Resveratrol Glucosides are Important Components of Commercial Wines

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Using a direct-injection HPLC method with isocratic elution and UV detection, the isomers of free resveratrol and their glucosides (polydatin) have been assayed in nearly 700 commercial red wines from most of the world's areas of production. The highest concentrations of polydatin were found in wines from the Midi and Rhone Valley of France, Canada, Italy, Spain and Portugal, and South America. In the last three regions, the polydatin concentrations exceeded those of free resveratrol which were the lowest of all categories examined, suggesting that the high sugar content of warm climate grapes may favor the glycosylation of resveratrol. In nine regions, the concentration of *cis*-polydatin exceeded that of *trans*-polydatin, the reverse being the case in five, yet in all *trans*-resveratrol concentrations exceeded those of *cis*-resveratrol. There was only a weak negative correlation overall between polydatin and resveratrol concentrations when all wines were included in the analysis. The low values for both polydatin and resveratrol in Californian wines are consistent with the notion that, despite high sugar content, some grapes may fail to express resveratrol synthetic enzymes due to genetic characteristics or to lack of environmental stress, and consequently little of the free resveratrol is available for glycosylation. The influence of cultivar was examined in wines from several regions. Among wines from California, Australia, South America and Canada, highest polydatin concentrations were found respectively in those from Zinfandel, Shiraz, Merlot and Pinot noir. Wines from the Northern Rhone Valley (predominantly Shiraz) had lower concentrations than those from the Southern Rhone where Mourvedre, Grenache, Carignane and Cinsault predominate. The high polydatin and very low resveratrol concentrations of Vintage Ports highlight enological techniques, particularly duration of fermentation, as important modulating factors. The concentrations of polydatin present in most red wines are likely to add significantly to the presumed health benefits attributable to resveratrol.

KEY WORDS: polydatin, resveratrol, phytoalexin, high performance liquid chromatography, Cabernet Sauvignon, Pinot noir, Shiraz, Merlot

Interest in resveratrol (3,5,4'-trihydroxystilbene) was initially stimulated by its role as a phytoalexin which is produced in vines in response to infection with pathogens such as *Botrytis cinerea* and *Plasmospora viticola* (3,12,18,19). Its importance as a biologically active product synthesized by grapevines was greatly expanded with the recognition that it appeared to be one of the main components of oriental herbal medicines used in the treatment of cardiac and inflammatory diseases and that it was present in plant extracts that were claimed to exercise beneficial effects upon hepatic lipid metabolism (1,14) and leucocyte eicosanoid synthesis (15) in animal models. Subsequent studies with pure preparations of resveratrol demonstrated its ability to inhibit the production of oxidized low-density lipoproteins (4) which are highly atherogenic in man (30) and to block the aggregation of platelets, a process that plays a role in the progression of atherosclerosis as well as in the final occlusive events leading to myocardial infarction and stroke (2,22).

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The presence of resveratrol in commercial wine (predominantly red wine) was first observed by Siemann and Creasy (25). This finding led to an explosion of research activity in the course of which it became clear that in addition to the *trans*-isomer as noted originally (17,20,24), other forms of this trihydroxystilbene were also present in red wine. These included *cis*-resveratrol (6,9,10,13,27,28), which in some wines is in higher concentrations than the *trans*-isomer. The next to be identified was the glucoside of *trans*-resveratrol (11,23). Subsequently, the glucosides of both isomers (polydatins) were also reported as red wine constituents (7,16).

