VITICULTURAL FACTORS AND RESVERATROL IN GRAPES AND WINE

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Introduction

In recent time the relation between food and health has been the subject of a considerable amount of media interest highlighting in particular how the second is deeply influenced by the first. It is primarily the medical profession who is leading in the direction of understanding this relation, in particular the risks of certain habits, aware of the need to prevent related illness not only to keep patients healthy, but also to contain the public health expenditure

One of the item attracting a lot of attention is wine, a product of ancient tradition and integral part of the Italian and Mediterranean culture. It is both an ancient and modern beverage, which is neither good or bad for health, but the effect of which depends on different factors like the amount drunk or the general health of the person drinking it. This is not the place to underline the health effect of abusing wine, it is worth instead to remember its actual beneficial effect to healthy people and in moderate consumption.

This last aspect, possibly already known to doctors, came to a lot of media attention about 15 years ago, when a very popular television program in the States, gave the news of an epidemiology research conducted by two French scientist (Renaud e De Lorgeril) published in 1992. The Authors studied the relation between the mortality rate by coronary disease (in men and women in 1987) and the consumption of animal fats in the diet of a sample of population in some European Countries (16) and Australia. Using a simple statistical method (the linear regression) it was immediately clear that the two were directly proportional: the higher the average consumption of animal fat calories, the higher the mortality. The two parameters were related. France however, did not get in to this picture. Its sample population (the towns of Lille, Strasbourg and Toulouse) were characterised by a high consumption of animal fat, but the lowest mortality by coronary disease, compared to the other Countries

This is the phenomenon called "French paradox" The next step was clearly to try to identify why the French, although eating so much animal fat, could boast the lower coronary disease incidence. Other risk factors were studied, like the blood pressure, the body mass index, smoking habits, but none of this parameters were lower than the other countries. With regard to wine consumption it was noted that it could be the parameter that could explained the "paradox": French people drank more wine than the other Countries and that could counter-act the effect of the high animal fat consumption. Considering that other alcoholic beverages did not present the same effect of wine, the doubt remained that it was not the actual alcohol content the responsible of the positive effect, but maybe other elements still not investigated. The two researcher honestly concluded that the protective effect of wine and its superiority compared to other alcoholic products, were only hypothesis that needed a more detailed study. As remarked above, this information broadcasted during a television show, was enough to suddenly increase the wine consumption in the USA.

One of the substances thought responsible (partially) for the beneficial effect of wine is the resveratrol.

The resveratrol in the vine

The resveratrol is a natural compound of phenolic origin belonging to the chemical species of the stilbenes. It can be found in 12 families of the plant kingdom including the *Vitaceae* and, within this family also in the *Vitis vinifera* L., which is the most important species, world wide, for the production of grapes, grapewine and rasins. In the vine the resveratrol is found as an induced substance (by biotic and abiotic elicitors) in the herbaceous parts and in the berries, and as a building factor in the wood In the first instance it behaves as a phytoalexin, synthesized *ex novo* in the leaf and berry (skin) in response to fungal attacks (noble rot primarily but also downy mildew, powdery mildew, *Aspergillus carbonarius,*) with the function of protect the plant from the damage of those organisms (Dercks e Creasy, 1989; Hoos e Blaich, 1990; Jeandet et al., 1995; Bavaresco et al., 1997b; 2003; 2008).

The plants that are genetically resistant to those diseases tend to produce high quantities of this compound and in a short period of time, while plants sensitive to fungal diseases tend to produce little of it and very slowly (Bavaresco e Eibach, 1987; Bavaresco, 1993; Bavaresco et al., 1994; Bavaresco et al. 2003). Various other stilbenes have been identified in the grapes and precisely: *trans*- and *cis*-piceid (*trans*- and *cis*-resveratrol glucoside) (Waterhouse e Lamuela Raventòs 1994; Mattivi *et al*. 1995; Romero-Pérez *et al*. 1999), ε-viniferine (dimer of *trans*-resveratrol) (Bavaresco *et al.* 1997a), pterostilbene (*trans*-3,5-dimetoxy-4'-hydroxy-stilbene) (Pezet e Pont 1988), piceatannol (*trans*-3, 4, 3', ,5'-tetrahydroxy-stilbene) or astringinine (Bavaresco *et al*. 2002), pallidol *(trans*-resveratrol dimer) (Landrault *et al*. 2002).

