as condensed tannins, are characterized by polymerization degree (PD) ranging mainly between three and 11, but up

to 17 and more (Iriti and Faoro, 2006). The total flavan-3-ol content in pulp, skin, and seed of different grape varieties is depicted in Table 6.

Flavan-3-ols are responsible for the astringency and bitterness in grapes. Catechin and epicatechin are epimers, with (+)-C and (–)-EC being the most common optical isomers found in nature. Both trans and cis forms are found in grapes, with the former occurring as (2R,3S) (+)-C and the latter appearing as (2R,3R) (–)-EC. EGC and GC contained an additional phenolic hydroxyl group when compared to C and EC, respectively. Catechin gallates are gallic acid esters of the catechins. EGC is found in grape skin, but GC is not found in significant amounts.

Proanthocyanidins, known as condensed tannins, are abundant phenolics in grapes (Gu et al., 2003). They are oligomers or polymers of flavan-3-ols subunits. The most common types of proanthocyanidins are displayed in Fig. 6. An ester bond between C2→C7 resulting in linkage of the flavan-3-ol units is called an A-type linkage. The linkages through C4→C8 bond and C4→C6 are called B-type linkages. In the United States, the daily intake of proanthocyanidins is approximately 57.7 mg/day, including monomers. Consumption occurs most commonly through apples (32%), chocolate (17.9%), and grapes (17.8%) (Gu et al., 2004). In grapes, the common types of proanthocyanidins are procyanidins, propelargonidin (epiafzelechin), and prodelfphinidin (epigallocatechin). Epicatechin is the major unit of condensed tannins from grapes, catechin the next most abundant.

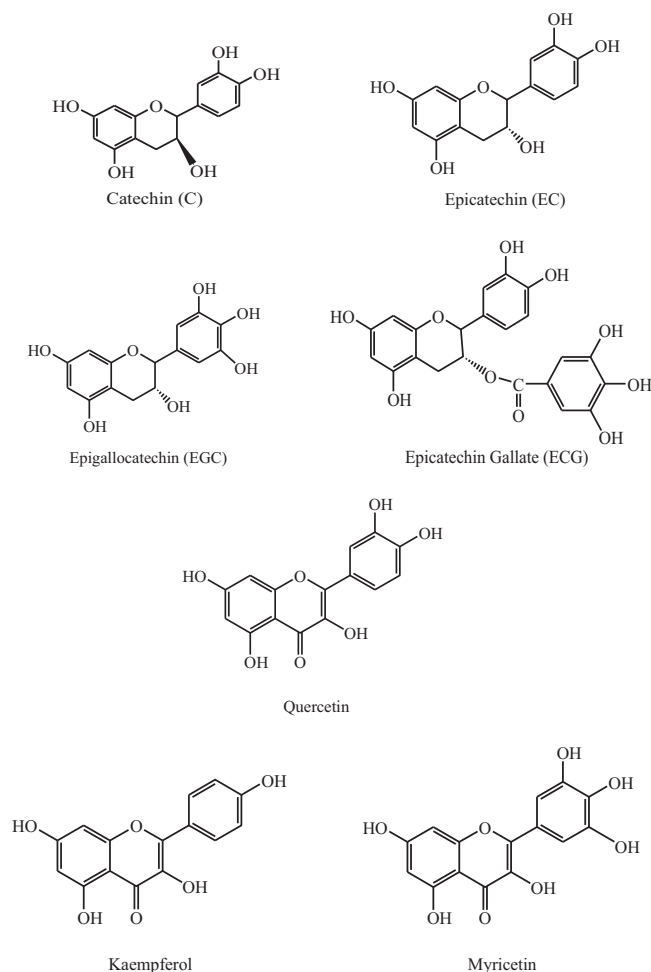


Figure 5 Structures of common dietary flavonoids.

Major phenolics in grape seeds are proanthocyanidins, such as gallic acid, the monomeric flavan-3-ols catechin, epicatechin, gallocatechin, epigallocatechin, epicatechin 3-*O*-gallate, procyanidin dimers, trimers, and more highly polymerized procyanidins (Prieur et al., 1994). The dimeric procyanidins are referred to as the B-series, while the trimeric procyanidins are considered the C-series (Fig. 6). Five different dimers (procyanidin B1, B2, B3, B4, and B5) and two trimers (C1 and C2) were identified from grape skin and seeds. Grape seeds contained 5~8% phenolics depending on the variety (Shi et al., 2003).

Stilbenes

Stilbenes (Fig. 7) are phenolic compounds that structurally exhibit two aromatic rings linked by an ethane bridge. More than 30 stilbenes and stilbene glycosides have been identified in plants (Soleas et al., 1997). These include resveratrol (RSV: 3,5,4'-trihydroxystilbene), piceid (a resveratrol glucoside), pterostilbene (a dimethylated derivative of resveratrol), and viniferins (resveratrol oligomers) (Langcake and Pryce, 1976). Stilbenes are responsible for the bright blue fluorescence

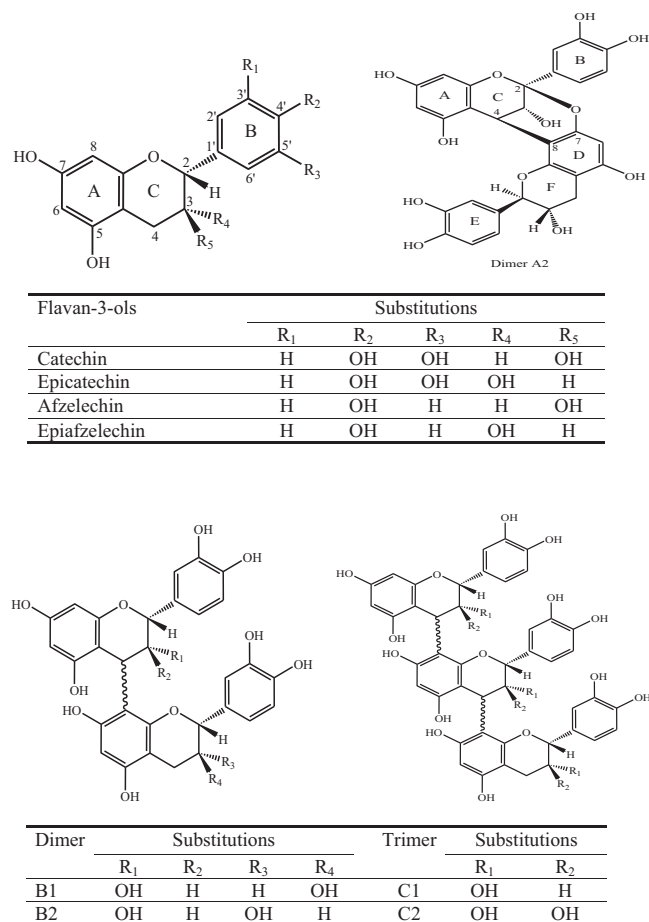


Figure 6 Structures of proanthocyanidins in grapes.

observed under long wavelength UV-light on grape leaf surfaces or grape berries.

