Wine Polyphenols and Health

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Giovanna Giovinazzo, Maria A. Carluccio, and Francesco Grieco

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Abstract

The various polyphenol families present in wine are important for a number of technological properties of wine such as clarity, hue, and palatal taste. Dietary polyphenols are associated with a wide range of health benefits, protecting against chronic diseases and promoting healthy aging. However, basic and clinical science is showing that the reality is much more complex than this and that several issues, notably daily intake, bioavailability, or in vivo antioxidant activity, are yet to be resolved. The concentration of phenolic compounds in wine is determined by viticulture and vinification practices, peculiar of different countries. Interesting are the effects of different yeast strains on the final concentration of polyphenols in red wine. We here summarize the recent findings concerning

G. Giovinazzo (✉) · F. Grieco
Institute of Sciences of Food Production (ISPA), National Research Council, Lecce, Italy
e-mail: giovanna.giovinazzo@ispa.cnr.it; francesco.grieco@ispa.cnr.it

M. A. Carluccio
Institute of Clinical Physiology (IFC), National Research Council, Lecce, Italy
e-mail: maria@ifc.cnt.it

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the effects of specific classes of polyphenol (soluble acids, flavonols, and stilbenes) on human health and propose future directions for research to increase the amount of these healthy compounds in wine.

Keywords
Wine · Soluble acids · Flavonols · Stilbenes · Yeast · Health

1 Introduction

Wine contains a large and diverse class of phenolic compounds known variously as "polyphenols" or "biophenols." These compounds contribute to the characteristic colors and flavors of wine and act as natural wine preservatives that allows a long aging process [1]. Polyphenols are extracted during crushing and fermentation when the juice is in contact with the grape skins and seeds. The amount of phenolic compounds in red wine is about six times higher than that in white wine because red juice has longer contact time with the grape skins and seeds. The concentration of polyphenolic compounds in red wine is approximately 1800–3000 mg/L [2].

There is emerging evidence that a functional diet can help in modulating the immune system responses to the inflammation processes through a variety of mechanisms based on the absorption and utilization by the human metabolism of specific compounds.

Polyphenols are the principal compounds related to the wine consumption benefits due to their antioxidant and free radical scavenging properties. This class of compounds has been proven to exert important health effects, acting against cancer pathologies [3] as well as reactive oxygen species (ROS) which are considered the main cause of different cardiovascular and neurodegenerative diseases.

Grapevine (*Vitis* spp) is the most cultivated fruit crop in the world, with an area dedicated to viticulture. The berries are harvested primarily for winemaking but also to provide fresh table grapes, raisins, and other minor products. Phenolic composition of grape is genetically driven and greatly affected by environmental factors. A major challenge for breeding of grapevine cultivars adapted to climate change and with high potential for winemaking is to dissect the complex plant metabolic response involved in adaptation mechanisms. Among plant products are the polyphenols, a large family of secondary metabolites, which are involved in plant responses to biotic and abiotic stresses. The most represented polyphenols in plants are the flavonoids, the cinnamic and benzoic acids, and the stilbenes. They derive from the phenylpropanoid metabolism, but flavonoids are ubiquitous in plants, whereas stilbenes are specific to certain plant families.

Other polyphenols, as the phytoalexins, are antimicrobial compounds synthesized in response to pathogen or herbivore attack. However, other roles have been described for stress-induced polyphenols, including the defense signaling of responses and protection against ultraviolet (UV) light damage [4, 5].

Phenolic compounds are secondary metabolites synthesized [4] during normal development of the berry grape in response to stress conditions.

A large-scale experiment involving cultivation of an association panel of a large number (more than 200) *V. vinifera* cultivars designed to represent the genetic and phenotypic variation encountered in cultivated grapevine and metabolomics analysis targeted to a large number of polyphenolic compounds (polyphenomics) was performed. Chemometrics analysis of the data showed large differences in polyphenol composition related to genetic factors, environmental factors (i.e., water stress), and genetic-environment interactions. Correlation networks shed light on the relationships between the different polyphenol metabolites and related biosynthetic pathways. In addition, detailed polyphenomics analysis confirmed that polyphenol reactions described in wine take place in the berries.

Finally, was reported a large-scale study demonstrating an influence of environmental influence (water stress) on the different classes of polyphenols but also cultivar differences in the types and extents of drought responses, with different molecules affected either positively or negatively and different impacts on grape and wine quality [6].

Grape phenolic compounds comprise several families, divided between non-flavonoids (hydroxybenzoic acids, hydroxycinnamic acids, and stilbenes) and flavonoids, based on the same C6-C3-C6 skeleton (flavonols, dihydroflavonols, flavan-3-ols, and anthocyanins). Each family is represented by several compounds differing by their hydroxylation level and by substitution of the hydroxy groups (methylation, glycosylation, acylation). For example, anthocyanins, the red grape pigments, are based on six aglycones, which can be mono- or di-glucosylated and further acylated with acetic, p-coumaric, and caffeic acid, giving rise to a large number of compounds [6]. Grape flavan-3-ols also show high diversity. They include several monomers (catechin, epicatechin, gallocatechin, epigallocatechin, and epicatechin 3-gallate) that are the constitutive units of oligomers and polymers (proanthocyanidins or condensed tannins), with degrees of polymerization ranging from 2 to over 100 in grape skin [6].