The stilbenes are found in the woody part of the vine as well (not induced by stress), like the branches (Langcake e Pryce, 1976, 1977), the roots (Bavaresco *et al.* 2000a, 2003), the seeds (Pezet e Cuenat 1996; Ector *et al.* 1996; Li et al., 2006), and the stalks (Bavaresco *et al*. 1997b, 2000b). They are probably involved in the resistance mechanism against wood decay.

The resveratrol as a good substance for human health

While the presence of this compound in the vine has been known for the past 30 years, its finding in wine is more recent. The first monitoring was made in 1992 by two researcher of the Cornell University. The resveratrol is found in wine as a result of extraction from the skins during the alcoholic fermentation (Mattivi et al., 1995; Pezet e Cuenat, 1996; Bavaresco et al., 1999).

The following malolactic fermentation is capable of increasing the quantity of resveratrol thanks to the ability of bacteria to release the compound in its glucosidic (piceid) form, with which it is partly found in the skins. The interest in this substance comes from some medical data according which the resveratrol was the active element in a popular Chinese and Japanese medicament known as "kojo-kon" (based on dried roots of *Polygonum cuspidatum*) prescribed for various ailments (like hyperlipemia, arteriosclerosis, allergies and inflammations).

Staying in the medical world and ahead of the discovery of resveratrol in wines, some researchers were looking at wine as a protective alcoholic beverage, particularly against circulatory and heart diseases; in 1990, for example, one study did show that the consumption of red wine (Bordeaux), but not white wine or ethanol, reduced platelet aggregation and increased the cholesterol-HDL, both positive factors for the human health. On this experiences, Siemann and Creasy based the hypothesis of a close link between resveratrol and the protective action of wine in relation to coronary disease. Then in 1992, as mentioned in the introduction to this article, the French Paradox stole the international attention..

From 1992 onward a large amount of studies have been produced, both from the medical profession (with the intention of finding more about the possible benefits to health) and from the world of viticulture and oenology.

The most important health claims are related to the ability of resveratrol to reduce the risks of cardio-vascular diseases (Bertelli *et al.* 1995, 1996); the preventive action against cancer (Jang *et al*. 1997; Bruno *et al*. 2003); the action against Alzheimer disease; the action as regulator of the immune system (Falchetti *et al*. 2001) and as phytoestrogen (Calabrese 1999). For more detailed reading on this medical aspect, we refer to the specialised publications (Frémont 2000; Cassidy *et al.* 2000; Andreotti 2005). It is worth remembering that this positive aspects are shown for moderate but consistent consumption of wine with a concentration of resveratrol even medium-low (up to 1-2 mg/L) (Bertelli 2003), on condition that the subject is healthy and, more importantly, not affected by liver complains. Other stilbenes compounds (piceatannol, pterostilbene, ε-viniferine, ecc) have shown positive activities on the human health, but there is little research to back it up.

The resveratrol has also shown the ability to both lengthen the life of some organisms (Howitz et al., 2003), but not yet human being, and to counter-act the negative effect of a hyper caloric diet (in rats) but in this case only with very high quantities, unthinkable with a normal consumption of wine (Baur et al. 2006).

It is also worth remembering that the positive effect of grape on health is linked to other anti-oxidant polyphenolic compounds as well, and not only to resveratrol and other stilbenes.

The viticultural and oenological world has been leading studies everywhere in the quest to understand which are the parameters that influence the quantity of resveratrol found and the possible ways to increase it, taking in to account that is always positive to have wines rich in it, (within the natural limits: up to 55 mg/Kg in grapes and up to 30 mg/L in wine). The benefits are both on the grape, because of the better natural resistance against diseases, and the wine, for the superior healthy qualities. The stilbenes are the only compounds with this double action.

Generally, the contents of resveratrol in red wines is higher then in white wines, because of the vinification technique which involves maceration on the skins for the red wines, with the resulting extraction of the substance (Mattivi et al., 1995).