RSV is synthesized by a wide variety of plant species, including grapes, peanuts, and mulberries in response to pathogenic attack and environmental stress such as injury, UV irradiation, or fungal infection. RSV was first detected in *V. vinifera* grape in 1976 (Langcake and Pryce, 1976), and found in wine in 1992 (Siemann and Creasy, 1992), though traditional Chinese medicine long used RSV to fight favus, suppurative dermatitis, gonorrhea, and hyperlipemia. In 1963, RSV was identified as the bioactive constituent of the dried roots of *Polygonum cuspidatum*. Synthesized in the leaf epidermis and the skin of grape berries, but not in the flesh, RSV exists in two isomers: the *cis* and *trans*, as shown in Fig. 7. Both forms are found in wine, although it appears that only the *trans* isomer is found in grapes. UV-light induction can lead to its isomerization from *trans* to *cis* (Trela and Waterhouse, 1996). Other compounds considered as oligomers of RSV and termed viniferins have also been found in grapevines as a result of infection or stress. The major components of these appear to be ϵ -viniferin (Fig. 7), a cyclic resveratrol dehydodimer, and α -viniferin, a cyclic resveratrol dehydrotrimer (Langcake and Pryce, 1976; Jeandet et al., 1997).

Table 5 Total flavonol content of different parts in grape variety

Grape	Total flavonols		Expressed as	Location	Reference
	Skin				
White grape <i>Vitis vinifera</i>					
Airén	99.8		$\mu\text{mol/kg}$ of fresh grape	Spanish grape cultivar; or non-Spanish grape cultivar	Castillo-Muñoz et al., 2010
Albillo	109.3				
Chardonnay	74.3				
Chelva	82.2				
Gewürztraminer	50.7				
Jaén	153.3				
Listán Huelva	46.8				
Macabeo	78.6				
Malvar	160.4				
Mantúo	72.2				
Merseguera	73.5				
Moscatel Alejandría	65.1				
Moscatel grano menudo	154.5				
Pardillo	75.7				
Parellada	30.8				
Pedro Ximénez	7.9				
Riesling	72.7				
Sauvignon blanc	41.5				
Torrontés	83.9				
Ugni blanc	84.7				
Verdejo	97.9				
Viognier	124.8				
	Skin				
Red grape <i>Vitis vinifera</i>					
Cencibel	169.57 ± 46.82		$\mu\text{mol/kg}$ of grape skins	Spain	Gómez-Alonso et al., 2007
	Skin	Pulp			
Brazilian seedless table grape					
BRS Clara	139.73 ± 3.68	3.20 ± 0.05	$\mu\text{mol/kg}$	Brazil	Lago-Vanzela et al., 2011
BRS Morena	114.02 ± 6.30	2.16 ± 0.11			
	Skin				
White & Red grapes <i>Vitis vinifera</i> L.					
Sercial (Maturity)	878.3		Quercetin equivalents in mg/kg of dried skin	Portugal	Perestrelo et al., 2012
Tinta Negra (Maturity)	725.6				

The level of *trans*-RSV from different grape varieties is shown in Table 7.

with the highest concentration in Nebbiolo (0.965 ng/g) and Croatina (0.870 ng/g) (Iriti and Faoro, 2006, 2009).

Carotenoids

Carotenoids, representative of isoprenoid tetraterpens (C40), were reported in ripening grapes (Baumes et al., 2002). Oxidation of carotenoids forms volatile and odoriferous compounds, such as β -ionone, damascenone, and β -ionol. Monoterpenes are major components of essential oils and represent C10 isoprenoids. Monoterpenes and C13-norisoprenoids are responsible for the primary varietal aroma of grapes.

Melatonin

Melatonin was quantified by a modified HPLC method and ELISA tests in extracts of eight different *V. vinifera* cultivars. The content of melatonin varied greatly among the cultivars,

HEALTH BENEFITS OF GRAPES

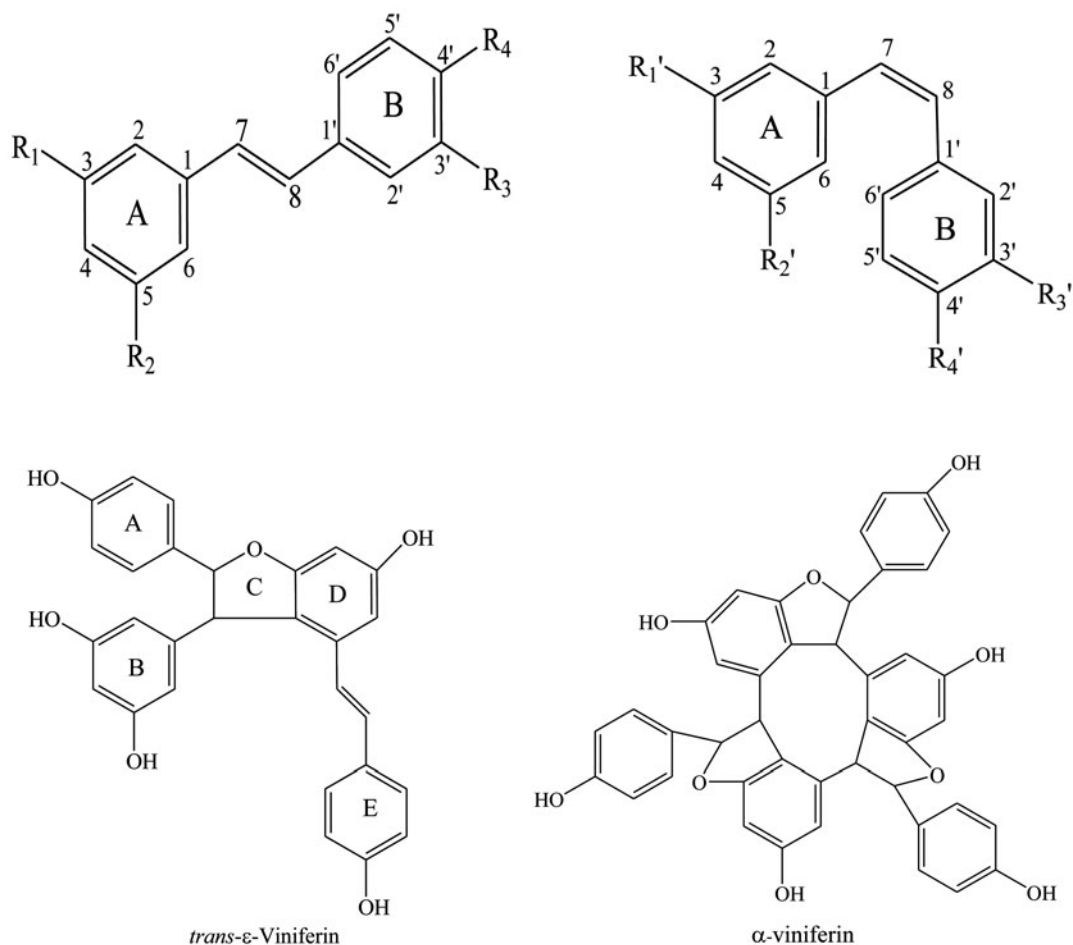
As the largest single fruit crop grown in the world, grapes are a good source of phenolic acids, flavonoids, and resveratrol, all of which have been purported to have positive health effects. Much epidemiological data, animal work, and cell culture evidence support the health benefits of grapes in the prevention of CVD and certain cancers (Katiyar, 2008; Nassiri-Asl and Hosseinzadeh, 2009; Yadav et al., 2009; Vislocky and Fernandez, 2010; Yu et al., 2011). Because of their high flavonoids and stilbenes content, strong associations exist between grapes and a lowered risk of chronic diseases.