In a previous publication (8), we reported the *trans*-resveratrol concentrations in red wines from a large range of countries and regions. Those from Burgundy, Oregon, Switzerland, and Bordeaux demonstrated the highest concentrations whereas low values were found in wines from most Mediterranean (Italy, Spain, and Portugal) and New World (California, Australia, South America) regions with the exception of Canada. Much of this variance could be explained by intrinsic properties of the cultivars from which these wines were vinted. For example, wines from Pinot noir grapes were almost invariably higher than Cabernet Sauvignon even when the vines were growing in neighboring vineyards. The contribution of enological practices is also a source of variability which we and others have explored (13,21,28). It is likely that this accounts for differences between individual wines within the same region, but it is less likely that the large, consistent, and reproducible differences between regions, especially when wines from the same cultivar (Cabernet Sauvignon) are compared can be attributed to this factor alone. The effects of climate, soil, and exposure (28) as well as the degree of fungal pressure to which the ripening berries are exposed (9) represent other important influences. In a recent report (6), we examined the *cis*-resveratrol concentration of 750 commercial wines from 15 countries and regions. The values for wines of any one region showed a reasonable correlation with those of the *trans*-isomer, the coefficient ranging from 0.525 (Rhone Valley) to 0.958 (South Africa). However, much greater variability was seen in the ratio of *cis:trans* resveratrol; this ranged from 0.22 (Italy) to 0.80 (Beaujolais). The present investigation to compare the polydatin and free resveratrol concentrations of commercial wines was undertaken to extend these observations for the following reasons:

(1) The data could provide useful insights into the possible origin of resveratrol free isomers from their glucosides during fermentation since *cis*-resveratrol is not detectable in grape skins (19,30), whereas *trans*-polydatin has been demonstrated in grape berries (31).

(2) Reasons have been advanced for considering all four forms of resveratrol as bio-available (5), and therefore, the cardioprotective potential of red wines is better represented by its total content of free isomers and glucosides so far as the biological effects of resveratrol are concerned.

Materials and Methods

An isocratic HPLC method as previously described was used to measure the isomers of resveratrol and polydatin by direct injection of 20 µL of untreated wine (7). The equipment comprised a ternary HPLC (Spectra-Physics, San Jose, CA, USA) coupled to an SP 8000 pump, SP 8875 autosampler and Chrom Jet integrator. LiChrosphere 100 CN, particle size 5 µm, packed in a column 250 × 4 mm i.d. obtained from Merck (Darmstadt, Germany) served as the stationary phase. Normal-phase elution of resveratrol free isomers and glucosides was accomplished with a mobile phase of water-acetonitrile-methanol (90:5:5, v/v/v) at a flow rate of 1 mL/min. The elution times were approximately as follows: *cis*-polydatin 18.8 min, *trans*-polydatin 19.6 min, *cis*-resveratrol 33 min, *trans*-resveratrol 48 min. Peaks were detected at 306 nm, close to the absorbance maximum of *trans*-resveratrol and *trans*-polydatin. The *cis*-isomers had significant absorbance at this wavelength allowing good sensitivity and precision for all compounds measured. *trans*-Resveratrol obtained from Sigma (St. Louis, MO, USA) and *trans*-polydatin isolated from the dried roots of *Polygonum cuspidatum* by a previously published method (31) were used as standards, and the corresponding *cis*-standards were prepared by UV-irradiation of the two *trans*-compounds.

Commercial wines were received directly from the winery or the negociant and were analyzed within two weeks of delivery. After opening for organoleptic testing to eliminate any that were flawed, a 10-mL aliquot was transferred to a glass vial, tightly stoppered, covered with foil and stored at 4°C for up to one week. Under these conditions the fall in concentration of any constituent never exceeded 3.5%.

Statistical tests were performed using the SAS Statistical Software Package (SAS Inst. Inc., Cary, NC, USA). These included Student's t-test for unpaired samples on groups demonstrating absence of skewness or kurtosis which, if present, led to log-transformation of the data; where certain groups were rather small numerically, significance was confirmed by Fisher's Protected LSD (26).