Viticulture factors and stilbenes

Although the synthesis of the resveratrol is unleashed by a few biotic and abiotic factors, an important role is played also by some vine growing elements, like grape variety, the rootstock the geographical region, the weather during ripening, the intensity of fungi attack and the cultural techniques.

Understanding the role of this factors is of paramount importance because this allows, where possible, to chose them according to the content of resveratrol, taking on account that the goal of the vine grower is the production of high quality grapes for the various oenological needs; the trick is to see whether the positive element of having grapes rich in resveratrol are compatible with a quality wine production. After all wine is mainly an hedonistic product, which can take benefit from healthy attributes, but they cannot become the essential element.

According to the available studies, the grape variety and the climate are the major links to the synthesis of the resveratrol, therefore, because the data related to the cultural techniques is highly influenced by the climate, it is hard to draw a general rule. It is however possible to point to some general direction as for the following.

Grape variety and rootstock

The effect of the grape variety is important and it can be deducted by the tests conducted on grapes and mono-varietal wines.
According to some Authors (Soleas et al. 1995b; Golberg et al. 1995, 1996; Sato et al. 1997; Eder et al. 2001) the grape varieties with higher production of resveratrol are Pinot noir and Cabernet Sauvignon but not always (Bavaresco 2003), if, for example, the data in Figure 1 is taken in to consideration. According Okuda and Yokotsuka (1996) who worked on 33 varieties planted in Japan in 1994, there is a significant effect of the genotype on the concentration of resveratrol in the berry, swinging from a 0.06 mg/Kg (white Pizzutello) to a 1.76 mg/Kg (Müller Thurgau).

Wine	Vintage	*trans*-Resveratrolo mg/L
Nero d'Avola	1995	11.9
Barbera d'Asti	1996	7.9
Chianti Colli senesi	1996	7.4
Monferrato Dolcetto	1996	6.7
Nero d'Avola + Perricone	1995	5.1
Montepulciano d'Abruzzo	1996	5.0
Bardolino classico	1996	4.7
Sangiovese + Canaiolo	1996	4.5
Torgiano Rosso	1995	4.1
Valtellina Rosso	1996	3.2
Taurasi	1993	2.4

Cabernet Sauvignon passito	1996	1.9
Chambave rouge	1992	1.8
Vallée d'Aoste Torrette superiore	1992	1.5
Vallée d'Aoste Nus rouge	1992	1.3
Oltrepò Pavese Barbera	1996	1.3
Vallée d'Aoste Pinot noir	1992	1.1
Colli Piacentini Pinot nero	1992	1.0
Vallée d'Aoste Gamay	1992	0.9
Colli Piacentini Gutturnio	1992	0.6
Vallée d'Aoste Enfer d'Arvier	1992	0.5
Vallée d'Aoste Chambave Moscato passito	1992	0.5
Vallée d'Aoste Donnas	1992	0.3
Lambrusco dell'Emilia	1996	0.3
Vallée d'Aoste Arnad Montjovet	1992	0.2

Fig. 1 : Average concentration of resveratrol in some Italian wines (Fregoni and Bavaresco, 1994; Bavaresco, 2003).

Normally the red varieties have a higher contents of stilbenes than white varieties, as shown on Figure 2 for the concentrations of resveratrol and its glucoside in some wines from Piacenza (Bavaresco et al., 2007b).

	trans-Resveratrolo mg/Kg PF	trans-Piceide mg/Kg PF	cis-Piceide mg/Kg PF
Barbera	0.071	0.234	0.136
Croatina	0.076	0.061	0.050
Malvasia C.a.	0.024	0.013	0.019
$DMS_{0.05}$	0.033	0.031	0.026

Fig. 2 Concentrations of stilbenes in grapes after the harvest in the major varieties grown in the area of Piacenza (Bavaresco et al., 2007b).

