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THE PROTECTIVE EFFECT OF ANTIOXIDANTS AND RESVERATROL IN WINE: THE NUTRACEUTICAL PROPERTIES OF WINE IN IRPINIA

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Abstract

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, Also for the "Aglianico", "Fiano" and "Greco" cultivars of Campania, whose phenolic profile and the quality of resveratrol present were analyzed, also highlighting the power of antioxidant and antimicrobial agents. Many valuable 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. Furthermore it has been seen that the Mediterranean diet has become the reference diet for the prevention of cardiovascular disease, for the specific advice to consume wine and antioxidants regularly. Red wines generally contain higher levels of polyphenolics than white ones. These compounds not only contribute to the colour, flavour, astringency, and bitterness of a wine but also serve to fight free radicals in the body that cause disease and ageing. Epidemiological studies pointed out that the consumption of red wine has been shown to increase the body's antioxidant capacity and is associated with a lower risk of mortality from cardiovascular diseases. There are two major classes of wine phenolics: nonflavonoids and flavonoids. The relative amount and distribution of these compounds depend on a variety of factors such as grape variety, vineyard location, climate, soil type, cultivation practices, harvesting time, production process, and wine ageing

Keywords: *Red wine, Irpinia, resveratrol , nutraceutical values, diet, antioxidant, Polyphenols*

Introduction

The contribution of wine to the Mediterranean diet are the conclusion of epidemiological studies, clinical intervention studies provide more specific scientific evidence they have demonstrated
as much as a 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 (1 -2).

Furthermore recent studies have shown that a strict adherence to the Mediterranean diet, with the presence of a correct use of wine, regular physical activity, leads to improvement and reduction in overall mortality (9%), mortality from cardiovascular disease (9%), incidence of cancer (6%), and incidence of Parkinson's and Alzheimer's diseases (13%) (3)
Furthermore also 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 (4-5)

The Mediterranean diet, which finds in Irpinia, wide application thanks to a fertile land and a favorable climate is precisely characterized by intake of vegetables, legumes, fruits, nuts e unrefined cereals, high but low olive oil intake saturated lipid intake, moderately high intake of fish, moderate intake of dairy products, especially in the form of cheese or yogurt, low in meat intake and poultry and a regular but moderate intake of ethanol, mainly in the form of wine and generally with meals [Figure 1] (6-7)

From the recent studies that have been carried out, the correlation between health and wine has become an innovative topic. Irpinia with the goodness of grapes and must derived from the Aglianico and Fiano cultivars typical of Southern Italy, it accentuates even more its fundamental role for health. It can be said that supplementing the regular diet with red wine increases the total antioxidant capacity in plasma, HDL lipoprotein, fibrinolytic and antithrombin activity, and vitamin C; it also reduces oxidative damage e platelet aggregation. Above all, the risk decreases of cardiovascular diseases (8- 9) .

Methods

Recent studies have shown that among wines, red wine is considered to have the highest effect
protective, due to its greater content of antioxidant substances released from grape skin
and seeds (polyphenols). Unlike white wine, during preparation these are immediately removed 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 (10-11)

In fact, unlike red wines, white wine contains hydroxycinnamic acids and tyrosol, which are also known to have antioxidants properties, but their effect on oxidative stress, plasma parameters and urinalysis taken from humans was not detected, In addition, red wines have a higher amount of procyanidin B compared to white, which further supports them antitumor activities in a more evident way. In fact, as already anticipated Together with ethanol, among the polyphenols, resveratrol is considered a key component as regards health effects. (12- 13)

In Campania (South Italy) 25,562 ha are dedicated to this cultivation. "Aglianico" (red wine), "Fiano di Avellino" and "Greco di Tufo" (white wines hereafter referred to as "Fiano" and "Greco"), typical cultivars of the territory, produce excellent quality wines. As shown by a recent study of phenolic compounds, obtained from grape canes belonging to the Campania cultivars "Aglianico", "Fiano" and "Greco", the total contents of phenols,

flavonoids, orthophenols and tannins were determined and the antioxidant activity. In addition, a comprehensive qualitative-quantitative study of the phenolic molecules present in the selected extracts was conducted by high-performance liquid chromatography coupled with multi-stage ion trap mass spectrometry (HPLC / ITMSn) and UV detection (HPLC-UV). Finally, the antimicrobial activity of the extracts against bacteria, viruses and fungi that cause human infections was also investigated. (14)