1. Epidemiological Evidence

Epidemiological studies suggest that phenolic-rich grapes sustain cardiovascular health and prevent certain cancer

Table 6 Total flavanol (flavan-3-ols) content of different parts in grape variety

Grape	Total Flavan-3-ols			Expressed as	Location	Reference
	Pulp	Skin	Seed			
Red & White grapes						
Vranec	0.05 ± 0.02	2.81 ± 0.13	16.7 ± 0.51	Catechin equivalents in mg/g fresh weight	Skopje, R. Macedonia	Ivanova et al., 2011
Merlot	0.08 ± 0.02	1.67 ± 0.04	18.4 ± 0.16			
Smederevka	0.04 ± 0.01	0.53 ± 0.15	24.5 ± 0.01			
Chardonnay	0.04 ± 0.001	3.08 ± 0.75	12.4 ± 0.14			
		Skin				
Brazilian seedless table grape						
BRS Clara		18.08 ± 1.20		Catechin equivalents in mg/kg	Brazil	Lago-Vanzela et al., 2011
BRS Morena		14.98 ± 1.38				
		Skin	Seed			
Red & White grapes <i>Vitis vinifera</i>						
Chardonnay		89 ± 34.5	1270 ± 223	mg/kg of fresh grape	Spain	Rodríguez Montealegre et al., 2006
Sauvignon		54 ± 15.0	730 ± 186			
Moscatel		63 ± 16.4	950 ± 185			
Gewürztraminer		97 ± 10.0	1340 ± 40			
Riesling		55 ± 6.7	1390 ± 278			
Vioigner		9.7 ± 0.00	560 ± 46			
Cencibel		92.8 ± 17.9	330 ± 83			
Cabernet Sauvignon		63.03 ± 14.4	720 ± 103			
Merlot		96.3 ± 29.9	870 ± 144			
Shiraz		40.77 ± 8.42	500 ± 46			
		Skin	Seed			
Red grape (<i>Vitis vinifera</i> & <i>Vitis labrusca</i>)						
Pinot Noir		56 ± 13	11187 ± 250	Catechin equivalents in mg/100 g dry weight	Santa Catarina, Brazil	Rockenbach et al., 2011
Isabel		156 ± 25	1188 ± 125			
Sangiovese		206 ± 13	6812 ± 331			
Negro Amaro		131 ± 33	4521 ± 191			
Cabernet Sauvignon		252 ± 26	5312 ± 125			
Primitivo		165 ± 19	5729 ± 72			
		Skin				
Red & White grapes <i>Vitis vinifera</i>						
Chardonnay		53 ± 18.5		mg/kg of fresh grape	Spain	Rodríguez Montealegre et al., 2006
Sauvignon		25 ± 5.6				
Moscatel		98 ± 14.0				
Gewürztraminer		50 ± 8.6				
Riesling		56 ± 4.4				
Vioigner		170 ± 24				
Cencibel		130 ± 30				
Cabernet Sauvignon		190 ± 39				
Merlot		130 ± 25				
Shiraz		200 ± 31				
		Skin				
White & Red grapes <i>Vitis vinifera</i> L.						
Sercial (Maturity)		92.5		Epicatechin equivalents in mg/kg dried skin	Portugal	Perestrelo et al., 2012
Tinta Negra (Maturity)		152.8				
		Skin				
Red & White grapes <i>Vitis vinifera</i> L.						
Kujundžuša		77.9 ± 0.29		Epicatechin equivalents in mg/kg	Croatia	Katalinić et al., 2010
Rkaciteli		27.8 ± 0.98				
Zlatica		88.6 ± 0.48				
Medna		30.3 ± 0.69				
Kuč		42.2 ± 3.24				
Maraština		25.5 ± 1.07				
Debit		93.2 ± 2.34				
Vranac		104 ± 1.61				
Trnjak		158 ± 1.35				
Rudežuša		75.9 ± 1.57				
Merlot		100 ± 1.33				
Babić		49.9 ± 1.53				
Lasin		91.8 ± 3.47				
Plavina		42.9 ± 1.35				



Stilbene	Substitutions							
	R ₁	R ₂	R ₃	R ₄	R ₁ '	R ₂ '	R ₃ '	R ₄ '
<i>trans</i> -resveratrol	OH	OH	H	OH				
<i>trans</i> -resveratrolside	OH	OH	H	GlcO				
<i>trans</i> -astringin	GlcO	OH	OH	OH				
<i>trans</i> -pterostilbene	CH ₃ O	CH ₃ O	H	OH				
<i>trans</i> -piceid	GlcO	OH	H	OH				
<i>trans</i> -piceatannol	OH	OH	OH	OH				
<i>cis</i> -resveratrol					OH	OH	H	OH
<i>cis</i> -resveratrolside					OH	OH	O	GlcO
<i>cis</i> -astringin					GlcO	OH	OH	OH
<i>cis</i> -piceid					GlcO	OH	H	OH

Glc: glucosyl (C₆H₁₁O₅).

Figure 7 Structures of major stilbenes in grapes.

and other diseases (Rimando and Suh, 2008; Bertelli and Das, 2009; Dohadwala and Vita, 2009; Kaur et al., 2009; Mukherjee et al., 2010; Sanchez et al., 2012). The credibility of grapes' health benefits is also ascribed to epidemiological studies from wines. In the early 90s the "French

paradox" paradigmatically changed the common perception of red wine and espoused the health effects of regular and moderate consumption of red wine (Renaud and de Lorgeril, 1992). The observed epidemiological relationship between wine intake and health benefits was attributed

Table 7 *Trans*-resveratrol content of different parts in grape variety

Grape	Trans-resveratrol		Expressed as	Location	Reference
	Skin	Seed			
Red grape (<i>Vitis vinifera</i> & <i>Vitis labrusca</i>)					
Pinot Noir	nd	nd	mg/100 g dry weight	Santa Catarina, Brazil	Rockenbach et al., 2011
Isabel	nd	3.75 ± 0.08			
Sangiovese	nd	1.11 ± 0.02			
Negro Amaro	nd	1.42 ± 0.07			
Cabernet Sauvignon	nd	nd			
Primitivo	nd	1.32 ± 0.11			
	Skin	Seed			
Red grape <i>Vitis vinifera</i>					
Cencibel	0.41 ± 0.29	nd	mg/kg of grape skins	Spain	Gómez-Alonso et al., 2007
	Pulp	Skin			
		Seed			
Noble & Carols muscadine grapes (<i>Vitis rotundifloia</i>)					
Seed mix of Noble & Carols		4.0 ± 1.1	mg/100 g fresh weight	Wray, GA, USA	You et al., 2012
Noble skin	1.42 ± 0.20				
Carols skin	1.05 ± 0.08				
Noble fruit	0.96 ± 0.17				
Carols fruit	0.95 ± 0.076				
	Pulp	Skin			
Brazilian seedless table grape					
BRS Clara	nd	nd	mg/kg	Brazil	Lago-Vanzela et al., 2011
BRS Morena	nd	3.91 ± 1.00			
		Skin			
White & Red grapes <i>Vitis vinifera</i> L.					
Sercial (Maturity)	8.1		mg/kg of dried skin	Portugal	Perestrelo et al., 2012
Tinta Negra (Maturity)	9.9				
		Skin			
Table grape (<i>Vitis vinifera</i> L.)					
Autumn Royal	1.76 ± 0.04		ppm	Chile	Lutz et al., 2011
Crimson seedless	0.98 ± 0.13				
Red Globe	0.77 ± 0.03				
Ribier	2.66 ± 0.01				
		Skin			
Red & White grapes <i>Vitis vinifera</i> L.					
Kujundžuša	0.27 ± 0.10		mg/kg of grape fresh weight	Croatia	Katalinić et al., 2010
Rkaciteli	0.26 ± 0.05				
Zlatarica	0.10 ± 0.04				
Medna	0.07 ± 0.05				
Kuč	0.09 ± 0.05				
Maraština	0.17 ± 0.02				
Debit	0.72 ± 0.05				
Vranac	0.78 ± 0.09				
Trnjak	0.41 ± 0.02				
Rudežuša	0.61 ± 0.03				
Merlot	1.02 ± 0.10				
Babić	0.44 ± 0.02				
Lasin	0.59 ± 0.02				
Plavina	0.30 ± 0.08				
	Pulp + Skin				
Wine grape (<i>Vitis vinifera</i> & hybrid)					
Cabernet Franc	119 ± 8		μg/100 g of fresh grape	New York, USA	Yang et al., 2009
Chardonnay	73 ± 9				
Pinot Noir	421 ± 54				
Riesling	80 ± 7				
Baco Noir	571 ± 30				
Catawba	72 ± 5				
Cayuga white	38 ± 2				

