Wine, Resveratrol and Health: a Review

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ABSTRACT

Several studies have cited the Mediterranean diet as an example of healthy eating. In fact, the Mediterranean diet has become the reference diet for the prevention of cardiovascular disease. Red wine seems to be an essential component of the diet, since moderate consumption of wine is associated with lower risk and mortality from cardiovascular disease. Evidence is also accumulating that wine helps prevent the development of certain cancers. Of all the many components of wine, resveratrol, which is a natural component specifically present in wine, has been identified as being mainly responsible for these health-promoting properties. Many value properties such as cardioprotective and anticarcinogenic activity have been attributed to resveratrol; however, its bioavailability is quite low. The bioactivity of metabolites derived from resveratrol, and the accumulation of resveratrol in vital organs are still under study, but there are high expectations of positive results. Other stilbene compounds are also considered in this review, despite being present in undetectable or very small quantities in wine. The present paper reviews all aspects of the health properties of wine, bioactive compounds found in wine, and their concentrations, bioavailability and possible synergistic effects.

Keywords: anticarcinogenic, cardioprotective, health, Mediterranean diet, resveratrol, wine.

The contribution of wine to the Mediterranean diet

The concept of the "Mediterranean diet" originated from several observational studies done in 1950's. Later, the Seven Countries Study, a cross-cultural investigation comparing middle-aged men from northern and southern Europe, was important in recognizing the role played by the Mediterranean diet in protection against heart disease [1]. Populations in Southern Europe suffer lower rates of coronary heart disease (CHD). In 1992 a study conducted by Renaud and De Lorgeril revealed that the incidence of heart infarction in France is about 40% lower than in the rest of Europe; this was termed the "French paradox", which appeared to be related to intake of red wine [2]. The Lyon Diet Heart Study showed a significant decrease in the risk of recurrence after a first myocardial infarction, under the Mediterranean diet pattern [3]. Many other studies suggest that the Mediterranean diet helps to prevent CHD and other vascular diseases and many types of cancer, as well as anti-inflammatory and degenerative diseases [4,5].

Apart from epidemiological studies, clinical intervention studies provide more specific scientific evidence. Many such studies have been carried out in various countries including Greece, Denmark, Australia and Spain. In particular, the PREDIMED study conducted in Spain, the study of Mediterranean-style diet in subjects with metabolic syndrome in Italy, the GISSI-prevention clinical trial in Italy and the Medi-RIVAGE study in France are significant [6,7]. The conclusions from these are: first, diet does indeed affect longevity; and second, an optimal diet for the prevention of coronary heart disease and cancer overlaps with the Mediterranean diet. Specifically, the adoption of a Mediterranean diet significantly reduces total cholesterol, triglycerides, blood glucose concentration, fibrinogen, homocysteine and diastolic/systolic blood pressures, while increasing HDL-cholesterol and apoA1 [8].

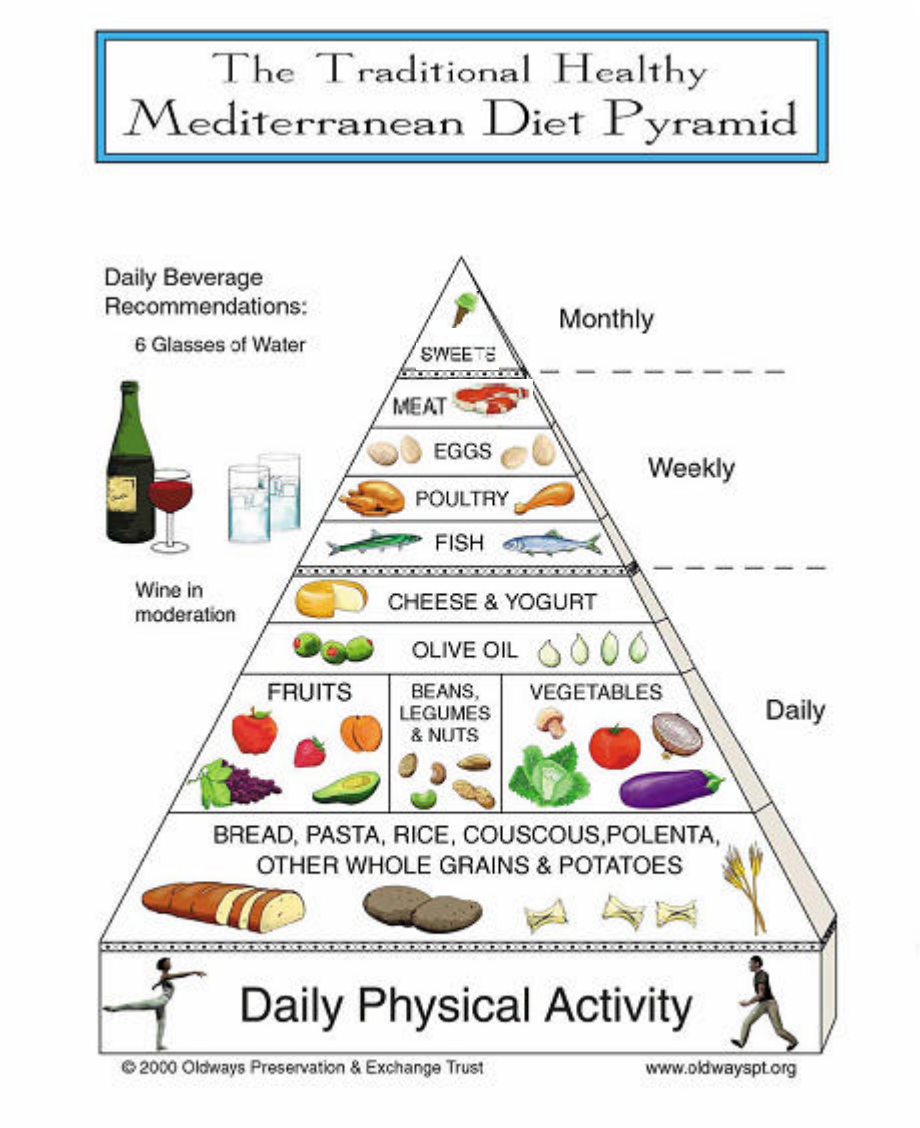
Recently, a review of all the prospective cohort studies, covering the period from 1966 to June 2008, has been published. It shows that closer adherence to a Mediterranean diet is associated with a significant improvement in healthy status, as seen by reduction in overall mortality (9%), mortality from cardiovascular disease (9%), incidence of cancer (6%), and incidence of Parkinson's and Alzheimer's diseases (13%) [9]. Of course the Mediterranean diet is not the only explanation for the relatively better health of Mediterranean people but unquestionably it seems to contribute to it. When the Mediterranean diet is combined with exercise, an additional cardiovascular protection is observed [10,11].

With respect to cancer, it should be recalled that cancer is the most extensive disease in Europe (http://www.who.int/research/en/ data and statistics section). In 2004 in Europe, there were an estimated total of 2,886,800 incident cases of cancer diagnosed and 1,711,000 cancer deaths. The most common incident form was lung cancer (13.2%), followed by colorectal cancer (13%) and breast cancer (12.8%) [12]. The effect of diet on cancer prevention has been widely proven. Various aspects of the Mediterranean diet have been associated with reduction of risk in several

cancer types, and it has been suggested that up to 25% of colorectal, 15% of breast and 10% of prostate, pancreas and endometrial cancers could be prevented by shifting to the Mediterranean diet [13].

The Mediterranean diet is characterized by high intake of vegetables, legumes, fruits, nuts and unrefined cereals, high intake of olive oil but low intake of saturated lipids, moderately high intake of fish, moderate intake of dairy products, mostly in the form of cheese or yogurt, low intake of meat and poultry, and regular but moderate intake of ethanol, primarily in the form of wine and generally during meals (Figure 1) [14,15]. The World Health Organization (WHO) adopted this pattern as a dietary guideline.