It has been shown that the classes of phenolic compounds detected were in agreement with those already reported in previous studies on the phenolic profile of grape shoots and included, in abundant quantities, phenolic acids, flavanols, flavonols, flavanonols, flavanones and stilbenoids. The phenolic composition was qualitatively and quantitatively influenced by the extraction pH: glycosylated forms were predominant at pH 1.00, procyanidin oligomers were very abundant in extracts at pH 7.00 and stilbenoids were more represented at pH 13.00 (15-17)

The grape cane extract from "Aglianico" was the richest in polyphenolic species at any pH. In the extracts of "Fiano", on the other hand, the lowest number of polyphenolic compounds was identified: 27, 37 and 18 respectively at pH 1.00, 7.00 and 13.00. Tartaric acid, derivatives of hydroxybenzoic acid glucoside of protocatechuic acid, exoside of syringic acid, derivative of hydroxycinnamic acid caftaric acid, flavanol cateches, stilbenoids resveratrol-C-glucoside, resveratrol and -viniferin were identified in all extracts, along with exoside af and viniferol. To the best of our knowledge, exoside afzelechin and viniferol E were first detected in grape canes. (18-19)

In light of recent evaluations, the research has focused on the nutraceutical qualities of red wine, compared to other categories of alcohol, in particular by focusing on phenolic compounds. The quantity of phenolic compounds heavy in wines depends on the grape variety and vintage, and it is highly influenced by viticultural and environmental factors such as light, temperature, altitude, soil quality, water, nutritional status, pathogenesis, development processes and winemaking process used (20-21)

This certainly affects the nutraceutical quality and the beneficial effects of this. In fact, as regards their cardioprotective effect, polyphenols in red wine they are able to act on several factors as a recent study highlights. In animal models it has been shown that the polyphenolic extract of the wine prevents development of cardiovascular problems and cancer. Al-awwadi and collaborators compared blood pressure, function cardiac, weight and reactive oxygen species in rats whose the feed had been integrated with the polyphenolic extract, ethanol or polyphenolic extract and ethanol together. They concluded that the polyphenolic extract was the most effective supplement to reduce cardiovascular risk (22-23)
Also in vivo experimental studies have shown that phenols in wine can promote a resistance to oxidation of LDL in the blood, an increase in antioxidant capacity and thus improve the function of vasodilators, inhibiting the synthesis of vasoconstrictors. (24-25) As for cancer, it is demonstrated their ability to block carcinogenesis and inhibit growth of tumors in whole animals and in cell cultures. Consumption of polyphenols from wine could take into account the lower risk of developing colorectal cancers, and breast cancer both through the reduction of oxidative damage and the variation of gene expression (26-27)

Among the polyphenolic compounds we also find anthocyans. [figure2] Anthocyanins, also known as anthocyans, are water-soluble flavonoid pigments which, depending on the pH, and in some cases complexing agents, can impart different colors such as red, purple and blue. They are widely found throughout the plant kingdom and can occur in almost any tissue of higher plants, including roots, stems, leaves, flowers, and fruit. Consequently they are considered a group of the major natural pigments in foods of plant origin, including red wines. Color is one of the most important attributes of red wines, and the main sources of red color in wines come from anthocyanins or their further derivatives which are extracted or formed during the winemaking process (28-29) These compounds

have the characteristic of be strong antioxidants; inhibit the growth of cancer cell, inhibit inflammation, act like vasoprotective, and have anti-obesity effects. The research shows that the anthocyanins are absorbed very quickly but with a rather inefficient bioavailability, this depends on the different chemical forms that anthocyanins have they can develop in the fermentation stages. (30 - 31)

Infact during fermentation and, especially in the first one or two years of aging, monomeric anthocyanins in wines undergo a wide variety of reactions and associations and several new pigments derived from anthocyanins are formed, extremely crucial for color stability. Typical concentrations of free anthocyanins in young and full-bodied red wines are around 500 mg / L, but in some cases they can be higher than 2,000 mg / L. Normally anthocyanins are found mainly in grape skins, with few exceptions, in the so-called "teinturier" grapes, which have anthocyanins both in the skin and in the pulp.(32-33)

