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Cardioprotective effect of red wine and grape pomace

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ABSTRACT

Several studies have related moderate consumption of red wine with prevention of cardiovascular diseases (CVD). According to epidemiological studies, those regions with high consumption of red wine and a Mediterranean diet show a low prevalence of CVD. Such an effect has been attributed to phenolic compounds present in red wines. On the other hand, by-products obtained during winemaking are also a significant source of phenolic compounds but have been otherwise overlooked. The cardioprotective effect of red wine and its byproducts is related to their ability to prevent platelet aggregation, modify the lipid profile, and promote vasorelaxation. Phenolic content and profile seem to play an important role in these beneficial effects. Inhibition of platelet aggregation is dose-dependent and more efficient against ADP. The antioxidant capacity of phenolic compounds from red wine and its by-products, is involved in preventing the generation of ROS and the modification of the lipid profile, to prevent LDL oxidation. Phenolic compounds can also, modulate the activity of specific enzymes to promote NO production and vasorelaxation. Specific phenolic compounds like resveratrol are related to promote NO, and quercetin to inhibit platelet aggregation. Nevertheless, concentration that causes those effects is far from that in red wines. Synergic and additive effects of a mix of phenolic compounds could explain the cardioprotective effects of red wine and its byproducts.

1. Introduction

Moderate consumption of alcohol has been associated with the reduction of cardiovascular diseases (CVD) (Castaldo et al., 2019). This phenomenon called "French Paradox" is associated with a high consumption of vegetables, vegetable oils, seafood, dairy products, and a moderate consumption of red wine of the French and Mediterranean diets (Ndlovu et al., 2019). The high consumption of wine by the French has been proposed as the explanation for the low CVD mortality rates (Galinski et al., 2016), more particularly to the high content of phenolic compounds present in red wines (Ndlovu et al., 2019). Other authors have questioned whether such cardioprotective effect is caused by alcohol itself or by the adverse effect related to alcohol consumption. According to Ndlovu et al. (2019), moderate drinkers present a lower rate of heart attack compared with non-drinkers. On the other hand, although alcohol abuse has been associated with kidney, liver and brain damage, phenolic compounds from wine have been proven to act against such damage (Fiore et al., 2020).

The International Organisation of Vine and Wine (2019), reported that the world produced 77.8 millions tons of grapes in 2018; however the total of the production broke down like this: 57% was used for wine production, 36% for the table and 7% for drying. The winemaking process generates large amounts of grape pomace. It is estimated that every 100 kg of grapes used for winemaking yields 20–25 kg of grape pomace (Muñoz-Bernal et al., 2018). According to Gómez-Brandón et al. (2019), worldwide grape pomace production ranges from 10.5 to 13.1 million tons annually. Grape pomace is constituted by stems, seeds and peels (Vorobiev & Lebovka, 2020). The harvesting and winemaking processes are short, and a large quantity of grape pomace is generated in a very short time (Beres et al., 2017). Even though grape pomace can be used for animal feeding and compost, only a small amount is reused and its disposal raises environmental concerns while representing a high cost to the industry (Beres et al., 2017; Muñoz-Bernal et al., 2018). Grape pomace is rich in phenolic compounds since not all the phenolic

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compounds present in grapes are transferred to the wine during maceration (Lingua et al., 2016b). According to Beres et al. (2017), around 70% of phenolic compounds remains in grape pomace after the fermentation-maceration process. Lingua et al. (2016), reported that the main flavonols in grapes are quercetin, myricetin, kaempferol, and syringetin among others. These compounds are present in grape pomace as free aglycones, the result of acid hydrolysis during winemaking. For this reason, several investigations have focused on the recovery of these phenolic compounds and their potential use as antioxidant agents and in the food, cosmetic, and pharmaceutical industries (Beres et al., 2017).

2. Phenolic compounds of wine and grape pomace

Phenolic compounds can be classified into two main groups, flavonoids and non-flavonoids (Haseeb et al., 2019; Salehi et al., 2019). Flavonoids are composed of two phenolic rings (A and B) linked by a pyran ring (C). Flavonoids are grouped according to the oxidation degree of ring C (Faggio et al., 2017) into flavanones, flavones, isoflavones, flavonols, flavan-3-ols, anthocyanins and proanthocyanins. Some examples of non-flavonoids are hydroxybenzoic acids like gallic acid; hydroxycinnamic acids like caffeic acid, and stilbenes (resveratrol) (Goufo et al., 2020; Murkovic, 2015).