Figure 1: Mediterranean diet pyramid



Within the Mediterranean diet, wine seems to be an essential component and may be partially responsible for health-promoting properties observed among the Mediterranean population. The starting point for wine and health studies was the “French Paradox”. In 1992, Renaud and De

Lorgeril [2] published a study confirming the association between death by cardiovascular disease and dietary intake. The higher the general dietary intake, the more people died from cardiovascular disease (CVD) in all European countries except for France. If wine intake was considered, the French population fitted perfectly the regression model.

From all the studies that have been carried out in the health-and-wine field, it can be affirmed that supplementing the regular diet with red wine increases total antioxidant capacity in plasma, HDL lipoprotein, fibrinolytic and antithrombin activity, and vitamin C; it also reduces oxidative damage and platelet aggregation. Above all, it diminishes the risk of cardiovascular diseases [16-19]. Recently the same conclusion has been established in diabetic subjects after myocardial infarction [20].

Although less evident, wine could have an influence on cancer risk. Moderate consumption of wine reduces the risk of non-Hodgkin's lymphoma [21], adenocarcinoma of the oesophagus, prostate cancer [22-24] and gastric cardia [25]. However, other authors have not found any relationship [26,27], and some even found a negative effect [28].

Among wines, red wine is considered to have more protective effect, due to its greater content in antioxidant substances released from the grape's skin and seeds (polyphenols). In the making of white wine, these are removed immediately from the must, which is left to ferment without them. As antioxidant capacity is strongly correlated with total polyphenol content *in vitro*, white wines present very weak antioxidant capacity [29]. Notwithstanding the fact that white wine contains hydroxycinnamic acids and tyrosol, which are also known to have antioxidant properties [30], their effect on the oxidative stress parameters in plasma and urine taken from humans has not been detected, as it has for red wines [31]. Additionally, red wines have higher procyanidin B content than white, which further supports their stronger anticancer activities [32]. The importance of polyphenols in the health-promoting properties of wine is discussed below. Together with polyphenols, ethanol is considered a key component with regard to health effects.

Ethanol

Consumption of alcohol entails both favorable and adverse effects, depending on scale. While moderate intake of alcoholic beverages is associated with lower overall mortality, notably due to reduced cardiovascular deaths, heavy drinking has deleterious effects, both physically and socially, and should be actively discouraged [33]. Apart from the obvious social consequences of alcoholism (e.g. violent deaths caused by homicides and suicides committed under the influence of ethanol intoxication), sustained consumption of large quantities of alcohol is associated with increased risk of cancer to the gastrointestinal tract [34,35], colon [36], breast [37], liver and rectum [38].

However, in the last two decades, many epidemiological studies have found that the curve of the relationship between alcohol consumption and total mortality, and especially cardiovascular mortality, is J- or U- shaped, respectively [39]. Risk of death is lower in moderate consumers than in non-consumers of alcohol, which strongly suggests that alcohol presents cardioprotective activity. In a meta-analysis of 51 studies, a reduction of 20% in cardiovascular risk was calculated, when alcohol consumption ranged between 0 and 20 grams/day [40]. This reduction has been widely described in patients with diabetes, high blood pressure, and who have suffered heart stroke [41]. The cardiological benefits of moderate alcohol consumption are attributed to an increase of HDL and fibrinolytic activity plus a decrease in platelet aggregation and insulin resistance. The probability of developing cardiac insufficiency is reduced by about 50% and the incidence of diabetes type 2 is also strongly reduced [20].

Some authors identify ethanol as responsible for the health-promoting properties of alcoholic drinks, as it is well absorbed and diffuses easily; ethanol has been reported to be one of the most bioactive compounds [42,43]. Possible differences in effect between different alcoholic beverages are still under discussion. Drinkers of wine, beer and spirits have been surveyed separately, but the findings suggest that there is a reduction in the risk of developing a myocardial infarction [44] or an ictus [45] of about 50% in habitual drinkers of any type of alcoholic drink. In contrast, other studies including a meta-analysis [46], epidemiology studies [47,48], clinical assays [49] and *in vitro* experiments [50] support the view that it is the polyphenol content of wine that is responsible for its health-promotion activity in respect of the cardiovascular system (www.predimed.org) [34].

Phenolic compounds

The findings that red wine presented more health-promotion activity than beer or spirits caused research attention to focus on phenolic compounds. Several studies have been undertaken to differentiate the effects of phenolic and other non-alcohol components of wine from those due to alcohol. In animal models it has been demonstrated that a red wine polyphenolic extract prevents the development of cardiovascular problems and cancer. Al-Awwady and collaborators compared blood pressure, heart weight and reactive oxygen species in rats whose feed had been supplemented with either the polyphenolic extract, ethanol or polyphenolic extract and ethanol together. They concluded that the polyphenolic extract was the most effective supplement for reducing cardiovascular risk [51]. Clifford and collaborators demonstrated that the consumption of de-alcoholized red wine as a part of a defined complete diet delayed tumor onset in transgenic mice [52].

The amount of phenolics in wines depends on the variety of grape and the vintage, and is highly influenced by viticultural and environmental factors such as light, temperature, altitude, soil type, water, nutritional status, pathogenesis, developmental processes and winemaking process

employed [53]. Reasonable ranges of content can be established for the different families of phenolics present in wine (Table 1).

Table 1: Levels of phenolic compounds in red and white wine.

Family	Phenolic compound	Young[a] Red Wine (mg/l)	Young[a] White Wine (mg/l)	Reference
Anthocyanins	Dp-3-glc Cy-3-glc Pt-3-glc Pn-3-glc Mv-3-glc Acetyl-derivatives *p*-coumaroyl-derivatives	90-400	_	[54,55]
Flavonols	Q-3-glc/glu/rut K-3-glc/glu/gal M-3-glc/glu I-3-glc	50-100	0-60	[55,56]
Flavan 3-ols	Catechin Epicatechin Gallocatechin Epigallocatechin Epicatechin-3-*o*-galate	4-120	15-25	[55,57]
Procyanidins	B1, B2, B4, C1	750-1000	20-25	[55,57]
Hydroxycinnamic acid derivatives	Caffeoyltartaric Coumaroyltartaric Feruloyltartaric	60-165	130-155	[55]
Tyrosol		7-83	12-36	[58-60]

[a]Young means not aged or fermented in oak. Abbreviations: Dp-3-glc, delphinidin 3-glucoside; Cy-3-glc, cyanidin 3-glucoside; Pt-3-glc, petunidin 3-glucoside; Pn-3-glc, peonidin 3-glucoside; Mv-3-glc, malvidin 3-glucoside; Q, quercetin; K, kaempferol; M, myricetin; I, isorhamnetin. glc, glucoside; glu, glucuronide; rut, rutinoside; gal, galactoside.

Regarding their cardioprotective effect, polyphenols in red wine are capable of acting on both short and long-term mechanisms such as NO-mediated vaso-relaxation, and can increase endothelial NO synthase expression. They also inhibit platelet aggregation *in vitro* [61]. *In vivo* experimental studies have demonstrated that wine phenolics can modulate resistance to human LDL oxidation [62,63], increase antioxidant capacity, enhance the production of vasodilators and inhibit the synthesis of vasoconstrictors [64]. Regarding cancer, they have been shown to block carcinogenesis and inhibit the growth of tumors in whole animals and in cell culture [65]. Consumption of polyphenols from wine could account for the lower risk of rectal [66], colon [67] and breast cancer [32] through both reduction of oxidative damage and variation in gene expression.