Results and Discussion

Figure 1 summarizes the results of polydatin determinations in wines from the major regions examined. The mean values of *cis*-polydatin were < 3 µmol/L in wines from California and Bordeaux. Those from South Africa, Burgundy, Australia, Oregon, Beaujolais, Spain and Portugal, Italy, and Central Europe had mean values >3 and <7 µmol/L in ascending order. Higher mean values were noted in wines from the Rhone Valley, South America, Canada, and the Midi region of France. There was a somewhat similar trend for *trans*-polydatin with mean values being rather low in wines from California, Oregon, Burgundy, and Australia; intermediate in those of Bordeaux, South Africa, Beaujolais, Central Europe, South America, and Canada; and relatively high in those from the Rhone Valley, Italy, the Midi, and Spain and Portugal.

For most wines, the mean content of the two isomers of polydatin were quite similar. In those from nine regions, the mean *cis*-polydatin concentrations were greater than the mean *trans*-polydatin concentrations and in five the situation was reversed. These differences were statistically significant ($p < 0.05$) for the higher *cis*-polydatin of wines from Oregon and the Midi, and the higher *trans*-polydatin of wines from Spain and Portugal.

Figure 2 illustrates the *cis*- and *trans*-resveratrol concentrations of these wines. In general, these results are in accord with those we have obtained previously (6,8) and support the conclusion that low resveratrol concentrations are present in Mediterranean (Italy, Spain, and Portugal) and New World (California and South America) wines with the exception of those from Canada and Oregon; high values were generally present in those of Burgundy and Bordeaux. The overall concentrations are, however, somewhat lower than those obtained in our earlier reports based upon direct-injection GC-MS assays. We have recently conducted a comparative evaluation of the latter with the HPLC method used in the present paper (29) and found that the GC-MS assay yields consistently higher results for both isomers although the correlation between them is

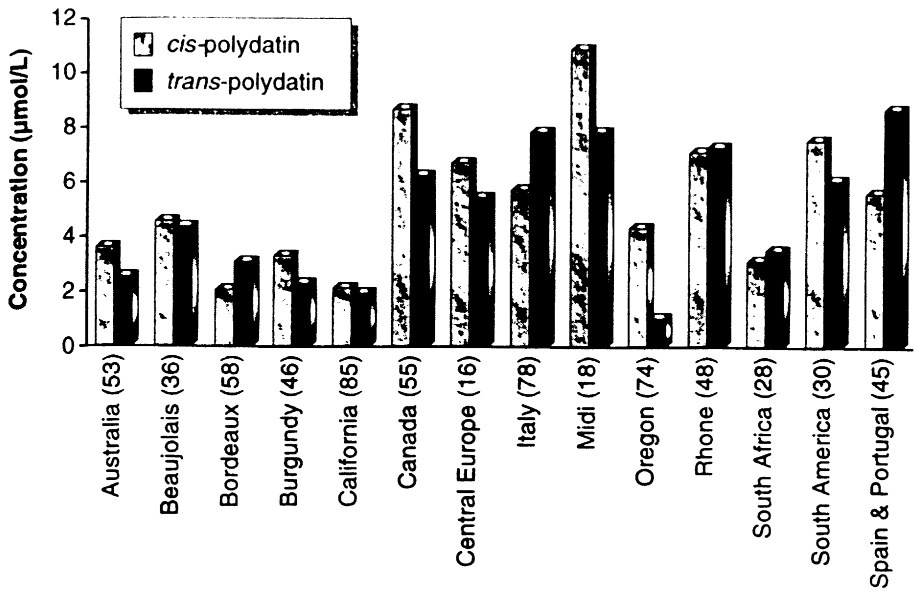

Fig. 1. Mean concentrations of polydatin isomers in commercial red wines from various regions. Number of samples in parentheses.