The flavonoid family includes the flavonols, such as myricetin, quercetin, and kaempferol, which exist both as aglycones and sugar conjugates. The non-flavonoids encompass hydroxybenzoic acids such as gallic acid, hydroxycinnamic acids, including p-coumaric, caffeic, and caftaric acids, and the stilbenes, such as *trans*-resveratrol and *cis*-resveratrol [5]. The synthesis of stilbenes in grape berry tissues is activated in response to fungal attack, to berry injury, and to ultraviolet irradiation [5].

The healthy physiological effects are especially associated to flavonoids and stilbenes [7], namely, quercetin, (+)-catechin, gallic acid, and trans-resveratrol [8]. The stilbene trans-resveratrol has gained great attention, and a number of scientific papers have appeared related to the moderate consumption of red wine for its ability to inhibit platelet aggregation and LDL oxidation and its beneficial effects in health. Since *trans*-resveratrol is postulated to be involved in the health benefits associated with a moderate consumption of red wine, it is one of the most extensively studied natural products.

The various polyphenol families present in wine [7, 9] are important for a number of technological properties of wine [7]. The knowledge about their qualitative and

quantitative profile in grapes is very important to predict wine aging attitude and can help to solve problems related to color stability, especially in the case of red wines that are destined to long aging periods [10]. The wine aging also changes the phenolic composition, as these compounds can suffer diverse transformations, like oxidation processes, condensation and polymerization reactions, and extraction from wood, usually associated to the changes in color and colloidal stability [11], flavor, bitterness, and astringency [12, 13]. The polyphenolic fingerprint can be useful for the classification of wines, since it can give us information about the variety, the geographic and winery origin, and even the applied winemaking technology [14].

During winemaking, only a fraction of the grape flavonoids is selectively transferred to the wine and a final yield strongly depending on the management of the contact of the liquid must, containing berry skin and seeds, with the solid parts of the grape bunches and on the grape variety [10].

The data concerning the extractable phenolics of the grape cannot be simply generalized to predict the wine composition, since a high variability in the extraction yield from grape to wine is introduced by the technological factors governing the winemaking process (such as temperature, duration and intensity of the liquid-solid contact, final ethanol concentration).

Many conditions (i.e., genetic, agronomic, technological, storage, etc.) linked to each other by complex and multifactorial phenomena affect both profiles and concentrations of bioactive compounds, either in grape or in wine [15].

2 Soluble Acids, Flavonols, and Stilbenes: Bioactive Compounds in Wine

Wine is a complex mixture of hundreds of molecules, some of them showing important biological properties, while others are mainly associated with its organoleptic characteristics. In particular, we describe specific classes of polyphenols such as phenolic acids (hydroxybenzoic and hydroxycinnamic acids), flavonols, and stilbenes (Fig. 1).

2.1 Phenolic Acids

In wine, there are two groups of phenolic acids: hydroxybenzoic acids and hydroxycinnamic acids [16]. Hydroxybenzoic acids, including gallic acid, protocatechuic acid, gentisic acid, p-hydroxybenzoic acid, vanillic acid, and syringic acid, derive from benzoic acid. Chlorogenic acid, as the main constituent of the hydroxycinnamic acid derivative group, increased with harvest time delay, and the same occurred with sinapic acid. The converse was true of caffeic acid and ferulic acid, which were also esterified with tartaric acid as the known compounds caftaric acid and fertaric acid, respectively [16, 17]. Hydroxycinnamic acids have gained an increasing interest in health because they are known to be potent antioxidants.

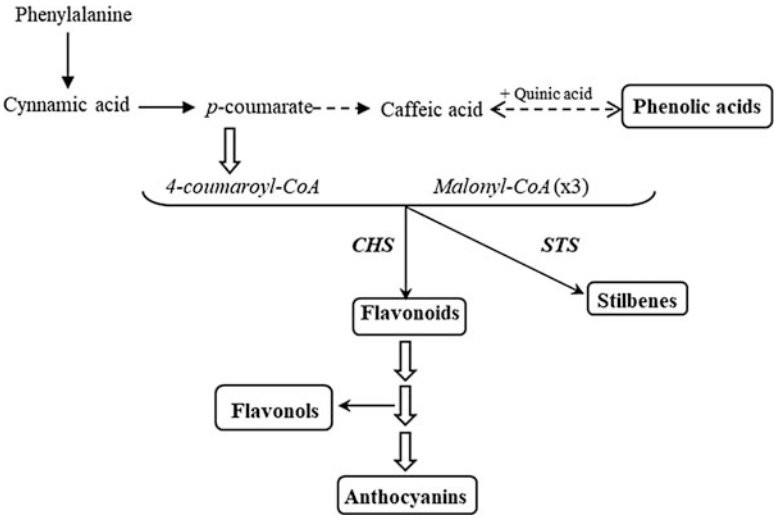

Fig. 1 Polyphenol biosynthesis pathway in grape tissues. *CHS* chalcone synthase, *STS* stilbene synthase

These compounds have been described as chain-breaking antioxidants acting through radical scavenging activity that is related to their hydrogen or electron donating capacity and to the ability to delocalize/stabilize the resulting phenoxyl radical within their structure. The free radical scavenger ability of antioxidants can be predicted from standard one-electron potentials.

