Abstract

Moderate consumption of red wine has been putatively associated with lowering the risk of developing coronary heart disease. This beneficial effect is mainly attributed to the occurrence of polyphenol compounds such as anthocyanosides (ACs), catechins, proanthocyanidins (PAs), stilbenes and other phenolics in red wine. This review focuses on the vascular effects of red wine polyphenols (RWPs), with emphasis on anthocyanosides and proanthocyanidins. From in vitro studies, the effect of red wine polyphenols on the vascular tone is thought to be due to short- and long-term mechanisms. NO-mediated vasorelaxation represents the short-term response to wine polyphenols, which exert the effect by increasing the influx of extracellular Ca²⁺, and the mobilization of intracellular Ca²⁺ in endothelial cells. Polyphenolic compounds may also have long-term properties, as they increase endothelial NO synthase expression acting on the promoter activity. In addition, they decrease the expression of adhesion molecules and growth factors, involved in migration and proliferation of vascular smooth muscle cells. Moreover, they inhibit platelet aggregation. However, a paucity of data as regards the bioavailability and metabolism of these compounds in human studies is a limiting factor to proving their efficacy in vivo.

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1. Introduction

For many numbers of years, considerable attention has been directed towards human behavioural habits that could either be considered risk factors or even protective elements for developing chronic pathologies. In particular, much effort has been devoted to elucidate the role of diet in preventing cardiovascular diseases. A so-called “Mediterranean diet” is thought to prevent cardiovascular diseases [1], as a consequence of its high content of antioxidants, which are crucial in ameliorating oxidative events implicated in many diseases. Similarly, moderate consumption of red wine has been associated with a lowering of the risk of coronary heart disease [2–4]. Red wine represents a rich source of polyphenols such as anthocyanosides (ACs), catechins, proanthocyanidins (PAs), stilbenes and other phenolics. Anthocyanosides (ACs) are flavonoids widely distributed in fruits and vegetables. They provide colour to red wines and to skins of red and black grapes [5]. Proanthocyanidins are another class of plant phenol metabolites widely occurring in fruits including grapes [6]. ACs and PAs are among the most important compounds in determining the quality of the red wine, because they greatly influence colour, bitterness, astringency, and chemical stability toward oxidation [7].

In addition to antioxidant/antiradical activity, red wine polyphenols (RWPs) were shown to possess many biological properties including the inhibition of platelet aggregation, vasorelaxing activity, modulation of lipid metabolism, and inhibition of low-density lipoprotein oxidation [2,3,8–11]. Thus, the health benefits of moderate consumption of red wine are founded on a multiplicity of actions. The biological properties of red wine stilbenes (trans-resveratrol) have been extensively reviewed [12–14]. Because ACs and PAs exert cardioprotective effects which are not only due to antioxidant/antiradical activity, the present review will consider the effects of ACs and PAs at vascular level with special emphasis on the vasorelaxing and the antiaggregating properties.

2. Proanthocyanidins and anthocyanosides in red grapes (Vitis vinifera) and wines

PAs (or so-called condensed tannins) are high-molecular weight polymers, made of flavan-3-ol units (Fig. 1) linked...
together by carbon–carbon bonds. Oxidative condensation occurs between carbon C4 of the heterocycle and C6 or C8 of the adjacent units. The flavan-3-ol unit may have a 3',4' dihydroxy substitution on ring B (catechin and epicatechin) and 3',4',5' trihydroxy substitution (gallocatechin and epigallocatechin). The term procyanidins indicates the polymers of catechin and epicatechin, the term prodelphinidins indicates the polymers made by gallocatechin and epigallocatechin. Dimers, trimers (among which procyanidin C1 is the most abundant), tetramers and oligomers up to 8 units are present in grape (*V. vinifera* L.) seeds, stems, and skins [6]. The procyanidin dimers B1–B4, characterized by the 4→8 linkage, are the most common in grapes (Fig. 2). The corresponding 4→6 linked isomers B5–B8, may also occur (Fig. 3). Until recently, complete characterization of PAs in grapes and wines has been impaired because of the difficulty of analysing high-molecular weight compounds. However, newly developed methods based on HPLC coupled with mass spectrometry has allowed the characteriza-

tion of complex mixture of grape seed extracts and in beverages [8,15–17].