We expect the genotypes of grapes resistant to diseases (interspecific hybrid and American vines) to have a higher concentration of stilbenes compared to sensitive genotypes, like varieties of *V. vinifera*. This has been confirmed in some cases (Creasy e Coffee 1988; Jeandet *et al*. 1991; Bavaresco *et al*. 1997a; Li et al., 2006) but not in others (Soleas *et al.* 1995a,b).In wines too, the published material is not consistent regarding the relation between stilbenes and resistant/sensitive varieties. According to Romero-Perez *et al.* (1996), the levels of resveratrol and piceid in wines of Spanish varieties of *Vitis vinifera* were related to their resistance to diseases. Also Lamikanra *et al*. (1996) have found higher concentrations of resveratrol in wines of *V. rotundifolia* (resistant to deseases) compared to wines of *V. vinifera* (low resistance). On the other hand however, Soleas *et al*. (1995b, 1997) and Eder *et al.* (l.c.), the concentration of resveratrol is higher in wine of *V. vinifera* compared to interspecific hybrid. Finally, in some other cases, wines of *V. vinifera* and wines of interspecific hybrid had similar concentrations of resveratrol (Korbuly *et al*. 1998) This contradictions are rather difficult to explain and are probably linked to the interaction with climate and cultural methods.

The variety has an impact on the quantity of resveratrol in the stalks at harvest too, as shown on Chart 1. The practical implication being that bits of stalks that inevitably remain in the fermenting mass of red grape, can become a source of resveratrol in the wine, as shown on Figure 3 (Bavaresco et al., 1997; 2000).

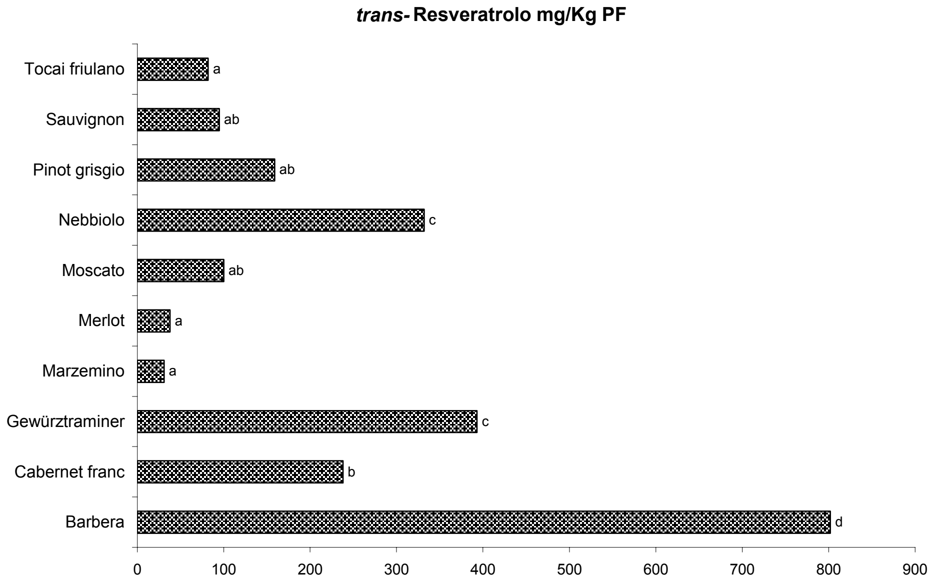

Chart 1: Content of resveratrol in the stalk at maturity depend from the variety Values followed by the same letter are not significant per p<0.05 (Test di Tukey). (Bavaresco et al., 1997b; 2000b)

Fig. 3: Extraction of trans-resveratrol after 4 days of maceration in hydro-alcoholic solution (11% v/v) in 5 varieties considering 0.3 g of stalk/100 mL (Bavaresco et al., 1997b; 2000b).

	trans-Resveratolo		
	mg/Kg of stems	Extraction %	µg/L alcoholic solution
Barbera	104.0	13.0	314
Cabernet franc	17.8	7.5	53
Marzemino	10.2	32.9	31
Merlot	10.2	26.8	31
Nebbiolo	30.0	9.0	92

The resveratrol in the seeds too is affected by the variety but the experimental data at this regard are limited and the wild species are the richest in it (Ector et al. 1996; Li et a., 2006); the maximum content is of 62 mg/Kg and can hardly migrate to the wine during the alcoholic fermentation.