Phenolic acids represent important fraction of wine phenolics, but their biological effects have been scarcely investigated. The interrelationship between antioxidative capacity and vasodilatory activity, two potentially beneficial biological effects, of phenolic acids from wine was examined. Antioxidative and vasodilatory effects of phenolic acids relate to the number of hydroxyl groups in the phenyl ring, degree of compactness and branching of molecules, and three-dimensional distributions of atomic polarizability of the tested molecules [18]. Caffeic acid has been shown to have neuroprotective effects against injury induced by 5-S-cysteinyl-dopamine, against Aβ-induced neurotoxicity and by inhibiting peroxynitrite-induced neuronal injury [19, 20]. Ferulic acid has been cited as an antidiabetic effect by lowering blood glucose and by increasing plasma insulin [21].

2.2 Flavonols

Four aglycones belong to the flavonols class: myricetin, quercetin, kaempferol, and isorhamnetin. The diversity in the flavonols structure is due to changes in the basic skeleton introduced by enzymes such as glycosyl transferase, methyl transferase, and rhamnosyl-transferase. In one plant species, dozens of different flavonoids may be present, and many of these are conjugated to various types of sugars. Both the basic

structure and the level of glycosylation determine the biological function and bioavailability of polyphenols in the human and animal intestines. Depending on their structure, these molecules have diversified activities.

Flavonols are found throughout the plant foods. The best-known flavonols are quercetin and kaempferol. Quercetin, kaempferol, myricetin, and isorhamnetin are flavonols presents in grape skins and stems as several different glycosides. Quercetin accumulates in grape skins to protect against damage from ultraviolet (UV) light. There are high concentrations of quercetin in wine made from sun-exposed grapes. Quercetin is readily extracted from grape skins during fermentation. Stems may contribute additional flavonols in whole cluster fermentations.

Quercetin glycosides may be hydrolyzed in wine to form quercetin aglycone. This process is similar to the hydrolysis that can occur with anthocyanins. Unlike anthocyanins, flavonol aglycones are stable in wine and can be used to monitor hydrolysis reactions. Quercetin may cause problems as a precipitate in bottled wines. Flavonols can interact with anthocyanins, enhancing their red color in a process known as co-pigmentation. This process may also help anthocyanin color stability.

Dietary flavonols inhibit LDL oxidation and so reduce the primary risk factor for atherosclerosis and related diseases. The animal studies are supported by human epidemiological studies, which show inverse correlations between the occurrence of CVD, certain cancers, and age-related degenerative diseases and the consumption of flavonol-rich diets [22–25]. Flavonols have been linked to protective effects against several specific cancers, including leukemia and pancreatic, breast, cervical, prostate, uterine, and urinary tract cancers. Subjects with regular flavonol intake have a 10–60% lower incidence of these types of cancer compared with subjects with low flavonol intake.

This protective activity results from both the action of flavonols as stimulators of antioxidant defenses and their direct inhibitory effects on cellular proliferation. Quercetin consumption has been reported to be inversely associated with breast cancer incidence [26].

2.3 Stilbenes

Stilbenes are a class of compounds with multiple pharmaceutically relevant properties. The stilbenes production in grape berry tissues is considered to be a part of the general defense mechanism since they display strong antifungal and antimicrobial activities [27].They are a group of plant phytoalexin polyphenols found in high concentrations in grapes, berries, nuts, and teas. In plants, their main function is to protect the plants against pathogens and fungi; therefore, their content is highly variable and increases with stress exposure. UV radiation, heavy metal exposure, and fungal infection may thus be utilized to enrich grapes with stilbenoids [28, 29].

Resveratrol (3,4_,5-trihydroxystilbene) may be found especially in red wine, grapes, and berries, at a concentration ranging from 0.1 to 15 mg/L. Nowadays, the primary source of resveratrol is the roots of perennial plant *Polygonum cuspidatum* (Japanese knotweed) [29]. Due to the positive health effects attributed

to resveratrol through so-called French paradox, its biological activity has been extensively studied. Most biological effects are assigned to trans-resveratrol, the more stable of the two isoforms. However, also cis-resveratrol, which is formed from trans-resveratrol upon UV light exposure, exhibits certain anti-inflammatory activity. Unless otherwise stated, the activities mentioned here apply to trans-resveratrol. Stilbenes are non-nitrogen polyphenols with acidic and amphiphilic character which causes their enrichment in biomembranes, where many of their targets occur (COX, 5-LOX, protein kinase B) [30]. Structurally, stilbenoids possess two aromatic rings connected by an ethylene or ethene bridge with a variety of substituents. Even though the presence of double bond suggests that stilbenoids exist in cis- as well as trans-form, the trans-form is more stable and the biologically relevant form. In nature, stilbenoids are synthesized from phenylalanine through multiple enzymatic reactions [31]. Stilbenoids are heterogeneously spread throughout the plant kingdom. They are especially abundant in *Gnetaceae*, *Pinaceae*, *Cyperaceae*, *Fabaceae*, *Dipterocarpaceae*, and *Vitaceae* families [32]. Resveratrol has a function of phytoalexin produced by specific plant species in response to biotic and abiotic challenges. It is thought to be one of the principal agents in the health-promoting effects of red wine [33]. Results of clinical studies show that the most important source of resveratrol and piceid are wines (98.4%) and grape and grape juices (1.6%), whereas peanuts, pistachios, and berries contribute to less than 0.01% [34]. Wine is the major source of resveratrol and piceid to the diet, ranging from 95% and 98.7% for *trans*-resveratrol and *trans*-piceid to 99.9% and 99.7% for *cis*-resveratrol and *cis*-piceid, respectively. Other food items such as grapes contribute by amount of 3.8% of total trans-resveratrol, whereas other contributors such as pistachios or berries provide less than 1% of the dietary total amount of trans-resveratrol and trans-piceid.