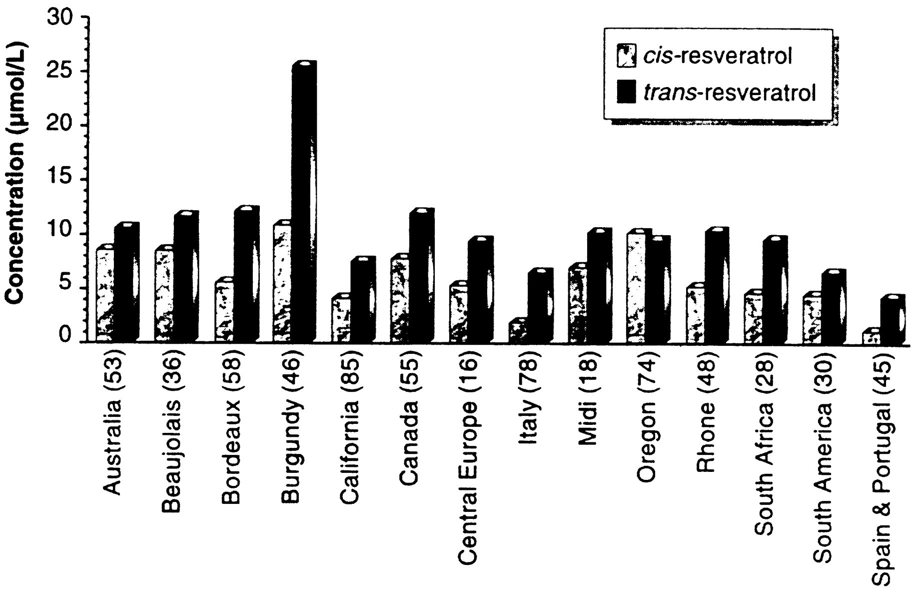

Fig. 2. Concentrations of resveratrol isomers. Number of samples in parentheses.

excellent. We have shown that this difference is partly due to the thermal breakdown of resveratrol glucosides to the free isomers.

Two features in the present data call for explanation. The first is the much higher relative concentrations of resveratrol isomers in Australian wines than those previously reported. The most plausible explanation is that the wines in the present survey contained many more from Shiraz grapes or Shiraz-Cabernet blends, whereas those that formed the basis of our earlier reports were predominantly from Cabernet Sauvignon. The latter wines contain much lower concentrations of resveratrol than the former, as will be subsequently described (Table 1). The second is the somewhat lower than expected resveratrol concentrations of Bordeaux wines which were less than those of Beaujolais in the present survey. We attribute this reversal in the previously noted pattern to the fact that the 1990 Bordeaux reds, which formed a high proportion of those tested, had substantially lower concentrations than earlier vintages, whereas the 1993 Beaujolais wines, which were not well represented in our earlier surveys, had much higher concentrations than those vintages that predominated in our GC-MS study.

When the individual values of *cis-* and *trans*-polydatin were summed for each wine, the means for each country and region were distributed as shown in Figure 3. The highest values were observed in wines from the Midi (18.9 µmol/L) followed by Canada (15 µmol/L), the Rhone Valley (14.6 µmol/L), Spain and Portugal (14.5 µmol/L). Mean values >12 µmol/L were also noted in the wines from South America, Italy, and Central Europe.

To illustrate the relative quantitative importance of polydatin isomers and resveratrol isomers in different wines, the sum of the latter is also presented in Figure 3. It is evident that in some, as indicated by a ratio >1, the polydatin isomers were present in higher concentration than the resveratrol isomers. The highest mean ratio was found in wines from Spain and Portugal (2.44); next came those of Italy (1.58) and South America (1.27). It is striking that wines from these three regions were the lowest in resveratrol isomer concentrations, suggesting that there may be a reciprocal relationship between the glucosides and free isomers in these wines consistent with the conversion of the former to the latter during extraction and fermentation. This notion is supported by the conversely low polydatin and high resveratrol content that characterized Burgundy wines. However, the argument is not substantiated by wines from the Rhone Valley and the Midi, where ratios close to unity were attributable to high concentrations of both polydatin and resveratrol. Indeed, a poor negative correlation overall existed between the glucoside and free isomer concentrations of the entire sample, and the correlation between *cis*-polydatin and *cis*-resveratrol was actually lower numerically than with *trans*-resveratrol, *trans*-polydatin showing similar paradoxical behavior.