Furthermore unlike other flavonoid compounds in red wines, anthocyanins do not intrinsically contribute astringency or bitterness to the mouth feel. Though anthocyanins are odorless and nearly flavorless, they can interact with some aroma substances and influence wine flavor (34)

Also it's also It is not possible to forget to mention the 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. Even more significantly, quercetin plays a pivotal role in reducing blood pressure by reduction of oxidative stress in a dose-dependent way. With respect to its bioavailability, quercetin is absorbed in humans and can reach high concentrations that are sufficient to increase plasma antioxidant capacity . Moreover, quercetin glucosides are among the polyphenols most readily absorbed in humans . (35 - 37)

Quercetin has multiple influences on immune system function, aside from its most commonly known mast cell stabilizing activity. Transcription factors involved in immune function are controlled by cytokines and quercetin appears to play a role. Cytokines are a major part of the immune system and function as mediators within the immune system and hematopoiesis, which is the process of creating new blood cells. (38) In vitro evidence demonstrates that quercetin downregulates cytokine gene expression and production in peripheral blood mononuclear cells, particularly NFkappaB expression and production. Quercetin can block angiogenesis in vitro and other signaling pathways including insulin-like growth factor, components of MAPK, and quercetin's free radical scavenging activity is attributed to several actions. Quercetin's ability to scavenge and bind transition metal ions affects lipid peroxidation. Free radical scavenging and reducing inducible nitric oxide synthase activity provides a supportive effect in circulation. Quercetin additionally supports vitamin C absorption. A double-blind, cross-over study evaluating the effect of 150 mg of quercetin daily demonstrated support of cardiovascular health. In macrophages, quercetin is metabolized to the active aglycone form by the enzyme ß-glucuronidase which leads to reduced expression of lipopolysaccharide (LPS)-induced cyclooxygenase (COX) (39-41)

Quercetin can be consumed through foods naturally containing quercetin or through supplementation. Quercetin primarily enters the diet as glycoside conjugates. One of the most abundant glycosidic forms present in plants is quercetin-3-glucoside (isoquercitrin), which is hydrolyzed in the small intestine and rapidly absorbed. Foods rich in isoquercitrin include leafy vegetables, broccoli, red onions, peppers, apples, grapes, black tea, green tea, red wine, and some fruit juices (table1.) . The amount of quercetin received from food is primarily dependent on an individual's dietary habits. Research has found a typical Western Diet provides approximately 0 to 30 mg of quercetin per day, but a diet rich in fruits and vegetables was estimated to provide more. It is also important to note, that the food content of quercetin reflects variations in soil quality, time of harvest, and storage conditions. (42-44)

This table summarizes the content present in the main food categories

Food	Amount
Grapes black (100g)	2,17 mg
Red Raspberry, raw (100g)	3.58 mg
Broccoli (100g)	1.80mg
Red onion (100mg)	1.80mg
Black tea (100g)	1.13 mg
Red wine	1.14 mg

Table1. Quercetin Content in Food

Furthermore, among the flavonils there are catechins and epicatechins with an important function in the wine world . Catechin and epicatechin are known as flavonols, flavon-3-ols, or procyanidins. They are present as monomers in grapes and wine and are the primary components of tannin. Both compounds are found in high concentrations in seeds and stems and may be found in the skins of immature grapes (45-46)

Recent studies have shown different concentrations of these flavonols in different wine categories, for example : Pinot noir has much higher concentrations of both compounds than Cabernet, Merlot, or Zinfandel. As grapes mature, the phenolics on the seed surface combine with other compounds to form the seed coat. As a result, seed phenolics become increasingly difficult to extract as seeds mature. Catechin and epicatechin are generally lower in wines made from grapes with riper, more developed seeds. Catechin is a useful indicator of seed extraction in wine. Fermentation practices that increase seed extraction such as extended macerations, higher temperatures, or aggressive punch downs usually result in an increase in catechin. Catechin and epicatechin concentrations tend to be low in Syrah/Shiraz. Catechin in Cabernet Sauvignon and Merlot can range from less than 10 to more than 100 mg/L depending on seed ripeness and winery production practices. Pinot Noir wines range from 30 to more than 400 mg/L reflecting the wide range of seed maturity in Pinot Noir at harvest. (47-49)