Resveratrol possesses numerous important bioactivities, including anti-inflammatory, antioxidant, anti-aggregatory functions, and modulation of lipoprotein metabolism [35–37]. It has also been shown to detain chemo preventive properties against certain forms of cancer and cardiovascular disorders and to have positive effects on longevity [38–42].

Anticancer activity of this compound is mainly due to induction of apoptosis via several pathways, as well as alteration of gene expressions, leading to a decrease in tumor initiation, promotion, and progression [43]. Resveratrol blocks the growth of lymphoma cells and increases their rate of cell death [44]. Resveratrol sensitizes chemotherapy-resistant lymphoma cells to treatment with paclitaxel-based chemotherapy [45], also reduces the production of growth factors, such as vascular endothelial growth factor and interleukin [33], and may reduce the ability of lymphoma cells to spread to other organs [46]. Finally, it was demonstrated that in vitro administration of resveratrol favorably altered gene expression in the androgen axis and in cell cycle regulators, providing potential anticancer benefit for prostate cancer [47]. Moreover, *trans*-resveratrol appears to protect against diabetes [48] and neurodegenerative disorders [49], due to induction of sirtuin 1 genes [50]. *Trans*-resveratrol might also contribute to increasing the life span of metazoans and mice by miming the effect of caloric restriction and thus decreasing age-related signs [51, 52]. Experimental studies have shown that resveratrol exhibits

both an anti-inflammatory and cardioprotective potential by inhibiting the expression of inflammatory mediators and the monocyte adhesion to vascular endothelial cells [53, 54]. Although resveratrol exhibits potent anticancer activities against transformed cells, its effectiveness is limited by its poor bioavailability, and as a dietary phytonutrients, it is most effective against tumors with which it comes in direct contact, such as skin cancers and tumors of the gastrointestinal tract. Furthermore, inhibition of sirtuin 1 by both pharmacological and genetic means abolished protein de-acetylation and autophagy as stimulated by resveratrol, but not by piceatannol, indicating that these compounds act through distinct molecular pathways. In support of this notion, resveratrol and piceatannol synergized in inducing autophagy as well as in promoting cytoplasmic protein de-acetylation [55].

3 Technological Approaches to Enhance Polyphenol Content and Antioxidant Activity in Wine

The winemaking steps determine the phenolic content of red wines that able the extraction of phenolic compounds from the grape berries. Numerous winemaking procedures have been developed to enhance the extraction of phenolic molecules, by preventing the several motives that affect the release of polyphenols from the berry tissues [56, 57]. Several investigations have studied the effect of the fermentation temperature during the winemaking process on the extraction of polyphenols, thus demonstrating that their concentration increased when wines were produced at higher fermentation temperatures [58, 59]. Moreover, it has recently shown the efficacy of thermo-vinification to improve a number of factors, such as the antioxidant potential and the polyphenolic and resveratrol content, in Pinot noir, Prokupac, Merlot, and Cabernet Sauvignon wines [60].

The impact of maceration time and of the utilization of enological additives (enzymes, sulfur dioxide) on the polyphenol content has been studied [57]. Gambuti and coworkers [61] have examined the effects of those factors during vinification of Aglianico grape must. The authors indicated that the simultaneous addition, during the pre-fermentation stage, of pectolytic enzymes and SO_2 increased the release of these molecules from grape tissues, thus resulting in a higher concentration of polyphenols in the produced wine. Comparable evidences were recently obtained by investigating experimental vinification of grape must from the Vranec cultivar [62, 63]. Also in this case, both increased maceration time and SO_2 addition augmented the final concentration of total polyphenols, anthocyanins, flavonoids, and flavan-3-ols in the final product, this effect action not dependent by the wine aging.

The action of diverse winemaking approaches in determining polyphenolic profile of red wines obtained from the Italian red cultivar “Negroamaro” has been recently studied. Were compared three different pre-fermentative steps: the traditional (7 days of maceration at 25 °C), the cryomaceration, (24 h at 0 °C using dry ice), and ultrasound (37 kHz, 150 W, 15 min at 30 °C) [64]. The authors demonstrated that the ultrasound action enhanced the release of all polyphenol classes,

whereas the cryomaceration only improved the anthocyanin content in the produced wine.

This evidence has been recently supported by a recent study of Ferraretto and Celotti [65]. They evaluated the effect of high-power ultrasound (20 kHz) on the phenolic structure of red wines and demonstrated that this physical treatment promote the polymerization of the phenolic compounds as the wine matures and consequently speed up the aging course of wines.