(Continued on next page)

Table 7 *Trans*-resveratrol content of different parts in grape variety (Continued)

Grape	<i>Trans</i> -resveratrol		Expressed as	Location	Reference
	Pulp + Skin				
Chancellor	117 ± 7				
Concord	65 ± 8				
DeChaunac	75 ± 6				
Marechal Foch	130 ± 8				
Niagara	53 ± 4				
Sheridan	112 ± 10				
Vidal Blanc	263 ± 16				

nd = not detected.

to the red wine phenolics transferred from grapes (Kinsella et al., 1993; Frankel et al., 1993a). A case-control study showed that increased consumption of grapes was linked to a decreased risk of cancer (Zheng et al., 1993). The data from Chaves et al. (2009) demonstrated that a modest intake of fresh grapes (1.25 cups) resulted in significant improvement in brachial artery flow mediated dilation within three hours of consumption compared to the consumption of sugar solution ($p < 0.05$), which was the control. Furthermore, chronic intake of fresh grapes can improve an individual's performance, which supports epidemiological data of the health benefits of grapes. In a double-blind, randomized, placebo-controlled intervention study, an integrative multi-biomarker (serum total cholesterol and LDL, glutathione) approach revealed the pleiotropic vascular health effect of eight weeks supplementation of 200 mg/day of monomeric and oligomeric flavanols from grape seeds in 28 male smokers (Weseler et al., 2011). Grape seed extract (GSE) was reported to be associated with a reduced risk of cutaneous squamous cell carcinoma (SCC) in Kaiser Permanente Northern California members with a pathology-verified SCC in 2004 (Asgari et al., 2011). Additionally, GSE significantly improved the grade of fatty liver change in nonalcoholic fatty liver patients by reducing alanine aminotransferase (Khoshbaten et al., 2010). A two-week dietary intervention study was conducted in 25 healthy subjects to investigate the influences of apple and grape juices consumption on body antioxidant status (Yuan et al., 2011). The results showed that apple and grape juice consumption increased plasma's total antioxidant capacity and reduced the concentration of malondialdehyde. Simultaneously, erythrocyte glutathione peroxidase and catalase activities were enhanced by fruit juice consumption, but without change of superoxide dismutase, suggesting that concomitant intake of apple and grape juice can boost antioxidant status in the body. Furthermore, grapes not only have a low mean in the glycemic index and glycemic load, but their phenolics have shown potential for lowering hyperglycemia, improving β -cell function, and protecting against β -cell loss, suggesting that grapes may have potential health benefits for Type 2 diabetics (Zunino, 2009).

Antioxidant Activity

Grapes, especially grape seeds, have been found to possess strong antioxidant activity. The antioxidant effects of phenolics in various grapes showed that antioxidant capacity was correlated with the concentration of phenolics in the system (Kanner et al., 1994). The antioxidant activity of red grapes has been correlated with both phenolics and/or flavonoid content (Teissedre et al., 1996; Meyer et al., 1997). Teissedre et al. (1996) evaluated phenolic fractions such as catechin oligomers, procyanidin dimers, and trimers from the seeds of a Petite Syrah wine for their antioxidant activity by inhibiting LDL oxidation in vitro. Procyanidin dimers B₂ and B₈, the trimer C₁, and the monomers catechin, epicatechin, and myricetin had high antioxidant activity. The procyanidin dimers B₃, B₄, and C₂; the monomers gallic acid, quercetin, caffeic acid, and rutin; and a group of compounds that included the dimer B₆, ellagic acid, sinapic acid, cyaniding, all showed weak antioxidant activity. Antioxidant capacities of phenolic extracts from 14 different fresh grapes were examined by measuring the inhibition of human LDL oxidation in vitro (Meyer et al., 1997). The inhibition of LDL oxidation ranged from 22 to 60% at 10 μ M gallic acid equivalents of total phenols. The relative LDL antioxidant activity correlated with the content of total phenols ($r = 0.89$, $p < 0.01$), with the level of anthocyanins ($r = 0.56$, $p < 0.05$), and amount of flavonols ($r = 0.54$, $p < 0.05$) in the grape extracts, while relative LDL antioxidant activity correlated strongly with the levels of flavan-3-ols ($r = 0.86$, $p < 0.01$), total phenols ($r = 0.79$, $p < 0.05$), and hydroxybenzoates ($r = 0.77$, $p < 0.05$) after seed crushing and longer extraction times were used. The total antioxidant capacities of the 14 wine grape varieties, expressed as micromoles (μ mol) of vitamin C equivalents per gram of fresh grape, were reported (Yang et al., 2009). Phytochemical extracts of Cabernet Franc contained the strongest antioxidant activity ($149.0 \pm 10.0 \mu\text{mol/g}$, $p < 0.05$), followed by Pinot Noir, Concord, Sheridan, Chancellor, Marechal Foch, Catawba, DeChaunac, Riesling, Niagara, Vidal Blanc, Baco Noir, Cayuga White, and Chardonnay. A statistically significant difference ($p < 0.05$) was observed among Cabernet Franc, Pinot Noir, Chancellor, Riesling, and Chardonnay. The total antioxidant activities of Pinot Noir and Concord were similar ($p > 0.05$), but lower ($p < 0.05$) than that of Cabernet Franc. The varieties possessing high total phenolic contents showed higher antioxidant

2. *In Vitro* and *In vivo* Studies

activities. This study revealed a strong correlation between total antioxidant activity and total phenolics ($R^2 = 0.98$, $p < 0.05$).

Among the many phenolics present in grapes, RSV, which is already widely recognized as a powerful antioxidant, is especially notable because of the strong correlation that exists in its concentration and the antioxidant capacity of grapes (Alonso et al., 2002). RSV induces heme-oxygenase 1 (HO1) in a dose- and time-dependent pattern and provides neuroprotection from free-radical or excitotoxicity damage in cultured mouse cortical neuronal cells (Sakata et al., 2010). The antioxidant activity of RSV, butylated hydroxytoluene, propyl gallate, and vitamins C and E were examined in chemical and biological systems (Soares et al., 2003). The chemical assays evaluated the capacity of these antioxidants to sequester 2,2'-azinobis(3-ethylbenzthiazoline-6-sulfonic acid) (ABTS^{•+}) and 1,1-diphenyl-2-picrylhydrazyl (DPPH[•]). RSV has been shown to possess a stronger 1,1-diphenyl-2-picrylhydrazyl (DPPH), 2,2'-azinobis(3-ethylbenzthiazoline-6-sulfonic acid) (ABTS), and hydroxyl radical-scavenging capacity than propyl gallate, vitamin E, and vitamin C. Additively, it was found that RSV lowers oxidative stress and regenerates α -tocopherol, which further strengthens the antioxidant defense mechanism (Ramprasath and Jones, 2010).