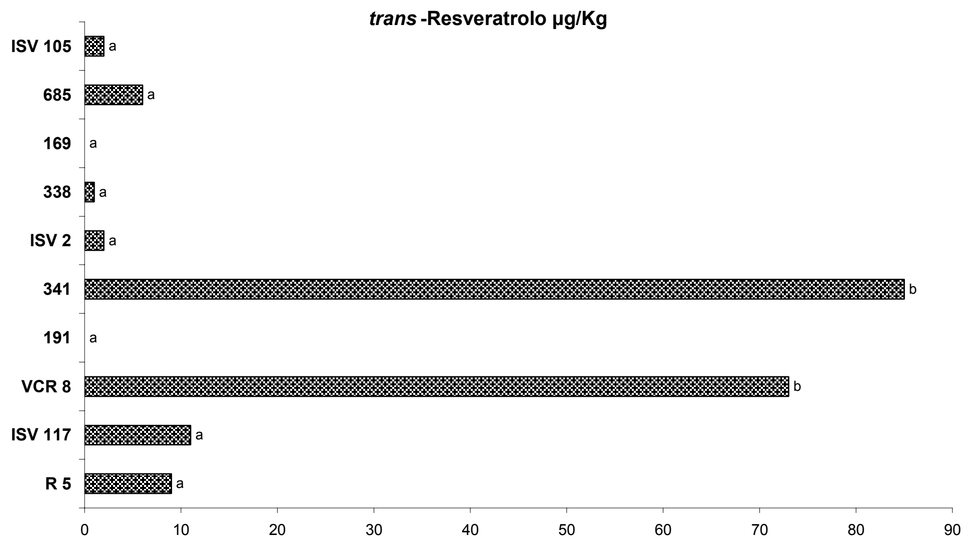

Chart 2: Concentration of trans-resveratrol in berries of ten clones of Cabernet Sauvignon, at harvest. Values followed by the same letter are not significant per p<0.05

The clone too plays an important role in the content of resveratrol in the grapes; Chart 2 shows data not published yet (Bavaresco et al.) related to some clones of Cabernet Sauvignon.

The impact of the rootstock on the resveratrol in the grapes could be important, but there are no experimental data at this regard.

Climate

The influence of the climate seems to be crucial. By climate we refer to the characteristics of a vineyard as given by geographical position (latitude, altitude, facing etc.) and the meteorological annual conditions for a particular vineyard in a particular area.

With reference to the effect of the latitude, only a comparison between wines is possible and the published records do not offer a clear answer. According to Goldberg *et al.* (1995,1996) wines produced in cold climates (especially Cabernet Sauvignon) have higher concentrations of resveratrol than wines produced in hot place, but according to another research by the same group (Goldberg *et al*. 1999) this is not always true; this contradiction can be explained by the interference of other unchecked elements, including the oenological practices. Experimental data on the effect of altitude of the vineyards on the synthesis of the resveratrol in the grape, conducted in Val Tidone (Piacenza) show an increase of stilbenes for up to 300m above sea level, to then decrease at higher altitudes (400 m) (Fig 4).

Fig. 4: Influence of altitude of vineyard on the concentration of stilbenes in grapes (Bavaresco et al., 2007b).

Altitude	*trans*-Resveratrol mg/Kg	*trans*-Piceid mg/Kg	*cis*-Piceid mg/Kg
150 m s.l.m.	0.012	0.065	0.019
240 m s.l.m.	0.059	0.086	0.055
320 m s.l.m.	0.087	0.186	0.123
420 m s.l.m.	0.070	0.074	0.053

The annual meteorological conditions, by acting on the intensity of fungal attacks in the vineyard, can have an effect on the synthesis of the stilbenes (Jeandet et al 1995; Martinez-Ortega et al. 2000). Even a light fungal attack (not visible to the naked eye, like *Botrytis*) is sufficient to trigger the synthesis of the stilbenes in the berries, and this happens at an increasing humidity between 70 and 80%, during the ripening period (Bavaresco et al., 2006b).
Also the temperature during the ripening period has a role, because is negatively linked with the quantity of resveratrol in the grapes and wines. (Li et al,., 2006; Bavaresco et al., 2006b, 2007a; Bertamini e Mattivi 1999).