In order to attribute an effect to a compound, it needs to be absorbed in sufficient quantity to exert its activity. A second requirement is that it must reach the tissues where it is expected to act before it is metabolized to inactive forms. This means that the bioavailability of these compounds is a critical factor. Because the absorption of polyphenols is dependent on how they are released from the food matrix, their bioavailability and the means by which they are effective in vivo are really complex topics on which there is still too little knowledge. In some cases bioavailability differs between food sources depending on the type of glycosides they contain. For example, human studies with orange juice have reported that hesperidin (hesperetin-7-O-rutinoside as it is found naturally in citrus fruit) has limited bioavailability. The enzyme hesperidinase converts hesperetin-7-O-rutinoside in orange juice into hesperetin-7-glucoside. The reason behind the shift in absorption site is that hesperetin-7-O-rutinoside is only absorbed in the distal part of the human intestine, after metabolism in the colon by certain strains of bacteria. However, hesperetin-7-glucoside metabolism and subsequent absorption can occur in the small intestine, and absorption into the blood stream is not only quicker but more efficient [68]. Absorption increases with dose – it is dose-dependent: absorption is linear within certain ranges and then becomes saturated. It depends on individual characteristics of the matrix, such as the levels of enzymes or transporters. The most efficient enzymes to metabolize phenolics are in the small intestine, liver and kidney such as glucosidases, UDP-glucuronosyl transferases, catechol-O-methyl transferases, sulfotransferases, hydrolases, esterases, cytochrome P450s, glutathione-S transferases snd quinone reductases. As a consequence phenolics are not in the same chemical form in biological fluids than in foods, where mostly are

converted into glucoronides, sulfates or methylated forms. Many factors may play some role in the bioavailability of polyphenols but they remain largely unknown. More human studies need to be conducted in this field to establish general principles affecting absorption *in vivo* [69].

Anthocyanins: these compounds have been reported to be strong antioxidants; they inhibit the growth of cancerous cells, inhibit inflammation, act as vasoprotectors, and have anti-obesity effects. It seems that anthocyanins are absorbed very rapidly but rather inefficiently [70]. However, the bioavailability of anthocyanins could have been underestimated due either to inaccurate methodology or to the different chemical forms that anthocyanins can take depending on pH. This could possibly explain why any therapeutic effects that anthocyanins have are contingent on sufficient bioavailability, in terms of exposure at the level of cells and at the level of the organism as a whole through the diet [71].

Flavonols: this family of flavonoids comprises some of the most prominent dietary antioxidants. Among the flavonols, quercetin can be singled out, for it presents a variety of pharmacological activities that provide protection not only against osteoporosis, certain forms of cancer, pulmonary and cardiovascular diseases but also against aging [72]. Even more significantly, quercetin plays a pivotal role in reducing blood pressure by reduction of oxidative stress in a dose-dependent way [73,74]. In the 1970's, it was reported to be mutagenic but more recently, studies *in vivo* indicate that quercetin is not carcinogenic. In fact, in the U.S.A. and Europe, supplements of quercetin are commercially available, and beneficial effects of quercetin supplements have been reported in clinical trials [75]. With respect to its bioavailability, quercetin is absorbed in humans and can reach high concentrations that are sufficient to increase plasma antioxidant capacity [76]. Moreover, quercetin glucosides are among the polyphenols most readily absorbed in humans [70].

Flavan-3-ol monomers: flavan-3-ols with various types of structure act as antioxidants, free radical scavengers and anti-carcinogens; they have cardio-preventive, antimicrobial and antiviral properties; and may also play a significant role in maintaining neurological health [77].

Relationships have been established between the structure of flavan-3-ols and their strong antioxidant and free radical scavenging characteristics; their antioxidant function depends on the ring structure and number of catechol groups [78]. However, there is evidence to the contrary that must also be considered, as flavan-3-ols may behave as anti-nutrients, pro-carcinogens, pro-oxidants, hemorrhage inducers, mutagens or hepatotoxins depending on source, type, quantity and the existence of other dietary factors [79].

The bioavailability of flavan-3-ols monomers is generally good although it differs markedly among different compounds. Catechin, which is present in high concentration in the plasma of persons who eat a Mediterranean-type diet, is able to reduce the progression of atherosclerosis

in vivo [80]. The fact that red wine is one of the main sources of catechin in diet supports the finding that wine has an anti-atherosclerotic effect [81].

***Procyanidins**:* these compounds are considered to be among the most effective antioxidants present in wines. When rabbits were fed with procyanidins from grape seed extract, the compounds were active in preventing lipid oxidation while in the digestive tract [63]. The consumption of proanthocyanidin-rich foods, such as red wine, has been shown to increase the plasma antioxidant capacity, to have positive effects on vascular function, and to reduce platelet activity in humans [82].

In contrast with flavan-3-ol monomers, procyanidins are less permeable through cell walls and so are absorbed less readily. In fact, their polymerization impairs intestinal absorption [70,77]. However, the health effects of proanthocyanidins may not require efficient absorption through the gut. These compounds may have direct effects on the intestinal mucosa and protect it against oxidative stress or the actions of carcinogens. Biological effects may be attributable not to direct actions of proanthocyanidins themselves but to actions of some of their metabolites formed by the action of colonic flora that can be more readily absorbed. Therefore, the quantitative importance of the degradation of proanthocyanidins into microbial metabolites must be further evaluated in humans.

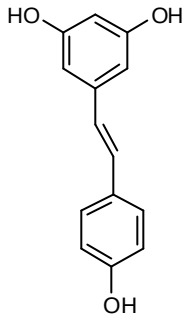
Hydroxycinnamic acid derivatives: these are the major phenols in white wine. Hydroxycinnamates have shown antioxidant and anti-inflammatory properties *in vivo* and *in vitro;* they contribute to DNA protection and help prevent Alzheimer's disease [83,84]. However, data are still too limited for an informed assessment of hydroxycinnamics [70].

Tyrosol: it has been described in both red and white wine. It exhibits high antioxidant capacity *in vitro* and *in vivo*. The main source of this compound from diet is olive oil; however, wine is another important source because the ingestion of red wine can promote endogenous generation of hydroxytyrosol. A single glass of red wine is equivalent to at least 25 ml of virgin olive oil in its capacity to increase hydroxytyrosol concentrations in the body [85,86].

It is notable that synergistic effects may occur among phenolic compounds. Synergy has been reported among the three phenols, resveratrol, caffeic acid and catechin [87,88]. Despite their relatively low plasma concentrations following moderate wine consumption, this synergy gives them useful biological activity, such as inhibition of oxidative stress. Interaction between polyphenols may influence their kinetics and metabolism. The lack of systematic information on the effects of other components on the bioavailability of polyphenols needs to be addressed, and more human studies should be conducted in this field to establish general principles affecting absorption *in vivo.*

Resveratrol

Resveratrol (3,5,4'-*trans*-trihydroxystilbene, Figure 2) is a member of the stilbene family of phenolic compounds. It was first isolated from the root of hellebore (*Veratrum grandiflorum* O. Loes) in 1940 [89]. In 1976 Langcake and Pryce detected it in *Vitis vinifera* grapevines [90]. Resveratrol is synthesized by leaf tissues in response to fungal infection or exposure to ultraviolet light but, until 1992, it was not detected in wine [91].

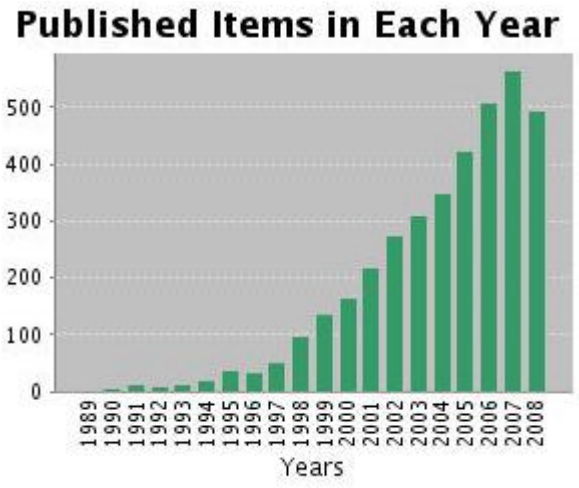


trans-resveratrol

Figure 2: Structure of resveratrol

In the last few years interest in resveratrol has increased due to its numerous health-promoting properties (ISI Web of Knowledge-Figure 3: 3736 bibliographic entries in the last 10 years).