Another investigation [66] has evaluated the consequence of different technological approaches on the polyphenolic profile and the antioxidant activity of wine produced from grape of the Italian cultivar Primitivo. The addition of tannins was more efficient in enhancing the concentration of phenolic molecule when compared in musts to the other considered technologies and the aging to get better wine antioxidant activity. Furthermore, a recent report indicated that protracted post-fermentation maceration up to 50 days increased the polyphenol concentration and, consequently, the potential healthy effect of the obtained wine [67]. However, a number of reports do not agree with this hypothesis.

However in contrast with the above findings, Mulero and coworkers [68] did not detect variation in the concentrations of the different types of phenolic compounds in three wines from Monastrell grapes, produced by separately adopting the protracted maceration, must fermentation by adding enzymes, or the traditional procedure above three technological approaches.

The pulsed electric field (PEF) technology represents a very promising approach because of its ability to enhance the extraction of polyphenolic compounds throughout the vinification process. The PEF pretreatments on Cabernet Sauvignon must gave substantial differences in the produced wines, since the same PEF-treated must showed an increase of 97% in the content of total flavonols of 32% in the content of total phenolics and of 62%, in the color, when compared to the untreated control [59]. The above findings were confirmed by similar investigations that analyzed the vinification of Cabernet [69], Merlot [70], and Syrah [71] grape musts after the application of the PEF step. Moreover, PEF treatment allowed the acceleration and enhancement in the extraction of phenolic compounds throughout the maceration step of winemaking process [72].

An interesting research have recently assessed the effects of a novel fermentation technologies based on the "Ganimede" that is able to trap the carbon dioxide (CO2) generated during the alcoholic fermentation on the phenolic contents of Cabernet Sauvignon wines [73] indicating that this device was able to increase the concentration of anthocyanins superior in the wines produced.

The mechanisms through which yeast influences the color and content of polyphenolic compounds of wine are currently being researched, but three modes of interaction between the yeasts and the polyphenolic component have been already identified. Some strains of yeast adsorb polyphenols on the cell wall. However, although it has been shown that yeast is one of the factors able of inducing the reduction of the polyphenol concentration in wines, it is unknown whether their adsorption on the cell walls is the only mechanism responsible of this behavior. The amount of biomass produced during the alcoholic fermentation is capable to adsorb

on the cell walls a significant amount of polyphenols. This capacity is likely to be strain-specific, since different yeast strains have a different composition of the cell wall. In fact, it could be hypothesized that specific yeast strains could perform a "differentiated" adsorption of the diverse polyphenol classes. The second type of interaction between yeast strains and the wine polyphenol is related to the microbial β-glucosidase enzymatic activity. In fact, the greatest part of anthocyanins is found in the wine as glucosidase derivatives (linked to a sugar); thus, in this state they are much less sensitive to chemical or enzymatic oxidation; therefore the β-glucosidase activity decreases color and stability, since it produces free anthocyanins in wine. The third mechanism regards the strain-specific secretion throughout the alcoholic fermentation, by some wine yeast, of polysaccharides capable to combine with the polyphenols and to form with them stabile complexes.

It has been shown that different yeast metabolites, including pyruvic acid, can react with the anthocyanins of the grapes giving rise to stable pigments during the maturation and aging of red wines [74]. Taken together, the above considerations highlight the pivotal role played by yeasts in modifying the polyphenolic profile of wines.

Indeed, several investigations have highlighted the ability of different wine yeast strains and of enological additives of microbial origin to improve the phenolic profile of red wines. The addition of β-glucanases or other yeast-derived enzyme preparations as enological additives increased the antioxidant potential of sparkling wines [75]. On the opposite, yeast lees have been demonstrated to lower the amounts of polyphenolic compounds [76] and anthocyanins [74] in wines, because they formed stabile complexes with the mannoproteins released by yeasts after their yeast.

Even though previous studies did not show any effect of yeast starters on the polyphenolic profile of Pinot noir [77], Cabernet Franc, and Merlot [78] wines, several recent reports indicated a correlation between the utilized yeast strain and the antioxidant capacity of the produced wine.

Brandolini and coworkers [79] carried out an investigation by evaluating the properties of wines produced by the separate inoculation of 19 strains of *Saccharomyces cerevisiae* in the same grape must. The antioxidant capacity and the polyphenol profile detected in the different wines were extremely different, thus showing the strain-specific yeast feature to differentially adsorb polyphenols during the vinification process. Kostadinović and coworkers [62] showed analogous evidence on Vranec and Merlot wines in Macedonia. The authors used different starter cultures to carry out vinification tests, where the strains demonstrated that they were capable to affect specifically the *trans*-resveratrol concentration and antioxidant activities in the final wines.

The employment of different yeast starter strains allowed the production of Pinot noir wines with a dissimilar polyphenolic content [80]. This study has analyzed how yeast selection can modify phenolic content in Pinot noir wine. In fact, five different yeast starters were tested in multiple vinifications, where the *Saccharomyces cerevisiae* strain RC212 was able to raise conspicuously the concentrations of total pigment, anthocyanin, and tannins. Recently, Carrascosa and collaborators [81] have recently shown that different yeast strains were able to produce Albariño wines

denoted with a specific polyphenol composition. The above findings were further confirmed by a recent report [82], where an unambiguous correlation between the yeast starter utilized to promote the fermentation process and chemical profile of wine was recognized, thus underlining the strain-specific yeast property to modify the color and the polyphenolic composition of the final product.