Anthocyanin pigments act as powerful antioxidants to help protect the plant from radicals formed by UV light and during metabolic processes. A positive correlation was found between anthocyanin content and antioxidant activities of red grape extracts (Meyer et al., 1997), grape juices, and red wines (Burns et al., 2000). Consumption of anthocyanin-replete diets in rats significantly improved ($p < 0.01$) plasma antioxidant capacity and decreased ($p < 0.001$) vitamin E deficiency-enhanced hydroperoxides and 8-oxo-deoxyguanosine concentrations in the liver (Ramirez-Tortosa et al., 2001). Cyanidin 3-*O*- β -D-glucoside (C3G) functioned as a potent antioxidant under oxidative stress in rats (Tsuda et al., 2000). Cyanidin-DNA copigmentation might be a possible defense mechanism against oxidative damage of DNA and may have in vivo physiological functions attributable to the antioxidant ability of anthocyanins (Sarma and Sharma, 1999). It was found that antioxidant capacity of proanthocyanidins from grape seeds is 20 times greater than vitamin E and 50 times greater than vitamin C (Uchida, 1980). However, in the study from Yang et al. (2009), neither anthocyanin nor RSV content correlated with total antioxidant activity of wine grapes. The lack of correlation could be a result of the nature of particular compounds, which may act additively or synergistically with other compounds. The total expressed antioxidant activity may be dependent on the relative proportions of each compound in the system.

Antiproliferative Activity

Grapes provide a rich source of phenolics such as RSV, which inhibit cellular events related to initiation, promotion, and progression of carcinogenesis both in vitro and in vivo, like breast cancer (Gehm et al., 1997; Schneider et al., 2000); prostate can-

cer (Hsieh and Wu, 2000; Narayanan et al., 2002); liver cancer (De Ledingham et al., 2001; Yang et al., 2009); colorectal and intestinal cancers (Wolter et al., 2001; Delmas et al., 2003); skin cancer (Adhami et al., 2003); lung cancer (Kimura and Okuda, 2001); blood cancer (Surh et al., 1999); and thyroid cancer (Shih et al., 2002). The inhibitory effects of 14 wine grape varieties on Caco-2 human colon cancer cells, HepG₂ human liver cancer cells, and MCF-7 human breast cancer cells in vitro were examined (Yang et al., 2009). Grape extracts displayed potent antiproliferative activity against the aforementioned human cancer cells in a dose-dependent manner. Cabernet Franc, Pinot Noir, Chardonnay, Catawba, Concord, Sheridan, Niagara, and Riesling showed relatively high antiproliferative activity toward both Caco-2 and HepG₂ cells while Cabernet Franc and Catawba exhibited relatively strong antiproliferative activity toward MCF-7 cells. One possible explanation may be that phytochemicals in grapes target different organs, resulting in different effects. Since antiproliferative activity in cells involves uptake, metabolic, and transcriptional events, it is not surprising that different cell types exhibit different rates of inhibition when presented with the same array of phytochemicals. For example, anthocyanidins directly cause human promyelocytic leukemia cells (HL-60) to generate intracellular hydrogen peroxide and trigger apoptosis, possibly through an oxidative stress-involved JNK signaling pathway (Hou et al., 2003). The molecular mechanisms associated with the antiproliferative effects of grape phytochemicals in cancer cells involve the activation of p53, the suppression of nuclear factor- κ B (NF- κ B), the activation of protein-1 (AP-1), induction of apoptosis, and the arrest of the cell cycle.

The antiproliferative activities of RSV may also be explained by the direct inhibition of ribonucleotide reductase, which efficiently scavenges the tyrosyl radical of the small protein that supplies proliferating cells with deoxyribonucleotides required for DNA synthesis (Schneider et al., 2000). RSV has been reported to inhibit DNA polymerase (Sun et al., 1998) and ornithine decarboxylase, a key enzyme of polyamine biosynthesis that is enhanced in cancer growth. However, the effects of RSV in breast cancer cell lines are inconsistent. For instance, it was found that RSV enhanced MCF-7 cell growth (Basly et al., 2000), and induced growth inhibition, S-phase arrest, apoptosis, and changes in biomarker expression in HL-60, SW-480, HCE-7, Seg-1, Bic-1, and MCF-7 human cancer cell lines (Joe et al., 2002). Conversely, RSV was observed to slow down the proliferation of several human malignant cell lines (Hsieh et al., 1999a). RSV induced significant dose-dependent inhibition in human oral squamous carcinoma cell (SCC-25) growth and DNA synthesis, and decreased viability and DNA synthesis capability of human promyelocytic leukemia (HL-60) cells through an induction of apoptosis by the Bcl-2 pathway (Surh et al., 1999). After investigating of the effect of RSV on growth, induction of apoptosis, and modulation of prostate-specific gene expression in DU-145, JCA-1, and PC-3 human CaP cells, Hsieh and Wu's study (2000) suggested that RSV negatively modulates CaP cell growth by affecting mitogenesis and inducing apoptosis. RSV might be responsible for the growth inhibition of

LNCaP cells by its modulation of multiple signaling pathways (Narayanan et al., 2002). Potter et al. (2002) have suggested that the antiproliferative activities of RSV on cancer cells are the consequence of its conversion to piceatannol by CYP1B1. After inoculation into mice, *trans*-RSV-3-*O*-D-glucoside (piceid) also inhibited the proliferation of Lewis lung carcinoma (LLC) cells, but only at a concentration of 1,000 μ M, while 2,3,5,4'-*tetra*-hydroxystilbene-2-*O*-D-glucoside was more effective with an IC₅₀ of 81 μ M. It was concluded that the antitumor and antimetastatic activities of the stilbene glucosides, piceid, and 2,3,5,4'-*tetra*-hydroxystilbene-2-*O*-D-glucoside might be due to inhibition of DNA synthesis in LLC cells and angiogenesis of human umbilical vein endothelial cells (Kimura and Okuda, 2001). It was also reported that pterostilbene, a natural methoxylated analog of RSV, suppressed the development of mammary lesions with an ED₅₀ of 4.8 μ M in a mouse mammary gland organ culture (Rimando et al., 2002). Cyanidin, pelargonidin, and delphinidin also displayed antiproliferative activity in two estrogen-dependent human breast cancer cell lines (MCF-7 and BG-1), but not in the estrogen receptor-negative MDA-MB-231 cell line (Schmitt and Stopper, 2001). Cyanidin and delphinidin contributed to the potent inhibitors of the epidermal growth-factor receptor and were found to inhibit the growth of human vulva carcinoma cell line A431 in vitro (Meiers et al., 2001).