ACs are water-soluble plant pigments, localized in the skin of the berries of red grape cultivars. The term ACs (or anthocyanins) refers to the glycosides of anthocyanidins (free aglycons). ACs may be acylated on the sugar moiety with aromatic and aliphatic acids. The 3-O-β-glucosides of cyanidin, peonidin, delphinidin, petunidin and malvidin are the most abundant in *V. vinifera* and red wines (Fig. 4).
The six-hydroxyl of the glucose may be acylated with acetyl, coumaroyl and caffeoyl groups. During storage and aging of red wines, ACs react with PAs to produce more acetyl, coumaroyl and caffeoyl groups. During storage and aging of red wines, ACs react with PAs to produce more acetyl, coumaroyl and caffeoyl groups. During storage and aging of red wines, ACs react with PAs to produce more acetyl, coumaroyl and caffeoyl groups. During storage and aging of red wines, ACs react with PAs to produce more acetyl, coumaroyl and caffeoyl groups.

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Because of their unstability, free aglycons of ACs are never found in grape or wine, except in trace quantities. The levels of ACs and PAs are highly variable due to differences in fruit source (cultivars of V. vinifera) and wine processing [20]. According to this author, a representative content of ACs is 400 mg/l in a red wine less than 6 months of age, not having fermented in oak barrels, and 90 mg/l in a red wine aged for about 2 years or fermented in oak barrels. White wines contain only trace amounts. Red wine contains greater amounts of PAs (750 and 1000 mg/l, young and aged respectively) vs. white wines (20–25 mg/l). The content of extractable PAs (1600–4300 mg/kg of grape) and ACs (300–1900 mg/kg of grape) in different cultivars grown in Italy was reported by Mattivi et al. [7]. Burns et al. [21] reported the total phenol content in 16 red wines selected to provide a range of origins, grape varieties and vinification methods. Total AC levels, measured using a colorimetric assay ranged from 101 to 325 μM (expressed as malvidin 3-glucoside equivalents).

3. Red wine polyphenols as protective agents against atherogenesis

Dysfunction of the vascular endothelial cells, and proliferation and migration of smooth muscle cells are among the factors contributing to atherosclerosis. Vascular endothelial syntheses and releases nitric oxide (NO), which in turns, promotes vasorelaxation (endothelium-dependent), reduces platelet aggregation, and limits the flux of atherogenic plasma proteins into the artery wall (Fig. 5). The vasorelaxant effect of NO occurs through the activation of guanyl cyclase leading to the accumulation of cGMP [22]. The interaction between wine polyphenols and cell metabolism in the vascular tissue has been extensively investigated. These studies aimed to support for the beneficial effects of wine consumption in preventing cardiovascular diseases. In several animal models, the administration of red wine, grape juice, dealcoholized red wine and PAs extract from grape seeds attenuated the development of atherosclerotic lesions [23–26]. In a pig model, the consumption of RWPs induced a partial reduction of thickness of intimal proliferation even if not statistically significant [27]. Several processes of vascular reactivity seem to be influenced by wine ingredients. Red wine supplementation modulated haemostatic function and prevented thrombosis in experimental animals [10,28,29]. Wine polyphenols were shown to modulate blood pressure, promote vasodilatation, inhibit smooth muscle cell migration and proliferation, and inhibit platelet aggregation.

3.1. Red wine polyphenols and vasorelaxation

Red wines and grapes exhibit endothelium-dependent relaxation of blood vessels via enhanced generation and/or increased biological activity of NO, leading to the elevation of cGMP levels [30,31,35,36]. In vivo RWPs were shown to reduce blood pressure in normo and hypertensive rats [33,34,37]. The administration of purple grape juice improved the endothelium dependent, flow-mediated vasodilation in coronary artery disease patients with impaired endothelial function [38].