The relationship is obviously more complex than

Table 1. Comparison of polydatin and resveratrol isomer concentrations of commercial red wines according to grape and region. All data are µmol/L±SEM.

	Polydatin			Resveratrol			Ratio[a]
	cis	*trans*	Total	*cis*	*trans*	Total	
CALIFORNIA							
Cabernet Sauvignon (28)	1.2 ± 0.4	1.4 ± 0.4	2.6 ± 0.7	1.1 ± 0.6	3.2 ± 0.8	4.3 ± 0.9	0.61 ± 0.14
Zinfandel (14)	3.6 ± 0.6	4.8 ± 0.8	8.4 ± 0.9	1.9 ± 0.3	5.5 ± 0.9	7.4 ± 0.9	1.14 ± 0.18
Merlot (16)	2.5 ± 0.5	1.7 ± 0.3	4.2 ± 0.6	4.7 ± 0.5	8.8 ± 1.3	13.5 ± 1.8	0.32 ± 0.09
Pinot Noir (14)	2.6 ± 0.6	1.8 ± 0.4	4.4 ± 0.6	12.2 ± 1.2	16.0 ± 1.2	28.2 ±2.0	0.15 ± 0.04
AUSTRALIA							
Cabernet Sauvignon (15)	0.9 ± 0.2	1.1 ± 0.3	2.0 ± 0.4	3.0 ± 0.7	5.7 ± 1.0	8.7 ± 1.4	0.24 ± 0.06
Shiraz (20)	5.6 ± 0.9	3.6 ± 0.7	9.2 ± 1.4	11.4 ± 1.8	13.9 ± 2.2	25.3 ± 3.6	0.36 ± 0.09
SOUTH AMERICA							
Cabernet Sauvignon (12)	4.9 ± 1.2	3.4 ± 1.0	8.3 ± 1.6	2.1 ± 0.6	4.2 ± 0.8	6.3 ± 1.3	1.21 ± 0.28
Merlot (8)	10.7 ± 3.3	9.9 ± 3.4	20.6 ± 5.1	5.8 ± 2.0	7.8 ± 2.1	13.6 ± 3.3	1.44 ± 0.56
Malbec (6)	7.8 ± 2.4	6.2 ± 2.1	16.0 ± 3.8	7.3 ± 2.5	8.6 ± 2.6	15.9 ± 3.2	1.01 ± 0.34
RHONE VALLEY							
North (22)	4.8 ± 0.8	3.9 ± 0.7	8.7 ± 1.2	6.4 ± 0.9	10.0 ± 2.0	16.4 ± 2.6	0.52 ± 0.14
South (26)	9.9 ± 1.4	10.9 ± 1.4	20.8 ± 1.8	4.9 ± 0.9	8.4 ±1.3	13.3 ± 1.7	1.47 ± 0.26
CANADA							
Cabernet Sauvignon (12)	7.1 ± 1.4	4.5 ± 1.5	11.6 ± 2.1	7.4 ± 1.5	10.8 ± 1.6	18.2 ± 3.0	0.65 ± 0.19
Pinot noir (16)	10.2 ±1.9	8.8 ± 2.0	19.0 ± 2.6	7.6 ± 1.9	12.9 ± 2.1	20.5 ± 2.9	0.93 ± 0.25