Figure 3: Growth in number of publications per year on resveratrol.



Resveratrol has been described as a compound that can prevent and/or reduce a wide range of diseases such as cancer [92,93], cardiovascular diseases, and ischemic damage [94]; it can also increase the resistance to stress and prolong the lifespan of various organisms, from yeast [95] to vertebrates [96]. Details on the bioactivity of resveratrol are provided below.

Resveratrol, and stilbenes in general, are commonly found in many plants of several different families including *Pinaceae, Moraceae, Liliaceae, Myrtaceae, Fagaceae, Vitaceae, Gnetaceae, Cyperaceae, Dipterocarpaceae* and *Leguminoseae* [97]. However, their dietary sources are rather limited: peanut and its derivatives, pistachio, berries, dark chocolate, and grapes and their derivatives. Of all of these, a grape present the highest content but red wine is the most notable dietary source of resveratrol (Table 2).

Table 2: Dietary sources of resveratrol

Source	Content of *trans*-resveratrol	Content of other stilbenes	Reference
Blueberry and bilberry (ng/g)	20	_	[98]
Cranberry juice (nmol/g)	0.93	0.14	[99]
Peanut butter (µg/g fw)	0.3	_	[100]
Peanuts (µg/g fw)	5.1	_	[100]
Pistachios (ug/g)	1.65	_	[101]
Chocolate (ppm)	2	7	[102]
Table grapes (µg/100 g)	65	117	[103]
Juice (mg/l)	0.5	4.23	[104]
White wine (mg/l)	0.13	0.57	[57,105]
Rosé wine (mg/l)	0.41	2.15	[57,105]
Red wine (mg/l)	1.9	6.21	[57,106-108]

Recognition of the health-promoting properties of resveratrol has resulted in the commercial production of red wine extract and stilbene capsules (www.newu.com, www.myvitanet.com, http://megaresveratrol.com), which are currently very important products in the "nutraceutic" market.

Resveratrol concentration in wine

Resveratrol is found in the seed and skin of grapes (not in flesh) and hence in grape juice and wine. Obviously its concentration in red wine is higher than in white wine because, in red winemaking, the must, grapeskin and often seed are in contact during the whole fermentation process. For the same reason, the levels of resveratrol found in rosé wines fall between the levels in red and white wines (Table 2).

The amount of resveratrol in finished wine varies widely depending on many factors: grape variety, geographic region, agronomic factors, climatic factors, plant stress conditions and

oenological practices. Bavaresco reviewed how the different viticultural factors affect resveratrol synthesis, and established that the Cabernet sauvignon and Pinot noir varieties are the best for producing wines with high resveratrol concentrations [109]. To obtain such wines, cooler climates with moderate rainfall and humidity during the ripening, sandy soils and quality-oriented viticulture, such as low yield or non-irrigated cultivation, are recommended. Regarding optimum oenological practices, all the processes that aim to maximize the extraction from skin are suggested [110,111]. It is difficult to predict the amount of resveratrol that a finished wine will contain because there are so many factors affecting resveratrol biosynthesis. Concentrations ranging from undetectable to 14.3 mg/l have been described [112,113]. Goldberg et al. (1996) [114] assayed 700 commercial red wines from most of the world's wine production areas and found high variability in both the concentration and form of resveratrol present (*cis, trans* or glucoside). In wines *trans*-resveratrol is the form of the compound present in the largest concentration, followed by *trans*-piceid. The *trans* forms are predominant over the *cis* forms. Piceatannol and viniferins have been found only in certain wines, as commented in the following section.

As resveratrol is a phytoalexin, synthesized by grapes after exposure to biotic or abiotic stress, the presence of resveratrol in grapes depends on the degree of stress exposure. Pathogenic attack [115,116], preharvest chemical treatments such as BTH or quitosan [117,118], and UVC [119] are potent factors that increase resveratrol content in grapes and consequently in wines. Another strategy proposed as responsible for increasing resveratrol in wine is the use of transgenic yeast [120,121]. In some cases, the conversion rate was higher than 20-fold [122]. These treatments are now applied specifically with the aim of producing wines enriched in resveratrol and, what is even more important commercially, wines with a constant and predictable high level of resveratrol over the years or vintages, since this would represent a proven added value for the product in nutritional and health terms, which can be exploited in the market.

Other stilbenes

Apart from *trans*-resveratrol, the presence of other stilbenes has been described in grapevine. Poutaraud reported the main stilbenes found in grapevine leaf, which are *trans*-resveratrol and its derivatives: piceid, pterostilbene, e-viniferin, and δ–viniferin [123]; of course, many of these compounds, including resveratrol, piceid, astringin and stilbene oligomers (viniferins), are also found in finished wines [124-127].

Two different types of reaction lead to the formation of stilbene derivatives from *trans*-resveratrol (the initial compound in the stilbene pathway) in susceptible grapevines and resistant cultivars, respectively. In susceptible grapevines, resveratrol is synthesized in large amounts early after an infection, but it is rapidly glycosylated into a non-toxic compound: piceid. In

resistant varieties, resveratrol is also synthesized in large amounts, but in this chemical environment it is rapidly oxidised into toxic viniferins [128].

Piceid (5,4´-dihidroxystilbene-3-*O*-ß-glucoside, Figure 4): resveratrol is glycosylated as piceid, which is protected from enzymatic oxidation processes. Piceid is the major stilbene component in grape juices. In red grape juices the average concentration is 3.38 mg/L for *trans*-piceid, and 0.79 mg/L for *cis*-piceid, in contrast with the much lower concentrations of *trans*-resveratrol, 0.50 mg/L, and *cis*-resveratrol, 0.06 mg/L. In white grape juices the concentration is, on average, 0.18 mg/L for *trans*-piceid [104].

The *cis*-piceid form, like *cis*-resveratrol, is typically found at lower concentrations and both *cis* forms are often less biologically-active than *trans* forms [129]. *Trans*- and *cis*-piceid are significantly active molecules against LDL oxidation *in vitro* [130]. It is also relevant that, in 1982, piceid was found to be an effective regulator of serum lipid concentrations [131]. Like resveratrol, piceid effectively and dose-dependently inhibits beta polymerization, suggesting that piceid could be of therapeutic value in Alzheimer's disease [132]. However, the glycosides show a lower bioavailability in comparison with aglycons [133,134]

Piceatannol (3,3´,4,5´-tetrahydroxystilbene, Figure 4): this stilbene is present in grapes and wine. The average concentration found in wines is 0.95 mg/L wine [124]. In respect of its bioactivity, in humans it is also the result of the hydroxylation in the liver of *trans*-resveratrol, which could act as a prodrug. This latter may be also produced by intestinal hydrolysis of *trans*-astringin [129].

The hydroxylated analogues of resveratrol, especially those with an *ortho*-hydroxyl group, exhibit pronounced antioxidant activity [135,136]. This may explain the high bioactivity of piceatannol, which is a protein kinase inhibitor that modifies cellular targets and exerts immunosuppressive, antileukemic, and anti-tumorigenic activities in various cell lines and animal models. Piceatannol inhibits the proliferation of T24 and HT1376 human bladder cancer cells by blocking cell cycle progression in the G0/G1 phase and induces apoptosis in cell lines and animal models [137,138].