Hence these flavanols bring many health benefits and their richness lies in foods such as green tea, wine and cocoa products, in a variety of fruits, vegetables and plant-based beverages . High concentrations of catechin can be found in fresh tea leaves, rock-rose leaves, broad beans, red wine, black grapes, strawberries, and apricots . Apples, blackberries, broad beans, cherries, black grapes, pears, raspberries, and chocolate are rich in epicatechin . The main dietary source of catechins is green tea (50-51) .

Catechins have potent antioxidant properties, although in some cases they may act in the cell as pro-oxidants. Catechins are reactive oxygen species (ROS) scavengers and metal ion chelators, whereas their indirect antioxidant activities comprise induction of antioxidant enzymes, inhibition of pro-oxidant enzymes, and production of the phase II detoxification enzymes and antioxidant enzymes. Oxidative stress and ROS are implicated in aging and related dysfunctions, such as neurodegenerative disease, cancer, cardiovascular diseases, and diabetes. (52-53)
Inflammation and oxidative stress are considered to be major causes of various chronic disturbances Several age-associated diseases such as cancer, neurodegenerative diseases—Parkinson's disease, Alzheimer's disease, cardiovascular diseases, and diabetes are linked to changes in oxidant-antioxidant balances and free radical damage . Due to their antioxidant properties, catechins may be beneficial in preventing and protecting from pathologies caused by oxidative stress (54-55)

Another fundamental phenolic compound is resveratrol [Figure 3]. Resveratrol (3,5,4'-trans-trihydroxystilbene) is a member of the stilbene family of phenolic compounds. It was first isolated from the root of hellebore in 1940 , and now is synthesized by leaf tissues in response to fungal infection or exposure to ultraviolet light but, until 1992, it was not detected in wine. Resveratrol is found in the seed and skin of grapes (not in the flesh) and then in grape juice and wine. As already highlighted, the concentration in red wine is higher than in white wine because, in red vinification, the

must, the skins and often the seeds are in contact during the whole fermentation process (56-57)

Recently research has focused on the great nutraceutical qualities of resveratrol, starting with wine. In fact, resveratrol has been described as a compound that can prevent and / or reduce a wide range of diseases such as cancer, cardiovascular disease and ischemic damage; it can also increase the resistance to stress and thus act against cellular stress and extend the life of various organisms, up to vertebrates. (58 -59)

In food components, resveratrol is rather limited, in small quantities it can be found in peanuts and its derivatives, pistachio, berries, dark chocolate, e grapes and their derivatives. Of all these, the grape it has the highest content and even more red wine, which is the food source with the highest content of resveratrol. Given the health recognition of its beneficial properties resveratrol has been produced on a large scale through nutraceuticals (60)

With regard to optimal oenological practices it is difficult to predict the amount of resveratrol that a finished wine can contain because there are so many factors that influence the biosynthesis of resveratrol. Concentrations ranging from undetectable at 14.3 mg / L have been described testing 700 commercially red wines from most of the world wine in several production areas and found a 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 most present in large concentrations, followed by trans-piceid. The trans forms predominate over the cis forms (61)

A recent study aimed to determine the content of transresveratrol, quercetin, catechin and epicatechin in monovarietal wines produced, with the same vinification derived from blends of Aglianico and Piedirosso which are the most common indigenous red grape varieties grown in the Campania region, against Nerello Mascalese which is a native red grape grown in Sicily with the aim also of establishing the relationship between the content of these phenols present in wine and the duration of maceration during the vinification. The study showed that after 10 days of fermentation on the skins, trans-resveratrol it reached its maximum concentration in Piedirosso and Aglianico while for the Nerello Mascalese grapes the highest level of trans-resveratrol was observed 20 days after initiation. The Piedirosso skins, on the other hand, released more this compound in the must; the maximum level of transresveratrol detected was almost 0.5 mg / l above the maximum concentration of trans-resveratrol in Aglianico e Nerello Mascalese. (62)