Moreover, a recent study has produced the identification of yeast starter cultures able to enhance the quality of the wine produced from the Italian red cultivar "Gaglioppo" a cultivar with reduced synthesis of anthocyanins [83]. The obtained evidences further evidenced the strain-specific capacity of wine yeast to modify the final amounts of total anthocyanins, total polyphenols, and total tannins.

Recently, Giovinazzo and coworkers (manuscript in preparation) highlighted a positive role of autochthonous yeast starter cultures for the enhancement of polyphenol content throughout the industrial production of Negroamaro wine. The statistical assessment of the experiment showed that the use of autochthonous strains increased the concentrations of several classes of polyphenols in the produced wines when compared to wines produced from the Sama grape must with commercial starter strain.

Taken together, the above-described scientific outcomes emphasize the relevance of the development and the industrial application of innovative biotechnological approaches in order to exalt the presence of healthy molecules in wine, thus improving "functional parameters" with the consequential enhancement of the final wine quality.

4 Wine Polyphenol Mechanism of Action Against Cardiovascular Diseases

Wine polyphenols have garnered much attention, especially with regard to their potential role in the protection against cardiovascular diseases. Indeed, red wine is thought to be responsible for the "French paradox" [84], a term used to describe the low incidence of cardiovascular disease in the French population despite their high intake of saturated fats.

Many preclinical and some clinical studies have identified a number of mechanisms and targets by which specific wine polyphenols could exert benefits against cardiovascular diseases. Wine polyphenols, including flavonols and resveratrol, have been shown to modulate the expression of inflammation-related genes involved in the atherosclerotic process as well as in chronic degenerative diseases.

Flavonols (quercetin, kaempferol, and myricetin) significantly downregulate the coordinated expression of the endothelial adhesion molecules, E-selectin, vascular cell adhesion molecule (VCAM)-1, and intercellular adhesion molecule (ICAM)-1, in human cultured endothelial cells activated by inflammatory triggers [85], thus decreasing the adhesion and subsequent trans-endothelial migration of monocytes into the intima of the vascular wall, i.e., processes that constitute the initial steps in the development of atherosclerosis. Flavonols have also been reported to significantly downregulate the expression of monocyte chemoattractant protein (MCP)-1

and macrophage colony-stimulating factor (M-CSF); both pro-inflammatory endothelial proteins guide monocytes into the subendothelial space, during inflammatory state [85]. The anti-inflammatory flavonol effects were mediated by the reduced activation of NF-κB and AP-1, whose binding sites are present in the promoter region of the pro-inflammatory genes including VCAM-1, ICAM-1, E-selectin, as well as MCP-1 and M-CSF [86]. Furthermore, flavonols also affected the inflammatory response by downregulating the expression of inflammation-related genes, like interleukin (IL)-6, IL-4, and tumor necrosis factor (TNF)-α. In human vascular endothelial cells, our research group reported that quercetin reduced inflammatory angiogenesis, a key pathogenic process contributing to atherosclerotic lesion formation, progression, and vulnerability, through inhibition of the pro-inflammatory enzyme cyclooxygenase (COX)-2 and gelatinases, the matrix metalloproteinase (MMP)-9 [87].

A limitation of the anti-inflammatory effect by flavonols in these in vitro studies is the use of flavonols at supraphysiological concentrations and as aglycone forms. It has been proven that after oral absorption, flavonols are rapidly converted to circulating conjugates through glucuronidation, sulfidation, or methylation. This accounts for the very low aglycone concentrations in human plasma (in the nanomolar range).

Few studies have investigated the effects of flavonol metabolites on vascular cell function. It has been shown that human quercetin plasma metabolites at physiologically significant concentrations were able to inhibit COX-2 expression in human lymphocytes. Furthermore, Tribolo et al. showed that quercetin and its phase II metabolites affected the expression of VCAM-1, ICAM-1, and MCP-1 in inflamed endothelial cells [88]. However, at 10 μM, quercetin metabolites showed a reduced ability to decrease the stimulated expression of these genes when compared with quercetin. This suggested that the chemical transformation of quercetin during phase II metabolism resulted in a reduction of bioactivity, at least with respect to regulation of inflammatory gene expression. However, at a vascular level, quercetin glucuronides can be freed of their sugar moiety by a deconjugation process performed by β-glucuronidases, and the free aglycone is delivered to tissues, particularly under inflammatory conditions [89]. In a vascular co-culture model represented by human arterial smooth muscle cells and endothelial cells, quercetin and its phase II metabolites at physiologically relevant concentration significantly decreased the stimulated expression of the vasoconstrictor endothelin-1 [90], involved in the endothelial regulation of vascular tone.

Many results obtained in cell culture studies have been replicated in animal model but not in human trials. However, several human studies have shown that quercetin can reduce blood pressure in hypertensive patients [91], although the precise mechanisms have not been elucidated.

In addition to flavonols, the anti-inflammatory action of wine polyphenols is exerted by resveratrol.