Astringin (5,4´,3´-trihidroxystilbene-3-*O*-ß-glucoside, Figure 4): astringin is rarely found at higher concentrations than *trans*-piceid in wines; the highest concentration of astringin reported, around 1.83 mg/L, was found in Italian red wines [124]. Astringin exhibits a very high free radical scavenging ability, providing good protection from ischemic injury [139]. It has been reported to have potential cancer-chemopreventive activity and to be significantly active against LDL oxidation *in vitro* [130,140]. Riviere has hypothesised that this stilbene could be of therapeutic value in Alzheimer's disease [132].

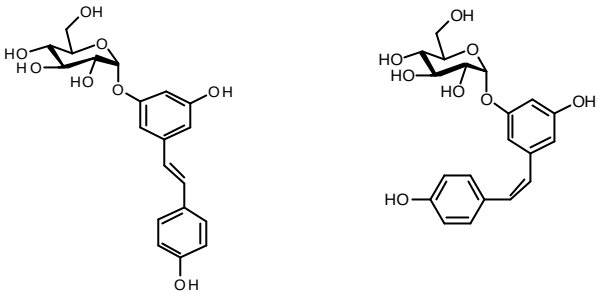
Pterostilbene (3,4-dimethoxy-4´-hydroxystilbene, Figure 4): this dimethylated resveratrol derivative is probably not synthesized by the same stilbene synthase as resveratrol, as described by Schoeppner and Kind [141]. It has been found in grapes, and its concentration can reach 0.68 mg/Kg [142]. To our knowledge it has not been described in wines yet, but is studied as a compound potentially present in wines, since it is found in grape berries [143]. Both pterostilbene and its natural 3´-hydroxy derivative possess interesting antileukemic properties, and from *in vitro* research, they may constitute effective and powerful drugs [144].

Stilbene oligomers: The viniferins are products of resveratrol oxidation by 4-hydroxystilbene peroxidases [145], particularly e-viniferin. In wine, viniferin levels range from non-detectable quantities to 20 mg/L [127]. Some of these resveratrol derivatives are known to have high bioactivity. Although less studied than *trans*-resveratrol, e-viniferin (dimeric stilbene, Figure 4) has been shown to have hepatoprotective [146] and antioxidant properties [147], to induce apoptosis of leukemia B-cells [148]; it inhibits human cytochrome P_{450} enzymes [149], noradrenaline and 5-hydroxytryptamine uptake, and monoamine oxidase activity [150]. The relative proportions of e-viniferin and resveratrol are very similar in all grapevines, confirming that both compounds are intimately connected biogenetically [151]. In addition to their well-characterized bioactive properties as "nutraceuticals" and pharmaceuticals, stilbenes such e-viniferin are also known to display significant anti-pathogenic properties, such as activity against downy mildew (*Plasmophara viticola*), grey mold (*Botrytis cinerea*), *Phoma medicaginis*, *Rhizopus stolonifer*, and a broad spectrum of microbes and fungi present during the storage of harvested fruit and vegetables [152].

Hopeaphenol is another oligomer, specifically a resveratrol tetramer (Figure 4), which has been found in North African wines at a concentration of 1.44mg/L [125]. Concerning its biosynthetic pathway in *Vitacaeous* plants, hopeaphenol may be formed from resveratrol via the dimer e-viniferin by oxidation catalyzed by peroxidases [153].

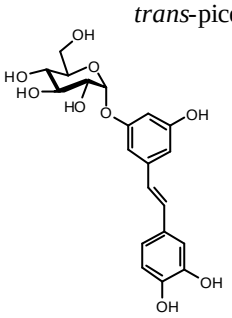
With regard to the consumption of stilbenes, a recent study in a Spanish adult population (40,885 subjects aged 35-64 years) has shown that 32% of the population do not consume any resveratrol or piceid in their diet; resveratrol represents only 21% of total stilbene intake (in contrast with piceid which contributes 54%), specifically 31µg/day [154]. In populations with other dietary patterns the contribution may be different but, at present, Spain is still considered a Mediterranean-type country in terms of diet.