Inhibition of Lipid Oxidation

Phenolics in red grape juice have been shown to decrease circulating levels of LDL cholesterol and to increase LDL receptor activity in human hepatocarcinoma HepG₂ and promyelocytic HL-60 cell lines (Dávalos et al., 2006). After treatment of LDL in cells, red grape juice increased levels of the active form of sterol regulatory element-binding protein-1 and mRNA expression of the LDL receptor as well as hydroxymethylglutaryl-CoA reductase. Conversely, red grape juice resulted in a reduction in the expression of CYP7A1, apolipoprotein B, ABCA1, and ABCG5. It was proposed that phenolics present in red grape juice disrupted or delayed LDL trafficking through the endocytic pathway, further affecting intracellular lipid homeostasis. The oxidation of LDL is an important event in the development of atherosclerosis. Several studies have indicated that grape and grape-seed extracts inhibit LDL oxidation (Frankel et al., 1993a; Teissedre et al., 1996). Frankel et al. (1993b) were first to demonstrate that *trans*-RSV reduced the copper-catalyzed oxidation of human LDL. In vivo, RSV blocked copper-catalyzed LDL oxidation in healthy human subjects by 70% and 81%, respectively, while also inhibiting ROS production and lowering lipid peroxidation in blood platelets (Olas and Wachowicz, 2002). RSV has been also found to inhibit copper-initiated and, to a lesser extent, 2,2'-azobis (2-amidinopropane) dihydrochloride (AAPH)-initiated oxidation of porcine LDL (Frémont et al., 1999). LDL peroxidation was blocked better by RSV than by a phenolic extract from red wine. When the effects of pretreatment with the anthocyanins (delphinidin, cyanidin, and their glycoside and

rutinoside derivatives) on DNA damage were evaluated in rat smooth muscle and in rat hepatoma cell lines using the Comet test, results showed that they were effective against cytotoxicity, DNA single strand breaks formation, and lipid peroxidation induced by *tert*-butyl-hydroperoxide (Lazzé et al., 2003). The effects of RSV on biomarkers of oxidative stress and on the activity of several enzymes in liver and kidney were examined in streptozotocin (STZ)-induced diabetic rats (Schmatza et al., 2012). RSV was shown to prevent TBARS increase; catalase and superoxide dismutase; and aminolevulinic acid dehydratase decrease in the diabetic groups ($P < 0.05$), suggesting that RSV possesses a protector effect against hepatic and renal damage induced by oxidative stress, evidenced by the decreased lipid peroxidation in the diabetic state.

Inhibition of Platelet Aggregation

The inhibitory effect of grape phenolics on platelet aggregation is one of the accepted mechanisms in cardioprotection. The inhibition of platelet aggregation by grapes was demonstrated in animal and human studies. Bagchi et al. (1998) showed that grape seed proanthocyanidin extract demonstrated higher protective effects than vitamin E or C alone, vitamin E plus C, and β -carotene against 12-*O*-tetradecanoylphorbol-13-acetate-induced lipid peroxidation and DNA fragmentation in liver and brain tissues as well as counteracting the production of free radicals in peritoneal macrophages of mice. Studies showed that 5–10 mL/kg of purple grape juice, but not orange or grapefruit juice, inhibited platelet activity and protected against epinephrine activation of platelets in dogs, monkeys, and humans (Osman et al., 1998; Folts, 2002). In a study which fed subjects with seven mL/kg body weight/day for 14 days, purple grape juice was shown to lower platelet aggregation, increase platelet-derived nitric oxide release, and suppress superoxide production (Freedman et al., 2001). After Concord grape juice was given orally (10 mL/kg/day) to subjects, serum antioxidant capacity was increased and LDL oxidation was decreased from 400 IU α -tocopherol per day (O'Byrne et al., 2002). Quercetin, the predominant grape flavonoid, suppresses platelet aggregation in vitro (Chung et al., 1993), and lowers thromboxane synthesis in vivo (Tzeng et al., 1991). RSV was observed to have vasorelaxation properties in endothelium-intact and endothelium-independent aortic rings via both nitric oxide-dependent and -independent mechanisms (Chen and Pace-Asciak, 1996). It has been suggested that the target for RSV inhibition of thrombin-induced platelet aggregation occurs through the prevention of calcium influx via storage operated calcium channels. RSV supplementation decreased the rate of platelet aggregation in rabbits that were fed a high cholesterol diet (Dobrydneva et al., 1999). Pretreatment of platelets with RSV was shown to inhibit lipopolysaccharide (LPS) and LPS plus thrombin-stimulated platelet adhesion to collagen and fibrinogen in a nondose-dependent pattern (Olas and Wachowicz, 2002). The release of NO \cdot has been suggested as a mechanism for the reduction of ischemia-reperfusion injury in rat

hearts after RSV treatments (Bradamante et al., 2003). The effects of extracts of grape seed (GSD) and grape skin (GSK) on collagen-induced whole blood platelet aggregation (PA) were examined in vitro (human platelets) and ex vivo (dog platelets) (Shanmuganayagam et al., 2002). The results suggest that the components of GSD and GSK, when present in combination as they are in red wine, grape juice, or in commercial preparation containing both extracts, have a greater antiplatelet effects than when present individually.

Anti-inflammatory Activity

The anti-inflammatory activity may be partially responsible for the chemopreventive and cardioprotective effects of phenolics present in grapes. In comparison to nonsteroidal anti-inflammatory drugs such as aspirin and piroxicam, RSV suppressed cyclooxygenase-1 (COX-1) hydroperoxidase activity and, to a lesser extent, cyclooxygenase-2 (COX-2) hydroperoxidase activity (Jang et al., 1997). RSV also inhibited induced COX-2 activity via targeting the protein kinase C (PKC) signal transduction pathway in human breast epithelial cells, blocking the translocation of PKC into the membrane (Subbaramaiah et al., 1998). RSV noncompetitively inhibited the activity of COX-1 in a dose-dependent manner, and decreased the expression of COX-2 both in in vitro and in vivo models while significantly reducing levels of PGD₂ in rats (Martín et al., 2004). It also dose-dependently inhibited induced production of PGE₂ in human peripheral blood leukocytes in vitro (Richard et al., 2005). It was observed that RSV lowered induced-COX-2 activity by inhibiting the expression of the enzyme via signal transduction pathways (Kundu et al., 2004), and blocked the inflammatory actions of cytokines, such as tumor necrosis factor- α (TNF- α) and interleukin-1 β (IL-1 β) (Culpitt et al., 2003). Pterostilbene exhibited moderate inhibition of COX-1 with an IC₅₀ of 19.8 μ M, and was weakly active against COX-2 with an IC₅₀ of 83.9 μ M, whereas RSV strongly inhibited both isoforms of the enzyme with IC₅₀ values of approximately 1 μ M (Rimando et al., 2002). Dietary RSV significantly inhibited chemically-induced liver tumorigenesis in rats, which could be linked to its anti-inflammatory action through hepatic COX-2 inhibition (Luther et al., 2011). Additionally, it was observed to have potential protective effects in cholestatic liver injury (Chan et al., 2011) when given (4 mg/kg/day, i.p.) for either three days or seven days after bile duct ligation (BDL) injury. The results showed that RSV significantly decreased TNF- α and IL-6 mRNA, lowered the number of Kupffer cells in the liver at the early stage of injury, as well as reduced hepatic fibrosis, collagen I α 1, and TIMP-1 mRNA on day seven. Anthocyanins present in grapes have also been reported to be anti-inflammatory (Wang et al., 1999).