In the light of what emerges, the research has moved to understand the bioavailability of this compound. In fact, numerous animal and human studies have demonstrated that the bioavailability of resveratrol is very low. Once absorbed, at least 70% resveratrol ingested is readily metabolized to form mainly derivatives of glucuronide and sulphate. The bacterial microflora of the colon can produce the metabolite dihydroresveratrol. The metabolites of resveratrol reach their maximum concentration in plasma about 30 minutes after taking; half-life of total metabolites is approximately 9.2 hours (63), but the plasma concentration of resveratrol and its metabolites depends on the administered dose (64)

A sample study enrolled some volunteers to whom it was done ingest 250 ml of red wine containing a note amount of resveratrol and up to six metabolites were measured: trans-resveratrol-3-O-glucuronide, cis-resveratrol-3-O-glucuronide, cis-resveratrol-3-O glucoside, free trans-resveratrol and, provisionally, resveratrol-4'-O-glucuronide and trans-resveratrol-4-O-glucoside. (65)

Given the in vivo concentration of the individual ingested metabolites and the hypothesis that the concentration of resveratrol may be much higher, further studies on the activity of its metabolites to validate further hypotheses .(66)

Results

Polyphenols, and especially resveratrol, were identified as the main components of wine

responsible for its beneficial properties for health. The Mediterranean diet has been recognized as one model diet to prevent various serious diseases, and heart disease in particular. Wine appears to be a key component of this diet, and a moderate, regular one consumption of wine (two glasses of red wine for day) is recommended. Wine is the main source of resveratrol in the diet, and despite its concentration varies widely between different types of wine, red wine generally contains a rather high quantity, as evidenced also by the studies conducted on wines from Campania . Resveratrol has antioxidant, cardioprotective, anti-carcinogenic, estrogenic, anti-inflammatory properties, neuroprotective, antidiabetic and anti-aging properties, and therefore resveratrol can be perceived as a future pharmacological agent. (67) An important topic is the anti-inflammatory action of resveratrol Inflammation is the central cause in the pathologies of arthritis, Crohn's disease and psoriasis, and may play a role in development of cardiovascular diseases e cancer. Resveratrol reduces inflammation by inhibiting prostaglandin production, cyclooxygenase-2 (COX 2) activity and iNOS by inhibiting the activation of NF-κB.

In view of its anti-inflammatory properties and antioxidant properties and its ability to modulate important inflammatory and anti-inflammatory pathways signaling and efficacy of glucocorticoids, resveratrol can act as a potential therapeutic strategy for disease control inflammatory, pulmonary and related diseases. Indeed, resveratrol is being considered for future pharmacological agents and can be used as an anti-inflammatory to combat oxidative states (68-69)

Other health promoting properties of resveratrol include its inherent antioxidant capacity which could be related to its chemopreventive effects. the antioxidant capacity is highlighted on cellular metabolism than in normality generates reactive oxygen intermediates (ROI) such as such as superoxide, hydrogen peroxide and hydroxyl radicals, which are usually detoxified intracellularly from enzymes such as glutathione, superoxide dismutase and catalase. However, an abnormal accumulation of these can lead to the occurrence of ROI (formation of free radicals), which are commonly referred to "oxidative stress". Exposure of macromolecules (lipids, proteins, DNA) to ROIs results in theirs oxidative modifications with harmful potential. (70-71) Moreover, recent studies have shown that, 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 (72)

Furthermore, this discourse is also linked to the role of resveratrol in protecting the cardiovascular system also in a preventive way. The most important point is that resveratrol a a very low concentration inhibits cell death by apoptosis, thus providing protection from various diseases including myocardial ischemic reperfusion injury, atherosclerosis and ventricular arrhythmias. Up doses facilitates apoptotic cell death, and behaves as a chemo-preventive alternative (73)