Resveratrol, like quercetin, has been reported to modulate the expression of inflammation-related genes involved in the cellular processes that control adhesion and migration of monocytes to vascular endothelium [92, 93]. We reported that

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GROUPS	POLYPHENOLS	PWPE		NWPE	
		µg/mL	µmol/L	µg/mL	µmol/L
HYDROXYCINNAMIC ACIDS	*p*-Coumaric acid	0.04 ± 0.03	0.24	0.04 ± 0.02	0.27
	Caffeic acid	1.26 ± 0.54	6.98	1.52 ± 0.81	8.41
	Caftaric acid	8.23 ± 1.12	26.37	8.01 ± 0.98	25.64
Total Hydroxycinnamic Acids		*9.53*		*9.57*	
FLAVONOLS	Kaempferol	0.05 ± 0.02	0.18	0.08 ± 0.04	0.30
	Quercetin	0.13 ± 0.05	0.42	0.14 ± 0.03	0.47
	Myricetin	0.04 ± 0.01	0.12	0.09 ± 0.02	0.29
Total Flavonols		*0.22*		*0.31*	
STILBENES	*trans*-Resveratrol	0.06 ± 0.02	0.24	0.02 ± 0.01	0.10
	trans-Piceid	0.20 ± 0.05	0.51	0.09 ± 0.03	0.24
Total Stilbenes		*0.26*		*0.11*	
TOTAL POLYPHENOLS		10.00		10.00	

b

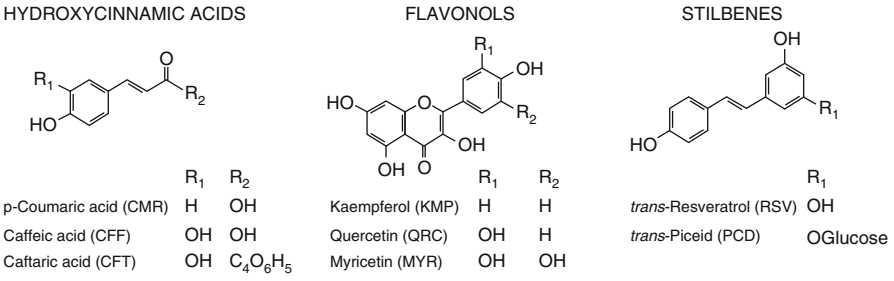

Fig. 2 Characterization of Primitivo wine polyphenol extract (PWPE) and Negramaro wine polyphenol extract (NWPE) polyphenol content and chemical structure of polyphenols. (**a**) Polyphenol content PWPE and NWPE (10 µg/mL). (**b**) Chemical structures of polyphenol groups identified in red wine extracts: hydroxycinnamic acids (*CFF* caffeic acid, *CMR* p-coumaric acid, *CFT* caftaric acid), flavonols (*KMP* kaempferol, *QRC* quercetin, *MYR* myricetin), and stilbenes (*RSV* trans-resveratrol, *PCD* trans-piceid)

resveratrol decreased monocytoid cell adhesion to human endothelial cells via reduction of VCAM-1 gene expression and by suppressing VCAM-1 promoter activity (see Figs. 2 and 3) [15]. In addition to VCAM-1, resveratrol also inhibited ICAM-1 and E-selectin, as well as MCP-1 and M-CSF [85, 93]. In human endothelial cells, monocytes, and smooth muscle cells, resveratrol strongly inhibited the expression of MMPs [85, 93, 94], responsible for the degradation of extracellular matrix, an essential event in atherosclerotic process, thus preventing plaque development, progression, and vulnerability. Furthermore, in endothelial and mononuclear cells, resveratrol inhibited, in a dose-dependent manner, the stimulated expression of tissue factor [96], a key regulator in the extrinsic pathway of blood coagulation. These anti-inflammatory and anti-thrombotic effects of resveratrol were at least in part mediated by lowered levels of intracellular ROS and the reduced activation of redox-sensitive transcription factors, NF-κB and AP-1 [85, 93, 96]. Part