A representative structure of the principal phenolic compounds present in grapes, wine, and grape pomace are represented in Fig. 1. The main difference among flavonoids relies on the substitution pattern of ring C. Flavonols have a double bond between C2 and C3 and a carbonyl group at C4 and are commonly glycosylated at C3 (Murkovic, 2015). Flavan-3-ols, compared with flavonols, lack a double bond, resulting in two chiral carbons that allow the attachment of different stereoisomers. Flavan-3-ols are commonly hydroxylated at C4, C3, C5, and C7 (Goufo et al., 2020), and in foods are non-glycosylated (Brenes et al., 2016). Anthocyanins, responsible for providing red wine with its hue, are the glycosidic form of anthocyanidins. They are normally glycosylated at C3, C5 and C7 (Murkovic, 2015).

Phenolic content and composition in wine and grape pomace depend on several factors such as growth region, climate, soil, grape variety, and

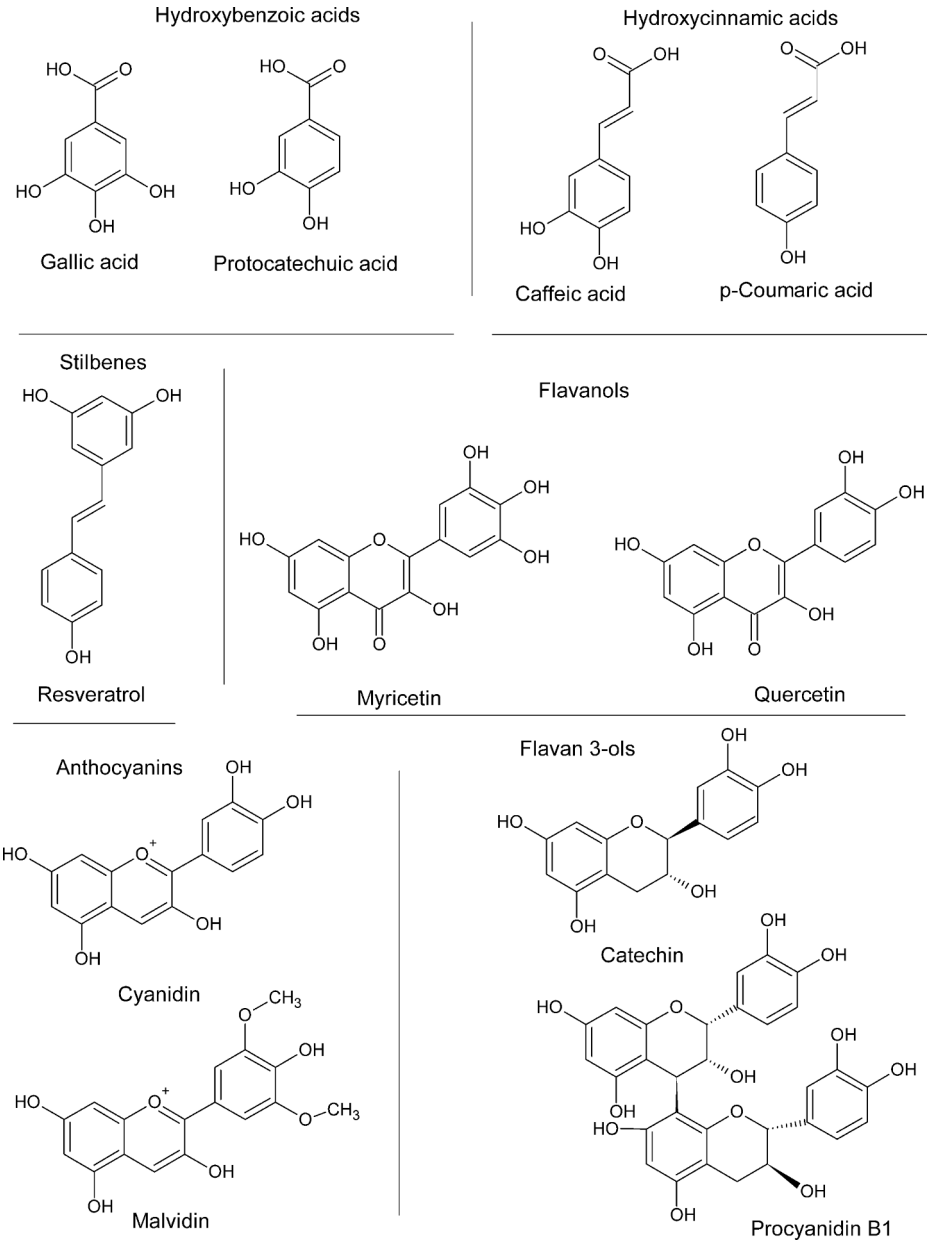

Fig. 1. Principal phenolic compounds present in wine and grape pomace.