Figure 4: Stilbene structures

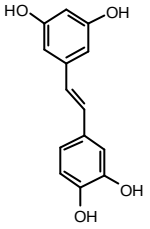


trans-piceid

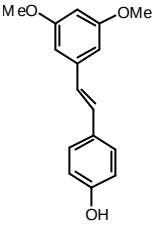
cis-piceid



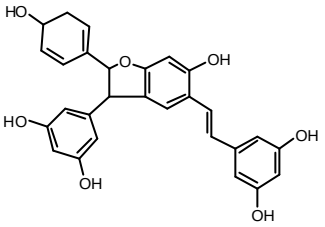
Astringin



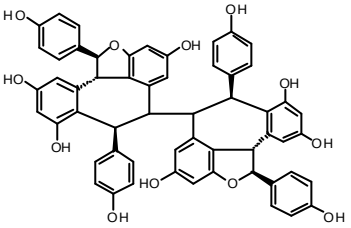
Piceatannol



Pterostilbene



e-viniferin



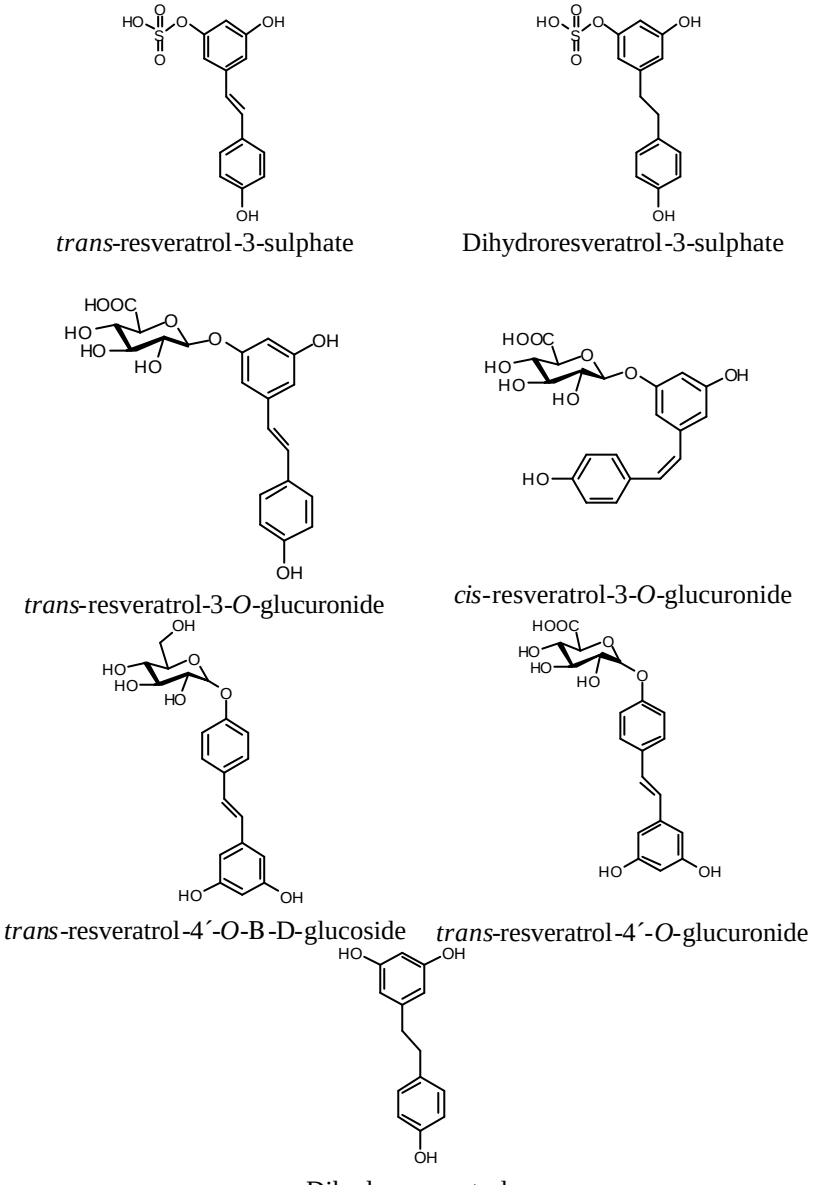
Hopeaphenol

Bioavailability and pharmacokinetics

Numerous studies in animals and humans have shown that the bioavailability of resveratrol is low. Once it is absorbed, at least 70% of resveratrol ingested is readily metabolized to form mainly glucuronide and sulphate derivatives. The colon micro-flora can produce the metabolite dihydroresveratrol. Resveratrol metabolites reach their maximum concentration in plasma approximately 30 minutes after intake; the half-life of total metabolites is approximately 9.2 hours [155]. Plasma concentration of resveratrol and its metabolites depends on the dose administered [156]. Five distinct metabolites are present in the urine after moderate consumption of red wine: resveratrol monosulphate, two isomeric forms of resveratrol monoglucuronide, dihydroresveratrol monosulphate and dihydroresveratrol [134] (Figure 5). In low density lipoprotein samples from volunteers who had ingested 250 ml of red wine

containing a known quantity of resveratrol, up to six metabolites have been measured: *trans*-resveratrol-3-*O*-glucuronide, *cis*-resveratrol-3-*O*-glucuronide, *cis*-resveratrol-3-*O*-glucoside, free *trans*-resveratrol and, tentatively, resveratrol-4'-*O*-glucuronide and *trans*-resveratrol-4-*O*-glucoside (Figure 5) [157]. Since the *in vivo* concentration of individual metabolites from ingested resveratrol can be much higher than that of resveratrol itself, further studies are needed of the activity of its metabolites.

Figure 5. Resveratrol metabolites



Bertelli et al (1996) [158] demonstrated that a fraction of resveratrol present in red wine (6.5 mg/L as *cis* and *trans* forms) was absorbed, in rats. After chronic consumption of moderate

amounts of red wine containing a known concentration of resveratrol, range from 100nM to 1μM. These values are consistent with those obtained in healthy volunteers after chronic administration of red wine and in a phase 1 clinical trial in healthy volunteers, in whom values ranged from 0.5 to 2μM. Resveratrol proved in vitro anticarcinogenic activity at doses ranging from 5 to 100μM, meanwhile the doses to the prevention of cardiovascular disease are between 100 nM and 1μM [159], which means that at modest dosages, resveratrol was pharmacologically active both in vitro and in vivo. These authors suggested that an average drinker of wine could, particularly in the long term, absorb a sufficient quantity of resveratrol to explain the beneficial effect of red wine on human health. More importantly, this could help to explain how a relatively low dose of resveratrol obtained from red wine or other dietary sources could be therapeutic in some cases [160]. A dose-dependent response has been observed, and at higher, but pharmacologically achievable doses, protective effects of resveratrol are more frequently observed, and the results are more dramatic [161].

Resveratrol binds to albumin and it has been suggested that albumin could be a natural polyphenol reservoir in the *in vivo* context, where it might play a pivotal role in the distribution and bioavailability of circulating resveratrol [162]. The accumulation of resveratrol in other organs such as the heart, liver and lung after chronic administration was described for the first time in 1996 [158] and has more recently been confirmed [163,164] and extended to the bile, stomach and kidneys [165].

It is also worth considering the potential interactions of resveratrol with other constituents of the diet. Resveratrol has been shown to synergize with both quercetin and ellagic acid in the induction of apoptosis in human leukemia cells [166], with ethanol in the inhibition of iNOS expression [167], with vitamin E in the prevention of lipid peroxidation [168], with catechin in the protection of PC12 cells from ß-amyloid toxicity [169], with nucleoside analogues in the inhibition of HIV1 replication in cultured T lymphocytes [170], and with tyrosol and B-sitoesterol in modulation of LDL oxidative stress and PGE_2 synthesis [171]. The absorptive efficiency of *trans*-resveratrol, (+)-catechin and quercetin was investigated after oral application to healthy human subjects in three media (white wine, grape juice and vegetable homogenate). The absorption of these three polyphenols was equivalent in the different matrices but, at peak concentrations of 10 to 40 nmol/l, is inadequate to permit circulating concentrations of 5 to 100 μmol/L consistent with *in vitro* biological activity [172]. Moreover, one finding that has often been overlooked is that quercetin, which is also present in red wine, is a picomolar inhibitor of resveratrol sulphation in both the liver and duodenum, thus increasing the bioavailability of resveratrol [165].

These health benefits are not coupled with adverse side effects. Most of the studies carried out on resveratrol toxicity describe the absence of adverse effects unless extremely high doses are

administered. Juan et al. (2002) found no adverse effects in rats after consumption for 28 days of the quantity of resveratrol equivalent to 1,000-times the content of this compound in red wine [173].

However there are still three issues that need to be addressed. The first is how much resveratrol can be taken and recovered from the organism; the second is how active the metabolites derived from resveratrol are. The third issue is the possible influence on resveratrol bioavailability in humans produced by the type of meal consumed in association with the ingestion of red wine. Researchers are starting to explore resveratrol treatment in combination with other agents in some preclinical studies.

Health-promoting properties

1. Antioxidant capacity: normal cellular metabolism generates reactive oxygen intermediates (ROI) such as superoxide, hydrogen peroxide and hydroxyl radicals, which are usually detoxified by intracellular enzymes such as glutathione, superoxide dismutase and catalase. However, an abnormal accumulation of ROIs can happen, which is commonly referred to as "oxidative stress". Exposure of macromolecules (lipids, protein, DNA) to ROIs results in their oxidative modifications with deleterious potential [174].

Resveratrol has an intrinsic antioxidant capacity that could be related to its chemopreventive effects. *In vitro*, the induction of detoxification enzymes has been shown after low doses of resveratrol [175]. *In vivo*, resveratrol has been shown to increase plasma antioxidant capacity and to decrease lipid peroxidation [176,177], which is strongly associated with the risk of coronary heart disease and myocardial infarction [178]. Studies in rat, pig and humans seem to indicate that resveratrol can suppress pathological increases in the peroxidation of lipids and other macromolecules *in vivo*, but whether the mechanism is direct, indirect or both, is not yet clear [179].

2. Cardioprotective capacity: resveratrol protects the cardiovascular system in a multidimensional way [180]. The most important point is that resveratrol at very low concentration inhibits apoptotic cell death, thereby providing protection from various diseases including myocardial ischemic reperfusion injury, atherosclerosis and ventricular arrhythmias. In higher doses it facilitates apoptotic cell death, and behaves as a chemo-preventive alternative [181].

2.1. Modulation of lipid and lipoprotein metabolism: resveratrol exerts antioxidant effects; hence it may suppress pathological increases of peroxidation in macromolecules such as lipids. In 1982 it was shown that resveratrol inhibits the deposition of cholesterol and triglycerides in the liver of rats, and decreases the rate of hepatic triglyceride synthesis [131]. Later, it was demonstrated that *trans*-resveratrol inhibits LDL peroxidation *in vitro* more than an extract of

red wine [182]. Recently, resveratrol has been detected in LDL particles from humans after consumption of red wine [157].

2.2. Anti-platelet aggregation: platelet aggregation is one of the major contributors to the process of atherosclerosis. Platelets stick to the endothelial surface of blood vessels. They can activate the process of thrombus formation and their aggregation could set into motion the process of vascular occlusion. Resveratrol prevents platelet aggregation *in vitro* [183] and *in vivo* [99]. Further research has shown that resveratrol reduces the formation of atherosclerotic plaques and restores flow-mediated dilation in rabbits fed a high-cholesterol diet [184].