Phytoestrogenic Effect

Some phenolics from grapes exhibit a phytoestrogen effect. Typically, RSV has been categorized as a phytoestrogen because

it acts as a partial estrogen receptor agonist at low levels and antagonizes the growth-stimulatory effect of E₂ at higher doses in the presence of 17- β -estradiol (E₂) (Lu and Serrero, 1999). The estrogenic properties of RSV appear to vary in cell lines. RSV can stimulate estrogen-regulated progesterone receptor (PR) expression in MCF-7 cells (Gehm et al., 1997; Bhat et al., 2001). It showed superagonist activity by inducing gene activity two- to three-fold more than estradiol, while displaying superagonist activity in MVLN cells—an estrogen-dependent MCF-7 cell line (Basly et al., 2000). Conversely, RSV has been shown to have no superagonist activity and actual anti-estrogenic activity through estradiol-induced gene expression inhibition in the MCF-7 cell line. In MCF-7, T47D, LY2, and S30 mammary cancer cell lines, RSV functioned as an agonist in the MCF-7 and the S30 cell lines, while antagonizing estrogen activity in T47D and LY2 cells. Bhat and Pezzuto (2001) also reported the anti-estrogenic activity of RSV in human endometrial adenocarcinoma through the suppression of PR expression, estradiol-induced alkaline phosphatase activity, and an estrogen receptor-mediated reporter gene.

Effects on the Cell Cycle and Apoptosis

Inhibition of cell cycle progression is a possible target for chemopreventive agents like grape phenolics. The effects of RSV on the cell cycle in tumor cells occur during the S-phase (Hsieh et al., 1999a; Wolter et al., 2001; Joe et al., 2002). However, a G₁-phase arrest by RSV was also observed in HepG₂ cells. RSV arrested stellate cells in G₁-phase by selectively reducing the level of cyclin D₁, and induced apoptotic cell death in HL-60 cells, particularly in cells arrested in the G₀/G₁ phase (Surh et al., 1999), which was linked to a decrease in the expression of the anti-apoptotic oncoprotein, Bcl-2. On the other hand, an RSV-induced arrest of HL-60 cells at the S/G₂ phase transition and a subsequent increase in the number of cells in the G₁/S phases have also been observed. (Ragione et al., 1998). This event was attributed to an increase in cyclins A and E and inactive cdc2, without any modification of p21^{WAF/CYP1} expression. The suppression effect of RSV on normal cell growth is accompanied by the accumulation of cells in the S and G₂ phases (Hsieh et al., 1999b). Similar to RSV, piceatannol is also a cell-cycle inhibitor that functions in the S phase.

Apoptosis, a programmed cell death, is necessary for the maintenance of normal tissue homeostasis. Grape phenolics are able to induce cell death both in vitro and in vivo. RSV has been reported to induce apoptosis in a number of cell lines (Hsieh et al., 1999a; Wolter et al., 2001; Joe et al., 2002; Kim et al., 2003). Conversely, it was found that RSV suppressed oxidative-induced apoptosis in a variety of cell lines, such as Swiss 3T3 mouse fibroblasts (Kutuk et al., 2004), rat pheochromocytoma (PC12) (Jang and Surh, 2001), and human retinal pigment epithelium (RPE) cells (King et al., 2005). It appears that RSV-induced apoptosis is accompanied by the induction of p53, activation of caspase 9, upregulation of Bax, and a decrease in

Bcl-2 levels. Consequently, RSV-induced cell death is tumor-specific and involves the CD95–CD95L system as the apoptotic trigger, suggesting that this system could activate a series of intracellular events culminating in the death cascade. In SW480 human colon cancer cell line, Delmas et al. (2003) found that the apoptosis induced by RSV was not mediated directly through modulation of Fas/FasL interaction, but was attributable to caspase activation and increased accumulation of Bax and Bak. In DU145 human prostate carcinoma cells, RSV upregulated Bax protein and mRNA expression in a dose-dependent manner, whereas Bcl-2 and Bcl-xL levels were not significantly affected (Kim et al., 2003). After treatment with RSV, the tumor suppressor p53-dependent pathway was monitored in the induction of apoptosis in HepG2 cells and JB6 mouse epidermal cells (Huang et al., 1999). Shih et al. (2002) indicated that, in thyroid cancer cells, RSV-induced cell death was blocked by addition of the p53 inhibitor pifithrin- α or by transfection of a p53 antisense oligonucleotide. Piceatannol has been also exhibited to be a potent inducer of apoptosis in human SK-Mel-28 melanoma cells (Larrosa et al., 2004).

Effects on the Signal Transduction

Grape phenolics are not only able to target signal transduction pathways, but also able to further act with different biological effects. Mitogen-activated protein kinase (MAPK) pathways, including p38, c-Jun N-terminal protein kinase (JNK), and extracellular signal-regulated kinase (ERK) are well-characterized mammalian signal transduction pathways which convert extracellular signals into intracellular events (El-Mowafy and White, 1999; Vanamala et al., 2011). The interaction between RSV and signal transduction pathways may explain many of the beneficial effects of RSV. TNF- α -induced JNK, activator protein-1 (AP-1), and MEK (MAPK kinase) activation were inhibited by pretreatment with RSV in U937 lymphoma cells (Manna et al., 2000). The modulation of ERK signaling by RSV suggests that RSV plays an important role in angiotensin II (Ang II)-induced proliferation and ET-1 gene expression in rat aortic smooth muscle cells (Chao et al., 2005). In porcine coronary arteries, RSV was found to inhibit the activation of p38, JNK1, and ERK1/2 by endothelin-1 (ET-1) (El-Mowafy and White, 1999). RSV has been reported to target MEK and ERK activation in the inhibition of cardiac fibroblast mitogenic signaling, proliferation, and differentiation into myofibroblasts (Olson et al., 2005). RSV down-regulated the HIV-1 protein Tat-induced proinflammatory responses such as MCP-1 and TNF- α via the inactivation of ERK1/2 in rat hippocampal slice cultures, which may be related to the anti-inflammatory mechanism of RSV (Lee et al., 2011). The anticancer properties of RSV are due partly to the activation of p53 and the inhibition of NF- κ B and AP-1 through the suppression of signaling cascades. RSV also induced apoptosis in wild-type p53 mouse fibroblast cells, but was not able to induce apoptosis in p53-deficient fibroblast cells (Huang et al., 1999). RSV-induced apoptosis and p53 activation via phosphorylation are mediated by the ERK and p38 pathways. AP-1

also provided a potential target for RSV. Induced AP-1 activity in human cervical squamous carcinoma (HeLa) cells using 12-myristate 13-acetate (PMA), and ultraviolet light-C (UV-C) demonstrated that RSV suppressed both PMA-induced and UV-C-induced AP-1 activity (Yu et al., 2001). Through the inhibition of AP-1 activity and ERK phosphorylation, topical application of RSV to mouse skin was found to inhibit TPA-induced COX-2 expression (Kundu et al., 2004). Recently, it was discovered that RSV down-regulates Smad2/3 phosphorylation and suppresses follicle-stimulating hormone (FSH β) expression via a SirT1-independent pathway in L β T2 immortalized mouse gonadotrope cells (Lan et al., 2011).