The amplitude of vasorelaxation changed as a function of the variability of wine constituents according to grape varieties, area of cultivation, and vinification methods. Consequently, the vasodilatory effect does not apply to all wines and the degree of vasorelaxation is correlated to the content and type of phenols. Endothelium-dependent relaxation was greatest for red wines produced “en barrique”, a procedure leading to high concentration of phenolic compounds [32]. A correlation between the phenolic content with vasodilatory effect was later confirmed by Burns et al. [21]. Sixteen red wines were selected to provide a range of origins, grape varieties, and vinification methods. The ability of the wines to act both as vasodilators ex vivo, and as antioxidants in vitro was strongly correlated with the phenolic content of wines. In addition, while the antioxidant...
activity was associated with different classes of phenols (gallic acid, resveratrol and catechins), vasodilatation activity was correlated only with the total content of ACs [21]. Investigations devoted to characterize the RWPs responsible for the endothelium-dependent relaxation activity [35,39–42] agree that monomeric catechins and simple phenols (benzoic acid, gallic acid and hydroxycinnamic acids) are devoid of effect. On the contrary, AC enriched fractions and oligomeric PAs (dimers, trimers and tetramers) were the active compounds. Threshold for relaxation by PAs oligomers was between 0.5 and 4 μg/ml [35,42]. Much higher concentration (>0.1 mg/l) were required for ACs [41]. The endothelium-dependent relaxation activity was lost when higher molecular weight polymers were assayed [41]. RWPs enhanced NO synthesis and cGMP accumulation only in the presence of functional endothelium. In denuded aortic rings, RWPs concentration 10³-fold higher was necessary to induce relaxation [43,45].

Besides NO, red wine affected the formation of other mediators of vascular tone, such as endothelium-derived hyperpolarizing factor [43] and prostacyclin [44]. In addition, the synthesis of a potent vasoconstrictor such as endothelin-1 is reduced by red wine in bovine aortic endothelial cells. The suppression occurred at transcriptional level. The decreased synthesis of endothelin-1 was associated with the inhibition of tyrosine kinase family of phosphorylating enzymes. The effect was correlated with the polyphenol content of red wine [45].

The mechanisms underlying NO-dependent vasorelaxation caused by RWPs were investigated [36,46,47]. All studies support for an increase in intracellular Ca²⁺ as the critical step for the activation of NO-synthase. RWPs increased cytosolic free Ca²⁺ by enhancing extracellular Ca²⁺ entry and by increasing Ca²⁺ mobilization from intracellular stores. The authors suggested that Ca²⁺ signaling pathways leading to NO production could involve the activation of multiple cellular targets (G-proteins, phospholipase C, tyrosine kinase), depending on the composition of the polyphenol mixture. In addition to increased NO synthase activity, RWPs may prolong the half-life and increase the bioavailability of NO, by reducing its degradation mediated by reactive oxygen species [27].

3.2. Modulation of gene expression by red wine polyphenols

All events previously described are responsible for a short-term response mediated by RWPs. Recent studies pointed out that polyphenolic compounds from several sources may also have long-term properties, as they are able to modulate gene expression in different cancer cell lines and in macrophages [48–50].

RWPs significantly increased NO synthase expression, acting on the promoter activity [51]. Thus, polyphenols not only activate the enzyme, but also increase its levels, which might lead to a long-lasting effect. Adhesion of leukocytes, monocytes and T-lymphocytes to the vascular endothelium is among the earliest events in inflammatory response and atherogenesis. Successively, accumulation of leukocytes in the arterial intima can make atherosclerotic plaque worsening. Adhesion process is facilitated by the action of endothelial-leucocyte adhesion molecules, which include intercellular adhesion molecule 1 (ICAM-1), E-selectin and vascular cell adhesion molecule 1 (VCAM-1). The expression of these molecules can be transcriptionally regulated by inflammatory cytokines such as interleukin-1 alpha and tumor necrosis factor alpha (TNF-α). It was reported that at 5 μg/ml, PAs extracted from grape seeds downregulated the TNF-α induced expression of VCAM-1.
in primary human umbilical endothelial cells, leading to a reduced adherence with leukocytes and T-cells [52,53]. Similar results were reported in one human study [54]. In systemic sclerosis patients, plasma levels of VCAM-1, ICAM-1 and P-selectin were found to be higher than in normal volunteers. The administration of 100 mg/day of PAs derived from grape seeds for 1 month attenuated the increased expression of these adhesion molecules.