[a]Ratio of total polydatin-to-total resveratrol

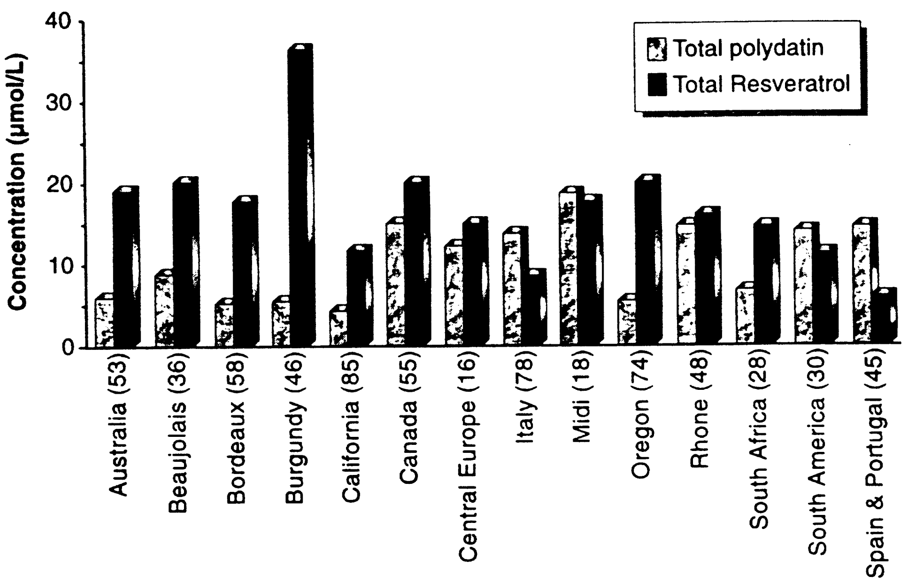

Fig. 3. Total polydatin and resveratrol concentrations of commercial red wines from various regions. Number of samples in parentheses.

that of precursor and product. We hypothesize that, while such a relationship does in part exist, it is modulated by factors such as the following:

(a) Sunlight, which increases the sugar content and may promote glycosylation reactions. The drying conditions would down-regulate resveratrol synthase unless actual UV-induced damage occurred. This would be more likely in berries with thin skins (*e.g.*, Pinot noir) than those with thick skins.

(b) Fungal pressure, which increases resveratrol synthase gene expression but also enhances its conversion to viniferins. Indeed, the balance between synthesis by the host and degradation of resveratrol by the parasite is probably the single most important factor in determining resveratrol concentrations in wines produced in climatic areas favorable to the growth of *B. cinerea* (13,24).

(c) Vinification techniques. For example, shorter extraction periods are likely to be required for the water soluble polydatins compared with the nonpolar resveratrol isomers, and the former are more likely to undergo loss during barrel fermentation. It is probable that conversion of polydatin to resveratrol is proportional to the duration of fermentation. These ideas are given credence by our analysis of vintage Port wines (n = 15) which in most instances had very low free isomer concentrations (means of 1.5 and 0.6 µmol/L for *cis* and *trans*, respectively), and yet had rather high polydatin concentrations (means of 10.7 and 4.5 mol/L for *cis* and *trans*, respectively). In the production of these wines which are only declared in exceptional years, fermentation is ab-

breviated by raising the alcohol concentration to retain sugars, but this intervention would also prematurely terminate the conversion of polydatins to free resveratrol. The climatic conditions during vintage years would also tend to promote high berry sugar content with greater availability of substrate for glycosylation reactions.

To examine the source of variability among certain wines, a number of subgroups within certain categories were examined. Table 1 presents a number of comparisons in which some significant differences were found:

(1) California wines from four different cultivars were compared: Cabernet Sauvignon, Zinfandel, Merlot, and Pinot noir. Those from Zinfandel had higher concentrations of total polydatin than the other wines ($p < 0.05$), but those from Pinot noir had the lowest content relative to resveratrol isomers as indicated by their mean ratio of 0.15 ($p < 0.005$).

(2) Major differences were found in comparing Australian wines from Shiraz and Cabernet Sauvignon grapes. The polydatin content of the latter was much lower than the former ($p < 0.001$), but since the concentrations of resveratrol isomers were proportionately reduced, there was no difference in the polydatin-to-resveratrol ratio.