Piceatannol inhibits both the protein-tyrosine kinase activity of p72^{Syk} and p56^{Lck} in lymphoid cells and the focal adhesion kinase in thrombocytes, while blocking the tyrosine kinase activity in human placenta (Palmieri et al., 1999). Banerjee et al. (2002) observed that RSV decreased mammary tumor incidence, tumor number, and extended cancer latency in female Sprague-Dawley rats by inhibiting the expression of NF- κ B, COX-2, and matrix metalloprotease 9. Although the mechanisms by which RSV suppresses NF- κ B activation remains uncertain, it was found that RSV inhibited TNF-induced NF- κ B activation by blocking phosphorylation and nuclear translocation of the NF- κ B subunit p65 by preventing NF- κ B DNA binding and by inhibiting I κ B kinase (IKK) activity via an upstream signaling component (Manna et al., 2000). Anthocyanidins directly cause human promyelocytic leukemia cells (HL-60) to generate intracellular hydrogen peroxide, thereby triggering apoptosis, possibly through an oxidative stress-involved JNK signaling pathway. It was observed that delphinidin both stimulates JNK pathway activation including JNK phosphorylation and c-jun gene expression, and activates caspase-3 (Hou et al., 2003).

Induction of Phase II Enzymes

Grape phenolics are proposed to interact with cellular defense systems, especially for phase II enzymes including NADPH: quinone oxidoreductase (NQO1), glutathione S-transferase, and UDP-glucuronosyl transferase (Yoshioka et al., 1995; Wu and Hsieh 2011). Thirteen wine grape varieties and 18 common phytochemicals were evaluated for their ability to induce mammalian phase II detoxification enzymes—NQO1 in Hepa1c1c7 murine hepatoma cells (Yang and Liu, 2009). Among the grape varieties analyzed, Cabernet Franc showed the highest inducible effect on NQO1 with the lowest induction concentration. Compared to the DMSO solvent-treated control cells, at 2 mg/mL concentration, the induction-folds of Cabernet Franc was 3.1 ± 0.3 . Quercetin, genistein, and resveratrol exhibited strong NQO1 induction activity among the 18 phytochemicals. Quercetin, at a concentration of 30 μ M, resulted in a maximum of 3.5 ± 0.2 -fold induction over control, while RSV caused a maximum of 2.2 ± 0.1 -fold induction over control at a concentration of 50 μ M. Thus, both RSV and quercetin could stimulate phase II detoxifying systems at the transcriptional level. An increase in NQO1 transcription in response to quercetin

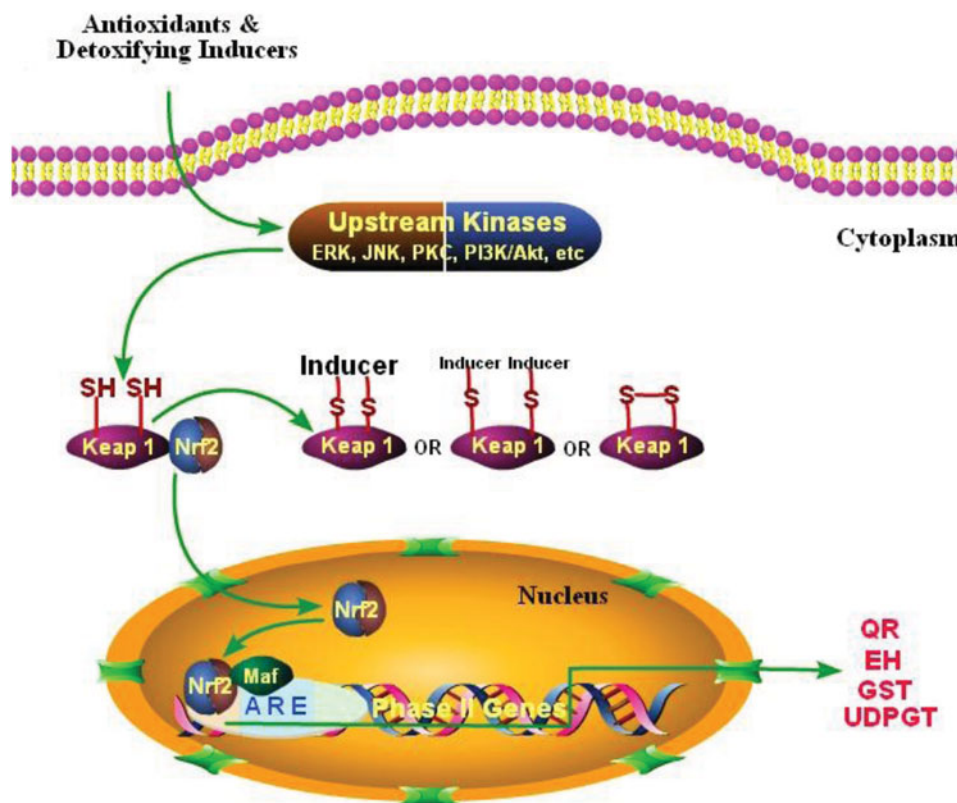


Figure 8 Activation of Nrf2 signaling and induction of phase II detoxifying and antioxidant genes (modified from Talalay, 2005). (Color figure available online.)

was documented, showing that quercetin induced a two-fold increase in NQO1 protein amount, and a three- to four-fold increase in NQO1 mRNA expression (Valerio et al., 2001). Phase II enzymes possess specific nucleotide sequences in their gene promoters, which are defined as the antioxidant-responsive element/electrophile-responsive element (ARE/EpRE), with the consensus sequence 5'-TA/CANNA/GTGAC/TNNNGCA/G-3' (Wasserman and Fahl, 1997). ARE/EpRE has been found to protect cells against carcinogens and oxidative stress. Several molecules, such as c-Jun, nuclear factor-E2-related factor 2 (Nrf2), ATF2, and ATF4, have been marked as potential modulators of ARE/EpRE (Itoh et al., 1999; Hayes and McMahon, 2001). For example, Nrf-2 is a transcription agent essential to Phase II enzyme induction. It is normally localized in the cytosol, where it is linked to protein-protein interactions with the chaperone Keap1. An inducer such as RSV and quercetin disrupts the Keap1-Nrf2 interactions, permitting Nrf2 to translocate to the nucleus and further bind to the ARE/EpRE (Fig. 8). Quercetin induced Nrf2-ARE-mediated NQO1 transactivation through enhancement of the steady-state level of Nrf2 at both the transcriptional and posttranslational stages, and reduced the steady-state level of Keap1 through 26S proteasome-independent degradation (Tanigawa et al., 2007). It showed that ARE activity induced by quercetin was markedly affected through silencing Nrf2 or Keap1 with their siRNA, indicating that both Nrf2 up-regulation and Keap1 down-regulation

activated by quercetin are essential for ARE-mediated NQO1 activation.

CONCLUSIONS

In numerous epidemiological studies, grapes have been associated with a lowered risk of chronic diseases. In vitro and in vivo studies have demonstrated that grape phytochemicals are involved in a broad spectrum of biological activities, including antioxidant activity, inhibition of cancer cell proliferation, induction of phase II enzymes, and reduction in lipid oxidation, which potentially explains the grape's role in decreasing the risk of chronic disease from a mechanistic perspective. Furthermore, RSV-mediated activation of life-extending genes in human cells may open a new horizon in grape research. Evidence from observing cell and animal models shows the benefits of grape phytochemicals in the reduction of cardiovascular risk factors due to a decrease in platelet activation, inflammation, and LDL oxidation, as well as improvement in endothelial function. However, the evidence for grape phytochemicals in prevention of cancers is less clear. Further research is required on the mode and dosage of application to maximize the benefits. Grapes are a reliable and rich source of phytochemicals, whose individual and summated actions are suggestive of future health benefits.

However, the additive and synergistic molecular mechanisms in grapes are not yet fully discovered. The interaction of the grape phytochemicals warrants further study as researchers attempt to investigate the mechanisms behind the grape's ability to reduce the risk of chronic diseases.

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