Another study used ACs from blackberry administered to carrageenan-treated rats, a model of acute lung inflammation. ACs reduced the upregulation of ICAM-1 in lung tissue [55]. The AC mixture used in this study differs from that found in wine, since cyanidin-3-O-glucoside was predominant (80% of the total ACs); nevertheless, it might be expected that a similar behaviour by ACs occurs in red wines.

3.3. Red wine polyphenols and vascular smooth muscle cells

Vascular smooth muscle cells contribute to the pathogenesis of atherosclerotic lesions, in as much as their proliferation and migration are critical events for progressive intimal thickening and development of arterial wall sclerosis. At the site of the lesion formation, the most potent mitogenic and chemotactic agent for vascular smooth muscle cells is platelet-derived growth factor (PDGF) released by platelets, endothelial cells and vascular smooth muscle cells themselves. PDGF exerts its biological effects via activation of two subtypes of transmembrane receptor tyrosine kinases, termed α and β PDGF receptor. Ligand binding to the β receptor promotes the activation of signalling enzymes which are important for cell migration and proliferation. Activation of phosphatidylinositol 3′-kinase (PI3K) and mitogen-activated protein kinase (MAPK) pathways as response to PDGF is implicated in vascular smooth muscle cells motility [56–58].

Then, the effect of RWPs on the proliferation and the migration of cultured vascular smooth muscle cells has also been investigated [59,60]. RWPs (1–100 μg/ml) inhibited rat aortic smooth muscle cells proliferation and DNA synthesis. Polyphenol fractions of different molecular weights, = 200–400 for monomeric components (ACs, catechins and flavonoids) and 1600–2000 for oligomeric PAs, showed similar antiproliferative effects. Two distinct mechanisms have been postulated. One involves the downregulation of cyclin A gene expression, through the decreased expression of transcription factors ATF-1 and CREB (cAMP-responsive element). The second is associated with the downregulation of PI3K activity, which is known to interfere with cell-cycle regulation via the upregulation of p27kip1 acting as inhibitor of cyclin-dependent kinase [61,62]. In addition to proliferation, RWPs (1–100 μg/ml) inhibited vascular smooth muscle cell migration through the specific inhibition of PI3K and p38MAPK, but not through other MAPKs and ERK 1/2 (extracellular signal-regulated protein kinase 1 and 2). The attenuation of the signals leading to vascular smooth muscle cell proliferation and migration could also be the consequence of the inhibition of PDGF β receptor by RWPs [63].

Vascular endothelial growth factor (VEGF) released from vascular smooth muscle cells is a powerful endothelial mitogen and stimulates the expression of adhesion molecules and monocyte chemotactic protein-1 [64]. Red wine administered to cholesterol-fed rabbits inhibited the expression of monocyte chemotactic protein-1, but this effect was found also in animals receiving white wine [65]. The exposure of vascular smooth muscle cells to RWPs (≥3 μg/ml) markedly reduced the overexpression of VEGF induced by PDGF and other growth factors such as α-thrombin and transforming growth factor-β1 [66]. This effect was due to a reduced phosphorylation of p38MAPK, in agreement with previous findings [60]. Because the phosphorylation of p38MAPK and VEGF expression in vascular smooth muscle cells were stimulated in the presence of reactive oxygen species, the authors concluded that the inhibition of VEGF expression by RWPs involves their antioxidant properties.

3.4. Red wine polyphenols and platelet aggregation

Platelets contribute to the rate of development of atherosclerosis and coronary artery diseases through several mechanisms [67]. While it is widely demonstrated the antiaggregating effect of alcohol [68], flavonoids [69–72] and resveratrol [12], the literature survey provided only fragmentary and contradictory information about the contribution of ACs and PAs to the inhibition of platelet aggregation.