winemaking process (Muñoz-Bernal et al., 2020). Several authors have studied the phenolic profile of wines. Non-flavonoids are present in grape skins and are extracted into wine at the beginning of the winemaking process. The main types of acid reported in red wine are hydroxybenzoic and hydroxycinnamic. Of the former, the most present is gallic, whereas the latter is mostly represented by caffeic and *p*-coumaric acids and their derivatives. Stilbene resveratrol is another non-flavonoid compound commonly reported in wines. The most characteristic flavonoids in grapes, wine, and grape pomace are flavonols (myricetin, quercetin and it glycosylated forms), anthocyanins and flavan-3-ols (monomeric and polymeric) (Salehi et al., 2019). The main anthocyanins reported for *Vitis vinifera* L. are glycosides or acylated forms of delphinidin, cyanidin, petunidin, peonidin and malvidin. Acylation is mainly done with either acetic acid, *p*-coumaric acid or caffeic acid. Also, some anthocyanin-derived pigments are reported in wines, knowns as vitisins. These compounds are not transferred during the winemaking process, instead, they are formed by the reaction between anthocyanins and yeast metabolites such as acetaldehyde, or between other phenolic compounds like hydroxycinnamic acids (Lingua et al., 2016b). The principal flavan-3-ols reported in wines are catechin and epicatechin. Other phenolic compounds such as phenolic acids, tyrosol and some procyanidins have been less frequently reported in wine (Ivanova-Petropulos et al., 2015; Lukić et al., 2019; Panceri et al., 2015).

Table 1 shows the principal phenolic compounds reported in red wines from different growing regions and grape varieties. It can be observed that gallic acid is present in highest amounts compared to vanillic and protocatechuic acids. On the other hand, caftaric, coutaric and fertaric acids are reported in highest content compared to their respective original hydroxycinnamic acid. Piceid, a glycosylated form of resveratrol has also been reported in higher content compared to resveratrol. Similar trend has been observed in flavanols. As can be observed in Table 1, flavonols derivatives are more abundant in red wine than their respective aglycones. From the five anthocyanins found in red wines, malvidin and its derivatives presented the highest content. Epicatechin and catechin as well as procyanidin B1 and B2 are the flavan 3-ols with highest content reported in red wines.

During the winemaking process, phenolic compounds of grapes are partially transferred to wine, however, due to the hydrophobic quality or hydrogen bonds, phenolic compounds remain attached to the skin of the grape's lignin-polysaccharide matrix (Nayak et al., 2018). Grape pomace is comprised by skins, seeds, and stems (Zhao et al., 2020). The primary hydroxybenzoic and hydroxycinnamic acids reported in grape pomace are gallic acid and caffeic acid respectively. Resveratrol and its glycoside form piceid are other non-flavonoids often reported in grape pomace. Table 2 shows the phenolic profile of grape pomace.

From Table 2 it can be observed that there are differences in the phenolic profile of grape pomace, compared with the phenolic profile from red wines. The main differences can be noticed in the presence of ethyl gallate and syringic acid. In the case of hydroxycinnamic acids, caffeic, *p*-coumaric acid and ferulic acids derivatives present higher abundance compared to wines. It has been reported the presence of phenylethanoids such as hydroxytyrosol and tyrosol and astilbin a flavanone in grape pomace. Flavonols and anthocyanins presented similar profiles compared to wines, and as observed in wines flavonols derivatives have been reported in higher amounts than their aglycone form. Flavan 3-ols is the family that presents more differences. Procyanidin B1, B2 and B3 present higher content than those reported in red wines. This is attributed to the presence of seeds and stems from grape pomace.

Regarding the content of flavonoids, flavan-3-ols represent the largest proportion of phenolic compounds in grape pomace (Brenes et al., 2016). Interestingly, each fraction of grape pomace is predominantly composed of a flavonoid group; anthocyanins in skins, flavonols in seeds, and flavan 3-ols in skin and seeds (Beres et al., 2017; Galanakis, 2017). The main anthocyanins reported are the glycosides of

Table 1
Phenolic compounds identified in wine and grape pomace.