2.3. Vaso-relaxant activity: resveratrol also promotes vasodilatation through multiple mechanisms, mainly the stimulation of Ca^{2+}-activated K^{+} channels and the enhancement of nitric oxide signaling in the endothelium [185,186].

2.4. Protection against ischemic damage: resveratrol may protect against ischemic damage during myocardial infarction. In rats, the perfusion of the heart with resveratrol before ischemic insult results in improved recovery of developed pressure and aortic flow, and reduction of infarct size [187]. In guinea pigs, the addition of resveratrol to drinking water for 16 days (~14 mg per kg body weight) significantly increased capacity to eliminate oxidants in cardiac muscle [188]. The main mechanism seems to be an increase in nitric oxide concentrations by both increasing the expression of nitric oxide synthase and decreasing the inactivation of nitric oxide by free radicals.

3. Anti-cancer activity: in 1997 Jang and colleagues reported the ability of resveratrol to inhibit carcinogenesis at multiple stages (initiation, promotion and progression) [93]. Their finding that topical application of resveratrol reduced the number of skin tumours per mouse by up to 98% triggered research on resveratrol all around the world. Resveratrol could slow tumour development through multiple complementary mechanisms. It inhibits the enzymatic activity of both forms of cyclooxygenase, which implies a reduction of the risk of developing many cancers. Another mechanism by which resveratrol could combat tumour formation is induction of cell cycle arrest and apoptosis. The anti-proliferative and pro-apoptotic effects of resveratrol in tumour cell lines have been extensively documented *in vitro* [189] and are supported by down regulation of cell cycle proteins [190] and increases in apoptosis [191] in tumour models *in vivo*. However, in some *in vivo* experiments resveratrol failed to affect cancer, which suggests that other factors such as dosage, delivery method, tumour origin and other components of the diet could all contribute to the efficacy of resveratrol treatment. Overall, *in vivo* studies clearly show great promise for this molecule in the treatment of cancers, although studies of the association between red wine consumption and cancer in humans are still in their initial stages. Clinical trials in phase I are being conducted in healthy people in order first to determine the

concentration of resveratrol and its metabolites in the plasma, urine, and feces of healthy participants; second, to correlate dose with systemic concentration of this drug and its metabolites in these participants; and thirdly, to determine the safety of this drug in these participants (http://www.cancer.gov/clinicaltrials/CCUM-2004-0535).

***3.1 Lung Cancer*:** currently, lung cancer is the most prevalent type of cancer in the world. In men, the highest incidence rates in the world are observed in Eastern Europe and in North America (European network of cancer registries: http://www.encr.com.fr/). Countries of Southern Europe still have low and stable mortality rates from lung cancer (e.g. Greece, Spain) or a report a relatively low rate of increase (e.g. Italy, Portugal). The most important risk factor of lung cancer is tobacco smoking; however, data suggest that a relationship with life style, which probably includes diet, could be possible. In fact, lower risk of lung cancer has been described among consumers of wine, particularly red wine, compared with consumers of other beverages [192]. Furthermore, high doses (2.5 and 10 mg/kg) of resveratrol were found to reduce significantly the tumour volume and weight, as well as metastases, in mice bearing lung carcinomas [193]; lower doses (500 ppm) had no effect on lung tumour multiplicity in A/J mice [194]. It is still not clear if resveratrol taken in diet reaches the lung tissue in sufficient concentration to be biologically active.

***3.2 Colon cancer*:** colorectal cancer (CRC) is common in the Western world and usually ranks high in incidence and mortality among malignancies in those countries. CRC differs dramatically from one country to another, and diet could be the major explanatory factor for these phenomena.

The efficacy of resveratrol in CRC has been extensively studied. In one study, treatment of the CaCo-2 cells with 25 μM of resveratrol caused a 70% growth inhibition. In another, resveratrol caused a significant decrease of ornithine decarboxylase (ODC) activity, a key enzyme of polyamine biosynthesis, which is enhanced in cancer growth. ODC inhibition resulted in the reduction of the intracellular putrescine content, indicating that polyamines might represent one of several targets involved in the anti-proliferative effects of resveratrol [195,196]. Oral administrations of high resveratrol doses in drinking water and diet have been demonstrated to reduce tumour incidence in mice [192]. The promising results in studies of the effect of resveratrol on colon cancer have led to clinical trial in which patients with colon cancer receive treatment with resveratrol and correlative laboratory studies will examine its effects directly on colon cancer and normal colonic mucosa. These studies will provide data on the mechanisms of resveratrol action and provide a foundation for future prevention trials, correlative studies and therapeutic clinical research with resveratrol. A prior report and compelling preliminary data suggest that resveratrol modulates Wnt signalling, a signalling pathway which is activated in over 85% of colon cancers

(http://www.cancer.gov/search/ViewClinicalTrials.aspx?cdrid=457861&version=patient&protocolsearchid=5057507; http://www.clinicaltrials.gov/ct/show/NCT00256334).

***3.3 Breast cancer*:** breast cancer is the most prevalent type of cancer in females in Europe. It is estimated that in the year 2000 there were 350,000 new cases of breast cancer in Europe, while the number of deaths p.a. from breast cancer was estimated at 130,000. The regions of lowest incidence are Southern and Eastern Europe, which could be associated with lifestyle factors (http://info.cancerresearchuk.org/cancerstats/types/breast/incidence). There seems to be a relationship with frequent alcohol consumption. Alcohol consumption increases the risk of breast cancer (CGHFBC, 2002). For each additional 10 grams of alcohol per day, the risk increases by approximately 10% [197]. However, other authors affirm that the association of this type of cancer with fat consumption, as well as with consumption of fruits and vegetables, is rather weak [198,199].

Resveratrol can induce growth inhibition and apoptosis in MDA-MB-231, a highly invasive and metastatic breast cancer cell line, by activating *de novo* the ceramide synthesis pathway [200]. In mice resveratrol supplementation delays spontaneous mammary tumour development and reduced metastasis [201]. In a population study conducted in Italy an inverse relationship was observed between resveratrol from grape consumption and breast cancer, but not for resveratrol ingested in wine [13]. Other authors have confirmed that the relationship between resveratrol and breast cancer is inconclusive based on analyses of data obtained from a case control study conducted in Switzerland [202].

3.4 Gastric cancer: one of the principal etiological determinants for gastric cancer is the chronic infection with *Helicobacter pylori*, which is inhibited by resveratrol [203]. The apoptotic signal engaged by resveratrol may be dependent on cell type, and may be related to differentiation status in several gastric adenocarcinoma cell lines [204].

3.5 Prostate cancer: this type of cancer is a major cause of death among men in European countries. There are no obvious or proven strategies for preventing this disease (http://www.WHO/europe.who.int). However, research studies published in the International Journal of Cancer show that drinking a glass of red wine a day may cut a man's risk of prostate cancer by half and that the protective effect appears to be strongest against the most aggressive forms of the disease. It was also seen that men who consumed four or more 4-ounce glasses of red wine per week have a 60 percent lower incidence of the more aggressive types of prostate cancer (http://www.cancer.gov/cancertopics/factsheet/red-wine-and-cancer-prevention).

Resveratrol induces apoptosis in several prostate cancer cell lines [205-207]. A recent study on LNCaP prostate cancer cell culture and xenograft models concludes that resveratrol may act through modulation of steroid hormone-dependent pathways to inhibit prostate cancer cell

growth in both culture and xenografts, but exposure *in vivo* may be of concern [208]. In addition, well-conducted animal experiments support the belief that resveratrol might have a clinical activity on human prostate cancer. However, it is impossible to make definite statements or conclusions on the clinical efficacy in cancer patients because of the great variability and differences of the study designs, small patient numbers, short treatment duration and lack of a standardised drug formulation. Although some results from these clinical studies seem encouraging, reliable or long-term data on tumour recurrence, disease progression and survival are unknown. At present, there is no convincing clinical proof or evidence that resveratrol might be used in an attempt to cure cancer of the prostate [209].