Demrow et al. [10] compared the effect of red and white wines (ml/kg), and grape juice (ml/kg) on platelet activity and thrombus formation in an in vivo dog model. Red wine and grape juice were effective as antiplatelet and antithrombotic compounds when administered intragastrically. Administration of white wine did not produce significant effects. Because the amount of ethanol necessary to produce the antiplatelet and antithrombotic activity is greatly reduced when red wine rather than pure ethanol was given, it was concluded that red wine contained platelet inhibitors in addition to ethanol. Rein et al. [73] reported the effects of dealcoholized red wine on platelet function in vitro and in vivo in healthy humans. In nonstimulated platelets, dealcoholized red wine added to whole blood induced platelet activation while suppressed the activation in response to epinephrine. A partial confirmation of these findings derives from the study by Russo et al. [74], who found in vitro a significant antiaggregating activity associated with a fraction of dealcoholized red wine containing procyanidins, ACs and catechins. No activity was associated to the other constituents: phenolic acids, flavonols, and polymeric PAs. However, dealcoholized red wine showed no effects when given orally to healthy subjects [73,75]. Other studies on
humans failed to show differences in platelet aggregation after red and white wine intake [76,77]. Further studies are needed to sort out these discrepancies.

4. Bioavailability of red wine polyphenols

Two-thirds of the total intake of polyphenols in the human diet has been estimated to be accounted by flavonoids, the most abundant being flavan-3-ols (catechins and PAs), ACs and their oxidation products [78]. Information about the absorption, distribution, metabolism and excretion of individual flavonoids in humans is scarce. Furthermore, most studies have been designed using flavonoids in the aglycone form rather than their glycosides, which predominate in plants. Because the term flavonoid is applied in general to a multitude of compounds, in this section we will focus on absorption and metabolism of ACs and PAs (dimers, trimers, oligomers and long chain polymers).

The question whether ACs are absorbed as free aglycone or in their glycoside form was approached for the first time by Paganga and Rice-Evans [79] who demonstrated the presence of ACs in human plasma, but without quantification. Later, several other studies confirmed that ACs are absorbed in the glycosilated form after oral consumption [80–85].

All studies performed in animals and humans agree that the bioavailability of ACs is limited [86–90]. In humans, plasma levels of total ACs are low, the order of magnitude being around 0.1 µM or less [82,83,91–93] and most of the ACs are excreted in urines during the first 4 h [83]. Between 1.5% and 5.1% of the ingested ACs were recovered in the urine of healthy subjects, within 12 h after consumption of 300 ml of wine containing around 218 mg of anthocyanosides. The AC levels in the urine reached a peak within 6 h from consumption [87]. More recent studies indicated that the amount of ACs excreted in urine was in much lower range, 0.04–0.1% of the dose [84,85]. After the ingestion of 400 ml of Lemberger wine (containing 270 mg of ACs) by healthy volunteers, red wine ACs were found in human plasma (C_{max} 42 ± 8 µg/l) and urine (cumulative excretion: 0.20–0.23% of the oral dose) as unchanged glucosides [93,94]. Other peaks detected in the urine samples showed similar absorption spectra as the ACs. These additional AC-like compounds may be metabolites of ACs, but the nature of the compounds was not elucidated [85,93]. Neither the aglycone nor glucoronide and/or sulphate derivatives were found in plasma and urines from subjects taking wine or other sources of ACs [80,83,88,91], but in some studies plasma and urines were not enzymatically treated. Recently, Wu et al. [95] reported methylated and glucoronidated AC metabolites in elderly women after ingestion of elderberry extract. Then the issue whether ACs undergo metabolism pre/post absorption requires further investigations. As ACs are bulky and polar molecules, it is expected that they are absorbed at gastro-intestinal level through a carrier-mediated system. Indeed, Passamonti et al. [90,96] reported that ACs are competitive inhibitors of bilitranslocase (K_{i} ranging from 1.4 to 22 µM), a carrier protein expressed on gastric mucosa [97] and in vivo experiments proved the involvement of the stomach in the absorption of grape anthocyanosides in rats. The structure–activity relationship revealed that monogluco-syl and diglucosyl ACs were better substrates than the corresponding aglycon [96]. The latter observation presents a further confirmation that glycosides are the preferred form for absorption. Furthermore, the ability of ACs to penetrate the gastric mucosa could be the explanation for the rapid appearance (≈ 5–20 min) of ACs in systemic plasma [83,88,89,91]. At the same time, the contribution of the upper part of the intestine in the process of absorption cannot be excluded.