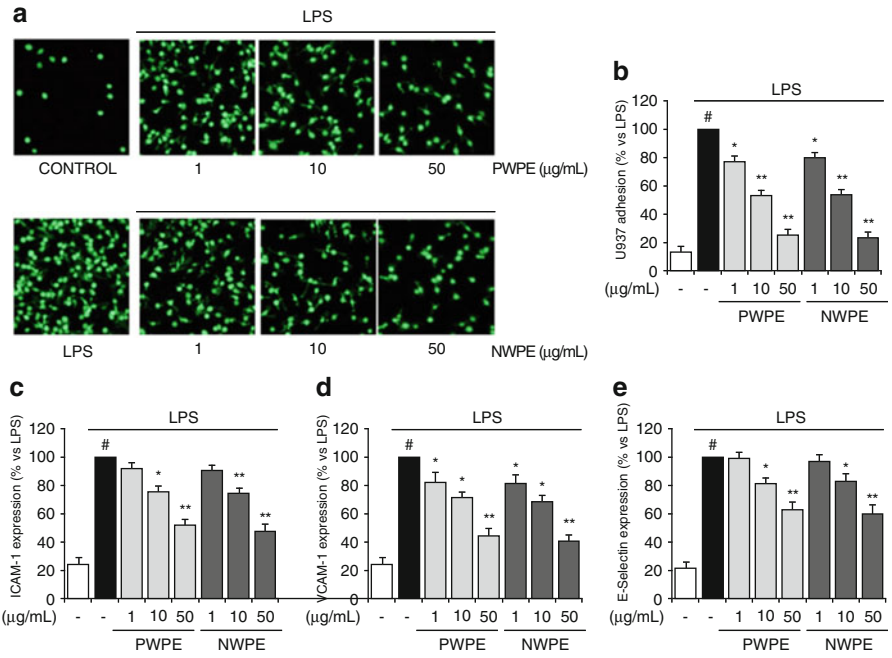

Fig. 3 Inhibitory effects of PWPE and NWPE on the monocyte adhesion to endothelial monolayer and on the expression of endothelial adhesion molecules. (**a**, **b**) HUVEC were pretreated with Primitivo wine polyphenol extract (PWPE) and Negramaro wine polyphenol extract (NWPE) (1–50 μg/mL) or vehicle (control) for 1 h and then stimulated with LPS 0.5 μg/mL for 16 h. HUVEC were co-cultured with calcein AM-labeled U937 monocytes for 1 h. The number of adherent U937 cells was monitored by fluorescence microscope (**a**) or measured by the fluorescence plate reader (**b**). (**c**–**e**) Cell surface expression of ICAM-1 (**c**), VCAM-1 (**d**), and E-Selectin (**e**) was analyzed by cell surface EIA. Each experiment was performed in triplicate. Data are expressed as the percentage of LPS-induced expression (mean ± SD). #p <0.01 versus control; *p <0.05; **p <0.01 versus lipopolysaccharide (LPS) alone

of the beneficial effects of resveratrol was also mediated by the upregulation of endothelial nitric oxide synthase (eNOS), involved in the regulation of vascular homeostasis. Most of the studies about the cardiovascular beneficial effect of resveratrol were performed by using its aglycone form; however it has been shown that piceid, a glycosidic form of resveratrol, also preserved the vascular anti-inflammatory properties, although at a lesser extent [85, 94].

As a critical point of in vitro studies, the cardio-vasculo-protective effects of resveratrol have been shown to occur at supraphysiological (10 μM) concentrations, which cannot be achievable through dietary intake. However, some beneficial properties of resveratrol have been also observed at dietary doses. In human endothelial cells, resveratrol at physiological concentrations decreased the stimulated expression of VCAM-1, ICAM-1, and MCP-1 [54], as well as the cytokines, IL-6 and CCXL2. A significant increase in eNOS expression in HUVEC has been reported also at lower concentration of resveratrol (1 μM), following repeated

stimulation for 6 days [97]. Physiological concentrations (0.1–1 μM) of resveratrol have also been reported to modulate the expression of genes involved in cell proliferation, blood pressure regulation, oxidative stress response, and autophagy in endothelial cells [98].

Another critical point for resveratrol efficacy is its low bioavailability. It is rapidly absorbed, metabolized, and excreted; however, in spite of its low bioavailability, evidence that beneficial activities occur in humans is beginning to emerge, and this phenomenon has been described as the "resveratrol paradox." This paradox could thus be related to a possible action of resveratrol metabolites [99] and/or to a synergistic effect of resveratrol with other polyphenols or micronutrients. Accordingly, resveratrol as a blend of polyphenols from grape extracts exhibited a greater inhibitory effects on the expression of inflammatory markers in vascular cell than resveratrol alone [85, 95], suggesting the occurrence of a synergism among resveratrol and other polyphenols.

Though resveratrol's potential utility in preventive medicine has been demonstrated using in vitro models, few clinical trials have also evaluated the effects of resveratrol on clinically relevant biomarkers. In healthy individuals, Agarwal and collaborators evaluated the effects of 1-month resveratrol treatment on endothelial response and plasma biomarkers [100]. Exposing cultured human coronary artery endothelial cells to plasma drawn post-resveratrol supplement resulted in significantly lower mRNA expression of VCAM-1, ICAM-1, and IL-8 than plasma drawn from the same subjects at baseline. This clinical trial highlighted for improved gene expression in vascular endothelium by resveratrol. A triple-blind, randomized, placebo-controlled, 1-year treatment with a resveratrol-containing grape supplement on stable patients with coronary artery disease [101] showed dose-dependently an increase of the anti-inflammatory serum adiponectin and a decrease of plasminogen activator inhibitor-1. Moreover, the transcriptional profiling showed a down-regulation of pro-inflammatory genes and a modulation of inflammatory transcription factors, confirming previous in vitro findings [102].

Moreover, in peripheral blood mononuclear cells of type 2 diabetes and hypertensive patients with coronary artery disease [102], the supplementation with resveratrol-containing grape supplement significantly reduced the expression of the pro-inflammatory cytokines CCL3, IL-1, and TNF-α and modulated inflammatory-related microRNAs. These clinical studies support the conclusion of beneficial anti-inflammatory and immunomodulatory effects of grape extract enriched in resveratrol for secondary prevention of patients with coronary artery diseases.

5 Conclusion

The precise nature of the role played by polyphenols in human health has been largely highlighted in these last years. A better knowledge concerning the composition and dynamics of polyphenol profile in red grape will help vinedresser and winemakers in producing grape-derived products and wines with high content of

phenolic antioxidants and considerable antioxidant activity, maintaining optimal organoleptic properties and a significant link with the original terroir.

Even though, a better understanding is still requested about the several different cellular mechanisms and complex pathways involved in wine polyphenol metabolism, the present findings suggest that the contribution of antioxidant phenols through a reasonable daily drinking of red wines may offer additional protection against in vivo oxidation and other damages of human cell components.

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