3.6 Other cancers

3.6.a Skin cancer: melanoma is less common than the familiar basal and squamous cell tumours of the skin, but much more fatal. In recent years, the melanoma rates in Mediterranean Europe have been increasing steeply, perhaps due to the amount of sun exposure [210] (http://www.encr.com.fr/).

Resveratrol can inhibit growth and induce apoptosis in melanoma cell lines [211]. Topical resveratrol has been tested for its efficacy against the development of several cutaneous disorders, including skin cancer and has been shown to inhibit tumour incidence and to delay the onset of tumorogenesis either pre- or post-UVB [212].

In contrast, *in vivo* studies appear to show that resveratrol is not an effective chemotherapeutic agent in inhibiting melanoma growth in animals. For example, oral administration does not inhibit the growth of melanoma cells inoculated in mice [92]. Again further preclinical studies are needed to confirm this finding.

3.6.b Oesophageal cancer: oesophagal cancer is common worldwide. The effects of resveratrol *in vitro* and *in vivo* are consistent in the inhibition of tumorogenesis [213,214].

3.6.c Thyroid cancer**:** resveratrol induces apoptosis in both papillary and follicular thyroid cancer cell lines [215].

3.6.d Pancreatic cancer**:** *in vitro* studies have shown that resveratrol enhances apoptosis in pancreatic cancer cells [216]. However, resveratrol given in diet (10 ppm) fails to show significant effects *in vivo* [217].

3.6.e Ovarian cancer**:** resveratrol inhibits ovarian cancer cell progression and angiogenesis by inhibiting HIF-1alpha and VEGF expression, and thus provides a novel potential mechanism for the anti-cancer action of resveratrol [218]. A recent study has shown that resveratrol could be a potentially useful agent for ovarian cancer therapy, and induces cell death through mitochondrial damage and cell cycle arrest [219].

3.6.f Liver cancer: resveratrol significantly decreases hepatoma cells by inducing apoptosis *in vitro* [220] and *in vivo* [221]. Resveratrol has been suggested as a biochemical modulator to enhance the therapeutic effects of 5-FU, and may be potentially effective in chemotherapy on murine liver cancer [222].

3.6.g Leukemia: anti-leukemic activity of resveratrol on cell lines has been widely described; it acts by inhibiting proliferation and inducing apoptosis [223]. For example, in HL-60 human promyelocytic leukemia cells, it is an inhibitor of ribonucleotide reductase, a key enzyme of DNA synthesis [224]. However, *in vivo* only weak potential anti-leukemic resveratrol activity was suggested when leukemic mice were supplied with high doses of resveratrol in diet [225].

4 Other properties

4.1 Estrogenic activity: due to the similarity of resveratrol to diethylstilbestrol, resveratrol can bind to both alpha and beta-estrogen receptors, thus acting as a phytoestrogen [226,227]. Estrogen replacement therapy has been shown to reduce the risk of cardiovascular disease and osteoporosis in postmenopausal women and may help prevent postmenopausal bone loss [228]. This activity is associated with reduction of breast cancer risk [229].

However, resveratrol estrogenic activity remains controversial, since some superagonist activities have been also described, and its chemopreventive effects are probably very complex [230].

4.2 Anti-inflammatory activity: inflammation is central to the pathology of arthritis, Crohn's disease and psoriasis, and may have a role in the development of both cardiovascular disease and cancer.

Resveratrol reduces inflammation via inhibition of prostaglandin production, cyclooxygenase-2 (COX-2) activity, and iNOS by inhibiting NF-?B activation [228,231]. In view of its anti-inflammatory and antioxidant properties and its capacity to modulate important inflammatory and anti-inflammatory signaling pathways and glucocorticoid efficacy, resveratrol holds great promise in potential therapeutic strategies for controlling lung inflammation and related diseases. In fact, resveratrol is being considered for future pharmacological agents and may be used as an anti-inflammatory reinforcement to combat oxidative challenges [232].

4.3 Neuroprotective activity: neural dysfunction and metabolic imbalances underlie many progressive neurodegenerative conditions such as Alzheimer's, Huntington's and Parkinson's diseases [233]. Resveratrol is capable of penetrating the blood–brain barrier and exerts strong neuroprotective effects, even at low doses. Resveratrol has been shown to combat the neuronal dysfunction caused in Huntington's and Alzheimer's diseases, through the SIRT1 pathway [234]. The same authors showed that only 500 nM per day, an amount which is provided in one glass of red wine, is needed to protect neurones. The prevention of Parkinson's disease is based

on the scavenging mechanism performed by resveratrol [235]. The efficacy of resveratrol against various different mechanisms has recently been confirmed, and resveratrol has been shown to be potentially useful in protecting against brain damage following cerebral ischaemia [236].

4.4 Anti-aging activity: resveratrol extends the lifespan of *S. cerevisiae, Caenorhabditis elegans* and *Drosophila melanogaster* and species of short-lived fish through activation of the sirtuin pathways [95,96,237]. More recently, Baur et al. have shown that resveratrol shifts the physiology of middle-aged mice on high-calorie diet towards that of mice on standard diet and significantly increases their survival. Specifically, studies in mice have shown that obese animals whose diet was supplemented with resveratrol not only lived longer, but were more active and produced fewer cases of the negative effects of a high-calorie diet such as increased insulin sensitivity; this diet also reduced insulin-like growth factor-1 levels, increased the number of mitochondria, and improved motor function [179].

4.5 Anti-diabetes activity: data in the literature indicate that resveratrol may play a role in the prevention of diabetes and diabetic complications [238]. An *in vivo* experiment revealed that resveratrol, administered to normal rats at the dose of 50 mg/kg body weight, diminished blood insulin concentrations at 30 min, without concomitant changes in glycemia. These findings suggest the direct insulin-suppressive action of resveratrol in the rat [239].

Conclusion and future research directions

The Mediterranean diet has become recognised as a model diet for preventing several serious diseases, and cardiac disease in particular. Wine seems to be a key component of this diet, and a moderate, regular consumption of wine (two glasses of red wine per day) is recommended. Polyphenols have been identified as the main components of wine responsible for its health-promoting properties. Within this group, the stilbene resveratrol is one of the most bioactive. Wine is the main source of resveratrol in diet, and although its concentration varies widely among different types of wine, red wine generally contains quite a high amount. Resveratrol has antioxidant, cardioprotective, anti-carcinogenic, estrogenic, anti-inflammatory, neuroprotective, anti-diabetes and anti-aging properties, and so resveratrol may be perceived as a future pharmacological agent. Its bioavailability is still under research but it has been suggested that an average drinker of wine could, particularly in the long term, absorb a sufficient quantity of resveratrol to explain the beneficial effect of red wine on human health. However, at this point in time, it is impossible to make a definitive statement or conclusion since human studies are still in initial stages and also because there is too much variability in the study designs. Which can be said is that, this molecule has great promise in the field of medicine.

Giving this encouraging perspective, there are several points, which should be followed up in future research. The first is to determine if and how red wine can be produced with a known and

constant concentration of resveratrol, to ensure that adequate doses are ingested. The second is to study in greater depth its bioavailability and specifically the bioactivity of resveratrol metabolites after absorption. Synergies with other compounds and the effects of different matrices and diets should also be taken into account.

From what is now known and accepted scientifically about the health benefits of the Mediterranean diet, it would seem advantageous for government authorities, the food and drinks industry and the food supply chain to promote the adoption and maintenance of this diet in the population as part of fundamental health care. The risk is already apparent, even among Mediterranean populations that consumption is departing from this beneficial diet, away from fruit, vegetables and red wine and towards more fats and meat. People need to be reminded that "your diet should be your first medicine".

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