Other questions that remain open concern the influence of alcohol, tartaric acid, a major organic acid in wine, and PAs to the efficiency of absorption. Results from the study by Bub et al. [88] tend to exclude the effect of alcohol on AC bioavailability, but the low number of subjects (6) is a limit to draw clearcut conclusions. On the other hand, tartaric acid increased the AUC of (+)-catechin metabolites in plasma of rats treated orally with a dose of 100 mg/kg of RWPs, suggesting that it can enhance the absorption and the bioavailability of polyphenols in red wine [98]. This observation needs to be confirmed in human studies.

In comparison with ACs, the bioavailability of PAs has received much less attention, maybe partially due to the complexity of structures, which makes their analysis difficult, and for the lack of commercially available pure standards. Few data are available in animals and in humans. Early studies were performed with radiolabelled PA extracts which did not allow discrimination between monomers, oligomers and/or metabolites. Feeding rats and mice with a radiolabelled mixture of grape PAs [largely dimers, plus (+)-catechin and (−)-epicatechin] permitted the identification in urines and faeces of some ill-defined PAs and of hippuric acid, ethylcatechol and various phenolic acids. The radioactivity was found in all the tissues of the animals within few hours after the ingestion [99,100]. Other data obtained from studies in chickens and sheep indicated that the radioactivity associated with PA polymers was completely recovered in the bowel and the faeces of the treated animals, thus showing a lack of absorption of these large molecules [101,102].

Procyanidin polymers were also shown to be degraded in vitro into low-molecular weight phenolic acids by a human colonic microflora grown anaerobically [103,104]. Dimers and trimers were uptaken at similar extent into Caco-2 cell layer, a well-established model for human absorption, while polymers adhered partially to the cell surface [105]. The fate of procyanidin dimers has been studied recently: procyanin B2 was found in plasma of subjects receiving 0.375 g cocoa/kg body weight, as beverage. The compound appeared in plasma as early as 0.5 h (16 nM). The maximal
concentration was reached by 2 h (41 nM). The single monomers and their metabolites were also detected indicating cleavage of the dimer in the digestive tract and bio-transformation [106]. The cleavage of procyanidin dimers B2 and B5 to the corresponding monomers at gastrointestinal level has been confirmed by other studies [107–109]. Monomers are then O-methylated and conjugated as glucoronides as described for other flavonoids [110]. In contrast, Donovan et al. [111] found that procyanidin B3, which is also present in wine, was not bioavailable: no trace of the compound was detected in plasma and urine after treating rats with a grape seed extract or procyanidin B3 alone. Nor procyanidins were cleaved to the bioavailable monomers. The reason for these discrepancies might reside in the experimental protocols and in the use of animal models. Rats were fasted before receiving procyanidin B2 [109]; in the study by Holt et al. [106], subjects consumed a flavanol-rich cocoa; in the study by Donovan et al. [111], rats were fed a standard semipurified diet supplemented with procyanidin B3 or the grape seed extract.

No studies thus far have addressed the issue of evaluating absorption and metabolism of PAs after wine drinking. It is then of utmost priority to eliminate this deficiency.

5. Conclusions

The interest in compounds present in red wine was stimulated by the claim that the regular consumption of this beverage could help in preventing cardiovascular diseases. In comparison with white wine, which does not share the same putative beneficial effects as red wine, the latter contains ACs and PAs in greater amounts. Then most of the studies reported in this review aimed to ascertain the contribution of these two classes of polyphenolic compounds to the overall effect of red wine. As shown by the large number of publications, ACs and PAs possess in vitro relevant biological activities and interact with many targets of the cell signalling pathways. However, the physiological significance of these findings depends on the assumption that ACs and PAs are bioavailable in the same chemical form as that used for the in vitro studies and can attain plasma levels as high as those used for in vitro studies. As reported in the previous paragraph, both assumptions are questionable. Even if most of the data were not obtained after wine drinking, few studies available about the plasma levels of ACs and PAs report values as 100 nM or lower, while concentrations used in vitro exceeded these values. In addition, no data are available to assess the distribution of ACs and PAs at the site of action in the unmetabolized form, as it would be required to mimic the situation of in vitro experiments. Among PAs, it is apparent that only dimers appear in plasma as the native compounds, but this observation needs to be confirmed in humans drinking wine. It is then imperative to acquire knowledge on the fate of red wine polyphenols after single dosing and in conditions simulating the regular consumption of this beverage.

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