Another beneficial function of Resveratrol could slow tumor 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 tumor formation is induction of cell cycle arrest and apoptosis. The antiproliferative and pro-apoptotic effects of resveratrol in tumor cell lines have been extensively documented in vitro and are supported by down regulation of cell cycle proteins and increases in apoptosis in tumor models in vivo. However, in some in vivo experiments resveratrol failed to affect cancer, which suggests that other factors such as dosage, delivery method, tumor 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 (74-75). A recent study involved resveratrol and activation of sirtuins pathways for an anti-aging action. More recently, Baur et al. they demonstrated that resveratrol changes the physiology of middle

age mice on a high calorie diet versus that of mice a standard diet and significantly increases them survival. In particular, studies in mice have shown that those obese animals whose diet was supplemented with resveratrol not only lived longer, but they were longer active without negative effects classics of a high-calorie diet such as increasing insulin sensitivity; this diet also reduced insulin-like growth factor 1 levels, increased the number of mitochondria and improved motor function (76-78)

Discussion

The 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. At present, it is impossible to definitively conclude the research since human studies are still in the early stages with still variable data. It can be said for sure that it is that this amazing molecule has many possibilities in the field of medicine and phytotherapy. Also for the "Aglianico", "Fiano" and "Greco" cultivars of Campania, whose phenolic profile and the quality of resveratrol present were analyzed, also highlighting the power of antioxidant and antimicrobial agents. The extracts produced could be safely used as antioxidants in various fields, such as the food and cosmetic industry, thus representing a response to the growing attention of consumers to health and the environment, and to the growing tendency to prefer natural preparations to obtain benefits for the health. Contrarily, little is known about the chemistry of polymeric polyphenols and their actual compositions in wines. In this regard, the the use of different but complementary techniques may be a successful future strategy for overcome such a drawback. In light of the benefits highlighted and the importance of diet as a primary medicine, the future prospects of research should lead to deepen two points. The first is to determine if and how red wine can be produced with a note and constant concentration of resveratrol, to ensure that adequate doses are ingested. The second point is to investigate its bioavailability and in particular the bioactivity of resveratrol metabolites after absorption. In addition, a greater synergy between the Mediterranean diet, the adoption of healthy lifestyles, the authorities, food industries, the food sector chain supply chain would favor dietary behaviors shifted towards the regular consumption of fruit, vegetables and red wine in spite of dietary fats and sugars

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Figure 1: Mediterranean diet pyramid

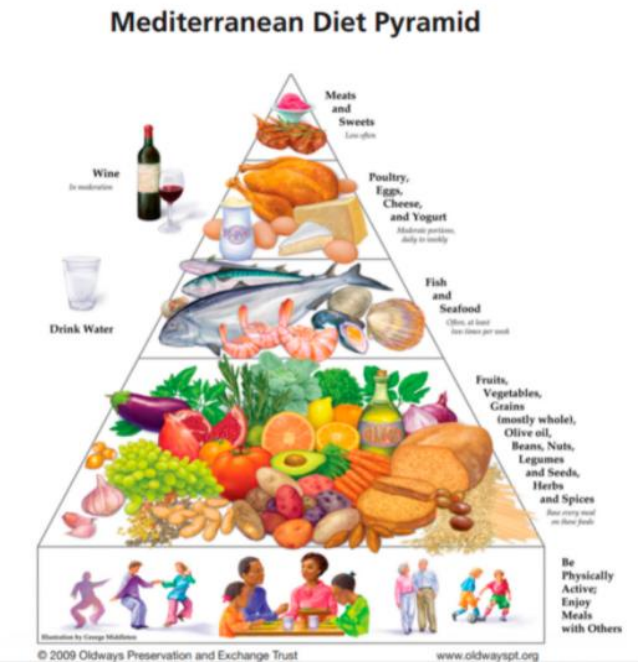

Figure 2 : Structure of Anthocyanins

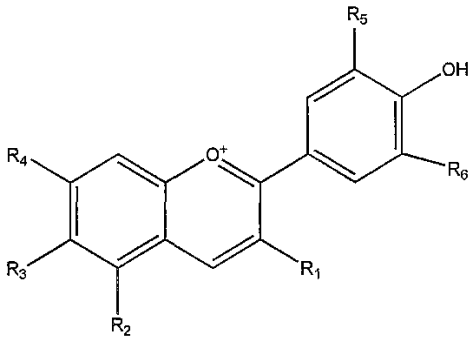

Figure 3 : Structure of resveratrol.