Soil

There is very little data on the effect of soil on resveratrol. In a test in pots a very calcareous soil induced in Merlot/3309 C, together with serious symptoms of chlorosis, a strong build up of resveratrol and other stilbenes in the grapes (Bavaresco *et al*. 2005; 2008) (Chart 3). The synthesis of this substances is encouraged by relatively calcareous soils (short of getting to the chlorosis point) as opposed to soils lacking calcium carbonate (de Andrés-de Prado et al., 2007). The effect of 'Terroir" on the stilbenes concentration, on the contrary, has never been highlighted in the Pinot noir of Bourgogne (Adrian *et al.* 2000).
It could be possible that the soil has an indirect effect on the stilbenes metabolism, interfering with the mineral and water nutrition of the plant.

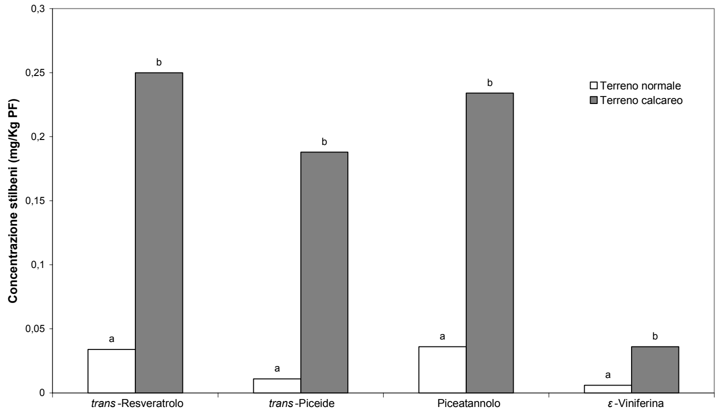

Chart 3: Soil role on stilbenes concentration in Merlot grape at harvest. (Bavaresco et al., 2005)

Cultural techniques

The fertilisation is an important factor which interact with the plant physiology, including the mechanisms of resistance to diseases. Nitrogen is a highly reactive mineral element - the plant absorbs it easily and react rapidly and intensely to the variations of its doses. The concentration of resveratrol in the grapes increases with the decrease of nitrogen (Bavaresco *et al.* 2001; 2007a) while the preliminary results related to potassium are not very clear (Bavaresco *et al*. 2006a).

According to tests conducted in France by Coulomb *et al*. (1999), a cupric treatment with Bordeaux mixture and a test with cupper hydroxide made on Cinsaut, 21 days before harvest, increased the levels of stilbenes (*trans*- and *cis*- resveratrol and piceid) in grapes, compared to non treated plants; the copper seems therefore to act like an elicitor in the stilbenes synthesis. Is evident that in some complete treatments plans, the use of Bordeaux mixture against mildew has produced wines (Mourvèdre, nel Languedoc-Roussillion) richer in *trans*-resveratrol compared to the wines from grapes treated with organic synthetic fungicides (Albert *et al*. 2002), except for the treatment with mancozeb+cymoxanil which induced instead a higher quantity. To prove the positive role of copper on resveratrol, some wine from Bourgogne and Loire (Tinttunen e Lehtonen 2001) and some Austrian wines (Otreba et al., 2006) from organic farming, have shown a higher content of *trans*-resveratrol compared to conventional wine. Further researches are however necessary in order to confirm this results.

With regard to winter pruning, the intensity of it did not influence the concentration of resveratrol in grapes of Valpolicella (Celotti et al. 1998), but the green harvest has been proven capable of increasing the concentration of resveratrol and its glycosides in grapes and wines of Charbourcin, an old French hybrid (Prajitna et al., 2007).

With regard to the training system, this has an effect on resveratrol quantities in Cabernet Sauvignon wines, (Bertamini e Mattivi l.c.) by intervening on the micro-climate at grapes level: a low isolation of the clusters is favourable in hot vintages and detrimental in cooler ones.

The thinning out of leaves at clusters level during veraison, on Barbera, Croatina and aromatic Malvasia di Candia in the area of Piacenza, did not have any effect on the resveratrol in hot and dry vintages but in fresher years it had a negative effect (Bavaresco, to be published).

According to preliminary results (Gebbia *et al*. l.c.), the low production of grapes per hectare and lack of irrigation did help the presence of stilbenes in wine.