(3) Among South American wines, those from Merlot had higher concentrations of total polydatin than wines from Cabernet Sauvignon and Malbec ($p < 0.01$), as well as a higher ratio of polydatin-to-resveratrol ($p < 0.05$). However, it is notable that for all these wines the ratio exceeded 1.0, pointing to relatively high glucoside content being a consistent feature of this region and independent of cultivar.

(4) Canadian wines from Cabernet Sauvignon had lower total polydatin content and polydatin-to-resveratrol ratio than Pinot Noir wines from the same region ($p < 0.01$ and $p < 0.05$, respectively). However, their polydatin concentrations were greater than those of Cabernet Sauvignon wines from South America ($p < 0.05$), Australia ($p < 0.001$) and California ($p < 0.001$).

No significant differences could be found in any of the parameters measured when making the following comparisons:

(1) Medoc versus St. Emilion and Pomerol to compare Bordeaux wines where Cabernet Sauvignon is the dominant grape with those in which Merlot predominates. This may initially seem surprising in view of the much higher polydatin and resveratrol concentrations of California and South American wines from Merlot compared with those from Cabernet Sauvignon (Table 1). Clearly, the latter cultivar when grown in unfavorable climatic conditions, as in Canada, is stimulated to produce much higher amounts of resveratrol matching those of Merlot which seems to be less sensitive to climate.

2. Cotes de Nuits versus Cotes de Beaune to compare wines made from a single grape (Pinot noir) in the North and South of Burgundy. This absence of a geographical effect strengthens the view that the differences between wines from the Northern and Southern Rhone Valley (*vide infra*) reflect the different cultivars from which they are vinted.

(3) Chile versus Argentina and Spain versus Portugal to assess how wide the differences might be between wines produced in adjacent countries from a large number of cultivars but by similar technologies and under broadly similar climatic conditions. It was not possible to compare the same cultivars in analyzing wines from Spain and Portugal. Although the numbers were small, there was good agreement between the composition of Cabernet Sauvignon, Merlot, and Malbec wines from Chile and Argentina.

(4) The wines of Italy from the regions of Piedmont (predominantly from Nebbiolo), Tuscany (chiefly Sangiovese) and Veneto (a wide range of different cultivars). The best explanation that can be offered for this negative finding at the present time is that these cultivars are similar in resveratrol production and are relatively insensitive to environmental influences.

(5) Wines from the Northern Rhone Valley, vinted from predominantly Shiraz grapes, had significantly lower concentrations of both isomers of polydatin ($p < 0.01$) compared with those from the Southern Rhone where a large range of cultivars (including Grenache, Mourvedre, Carignane, and Cinsault) are employed. Since their contents of resveratrol isomers were similar, a higher polydatin-to-resveratrol ratio was present in Southern Rhone wines ($p < 0.001$).

Conclusions

The data presented establish polydatins as important constituents of red wines which in those from several regions equal or exceed the concentrations of free resveratrol. It seems virtually certain that the polydatins are extracted from the berries (skins) during fermentation and that they are, at least in part, converted to the corresponding free isomers during this process. While there did not seem to be major differences between different vintages of the same generic wines, the numbers were not adequate to permit valid statistical analyses of this important issue. Multiple factors including gene expression, climate, and enological procedures undoubtedly predetermine and subsequently modulate the absolute and relative concentrations of polydatin and resveratrol in an individual wine. Some of these have been explored and discussed in this report but definitive answers must await prospective studies which can only be performed on site. While we have commenced such investigations for Ontario wines, it is our hope that the present survey, one of the largest and geographically most comprehensive yet conducted into the chemistry of wine, will act as a stimulus and a challenge to scientists in the various wine-producing regions to develop experimental protocols designed to test the hypotheses we have advanced, thus definitively elucidating the origin and regulation of this intriguing family of molecules which are certainly important in the life of the grape, and possibly also to human health.

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