Very interesting are some results on the interaction between resveratrol and ochratoxin A (OTA) in grapes (Bavaresco et al., 2008) and wine (Perrone et al., 2007). The resveratrol is produced by the plant as a reaction from an attack of *Aspergillus carbonarius*, the major responsible for the production of OTA (Bavaresco et al., 2003, Vezzulli et al., 2007a), and wine rich in OTA are rich in resveratrol as well; the opposite, however, is not true, so wines rich in resveratrol are not always rich in OTA. Where this happens it could be possible that the resveratrol acts (on the subject taking it) as an antidote towards OTA (Jeswal, 1998).

Artificial methods to increase the presence of resveratrol and other stilbenes

Finally, there are methods which have nothing to do with cultural practices, to intervene in the synthesis of this substances. For example the treatment made on Barbera grapes with a solution (in alcohol) of methyl giasmonate (10 mM), in three different stages (fruit setting, veraison and 45 days later) has increased the level of resveratrol in the harvested grapes, from 0,03 mg/Kg to 0,32 mg/Kg (Vezzulli et al., 2007b).

A further method is the irradiation of the grapes with UV rays. This is a method used by Paronetto and Mattivi (1999); they have irradiated for 100 days with UV-C rays the semi-dried grapes of Corvina, Rondinella, etc, used in the production of Amarone and Recioto della Valpolicella, managing to double the concentration of resveratrol. The same effect, but with a shorter exposure time (10 minutes), has been studied on some wild species (Cynthiana, *V. aestivalis*; Noble, *V. rotundifolia*) (Threlfall et al., 1999). Treatments with UV rays on table grapes after harvest increased the concentration of resveratrol (Cantos et al., 2000; Moriartry et al., 2001).

Another factor able to increase the levels of resveratrol in grapes is the treatment with ozone (8 ppm) in storage rooms at controlled environment in the Napoleon grape variety (Artés-Hernandes et al., 2003).

We finally mention the BTH (benzothiadiazole) which increased by a 40% the concentration resveratrol in grapes of Merlot (Iriti et al., 2004) and abscisic acid (ABA) which increased by 1,2 times the level of resveratrol in the Japanese grape Kyoho (Ban et al., 2000).

Conclusions

As well as the viticultural factors analysed in this article, the concentration of resveratrol and the others stilbenes in the wines is affected by the oenological techniques, which controls the extraction of the components in the skin and their relatively efficient conservation during the vinification and storage process The composition of the base material (grape) is however crucial, because the grapes with a poor contents of stilbenes, will never produce wines rich of it.

At the moment the scientific research is focused on the genetic bases of the synthesis of stilbenes, so as to understand and manipulate their expression in the future. For example it will be possible to intervene with the assisted selection (through molecular markers) in new programmes of genetic improvement by clonal selection, cross breading or hybridization , or by manipulation of the metabolic path of stilbenes. In Japan a GM vine (genetically modified), highly capable of producing resveratrol, has already been produced (Nakajiama et al., 2006). The practical outcome of this studies is on one hand the possibility to improve the defence mechanisms of the vine against diseases, and on the other hand the production of a healthier product.

In conclusion, although the vine is considered like a medicinal plant, is essential to remember that, the wine cannot be drunk as a medicine and it does not cure any ailment. To drink wine properly is, first of all, part of a cultural attitude and lifestyle. Only with this message it will be possible to win new consumers whom, once educated to good drinking, will then be able to appreciate the health credentials as well.

Summary

The resveratrol is a phenolic compound synthesised by the herbaceous parts and by the skins and berry and is believed to have health properties. This substance belongs to the chemical species of the stilbenes (diphenylethylene) which includes other compounds as well like the piceatannol, the piceid, the pterostilbene, the viniferine and the pallidol, which are produced by the plant as a defence from biotic and abiotic stress especially after fungal attacks. The research made on the activity of the resveratrol on the human organism, after consumption either as grape or the transformed product (especially wine), highlight various positive effects for the health, like the reduction in cardio vascular incidence, and a preventive action against cancer. The concentration of resveratrol in the grape is related to different viticulture factors, like the grape variety, the rootstock, the soil, the climate, and the cultural techniques, all discussed in the present article.

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