Phenolic compounds	Wine variety	Content range (mg/L)	References
Hydroxybenzoic acids			
Gallic acid	Pinotage, Teran, Plavac Mali, Merlot, Cabernet Sauvignon, Carménère, Malbec, Syrah, Vranec, Crljenak kaštelanski, Tempranillo, Pinot Noir, Tannat	6.86–84.10	Del-Castillo-Alonso et al., 2020; Generalić Mekinić et al., 2019; Ivanova-Petropulos et al., 2015; Lingua et al., 2018; Lukić et al., 2019; Panceri et al., 2015; Rutan et al., 2018; Valentin et al., 2020; Vidal et al., 2018
Vanillic acid	Teran, Plavac Mali, Merlot, Cabernet Sauvignon	0.46–13.42	Lukić et al., 2019; Panceri et al., 2015
Protocatechuic acid	Merlot, Cabernet Sauvignon, Crljenak kaštelanski, Tempranillo, Tannat	0.60–26.20	Del-Castillo-Alonso et al., 2020; Generalić Mekinić et al., 2019; Panceri et al., 2015; Vidal et al., 2018
p-hydroxybenzoic acid	Teran, Plavac Mali, Merlot, Cabernet Sauvignon, Crljenak kaštelanski,	0.42–6.59	Generalić Mekinić et al., 2019; Lukić et al., 2019
Ellagic acid	Teran, Plavac Mali, Merlot, Cabernet Sauvignon	1.06–4.20	Lukić et al., 2019; Panceri et al., 2015
Hydroxycinnamic acids			
Caftaric acid	Pinotage, Teran, Plavac Mali, Merlot, Cabernet Sauvignon, Syrah, Vranec, Tempranillo, Pinot Noir, Tannat	7.47–64.80	Del-Castillo-Alonso et al., 2020; Ivanova-Petropulos et al., 2015; Lingua et al., 2018; Lukić et al., 2019; Panceri et al., 2015; Rutan et al., 2018; Vidal et al., 2018
Caffeic acid	Pinotage, Teran, Plavac Mali, Merlot, Cabernet Sauvignon, Carménère, Malbec, Syrah, Vranec, Pinot Noir, Tannat	0.47–58.90	Ivanova-Petropulos et al., 2015; Lingua et al., 2018; Lukić et al., 2019; Panceri et al., 2015; Rutan et al., 2018; Valentin et al., 2020; Vidal et al., 2018
Coutaric acid	Pinotage, Teran, Plavac Mali, Merlot, Cabernet Sauvignon, Syrah, Vranec, Tempranillo, Pinot Noir	2.70–19.30	Del-Castillo-Alonso et al., 2020; Ivanova-Petropulos et al., 2015; Lingua et al., 2018; Lukić et al., 2019; Rutan et al., 2018
p-Coumaric acid	Vranec, Cabernet Sauvignon, Merlot, Tannat	0.50–92.00	Ivanova-Petropulos et al., 2015; Panceri et al., 2015; Vidal et al., 2018
Ferulic acid	Teran, Plavac Mali, Merlot, Cabernet	0.04–21.12	Lukić et al., 2019; Panceri et al.,

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Table 1 (*continued*)

Phenolic compounds	Wine variety	Content range (mg/L)	References
	Sauvignon, Carménère, Malbec		2015; Valentin et al., 2020
Fertaric acid	Syrah, Vranec, Cabernet Sauvignon, Merlot, Tannat	2.81–20.60	Ivanova-Petropulos et al., 2015; Lingua et al., 2018; Vidal et al., 2018
Stilbenes			
Resveratrol	Carménère, Malbec, Vranec, Cabernet Sauvignon, Merlot, Crljenak kaštelanski, Tempranillo, Pinot Noir	0.02–21.30	Del-Castillo-Alonso et al., 2020; Generalić Mekinić et al., 2019; Ivanova-Petropulos et al., 2015; Panceri et al., 2015; Rutan et al., 2018; Valentin et al., 2020
Piceid	Teran, Plavac Mali, Merlot, Cabernet Sauvignon, Vranec	0.78–48.50	Ivanova-Petropulos et al., 2015; Lukić et al., 2019
Flavonols			
Quercetin	Teran, Plavac Mali, Merlot, Cabernet Sauvignon, Carménère, Malbec, Syrah, Petit Verdot, Vranec, Crljenak kaštelanski, Tempranillo, Pinot Noir	0.27–45.86	Del-Castillo-Alonso et al., 2020; Generalić Mekinić et al., 2019; Ivanova-Petropulos et al., 2015; Lingua et al., 2018; Lukić et al., 2019; Panceri et al., 2015; Pérez-Navarro et al., 2018; Rutan et al., 2018; Valentin et al., 2020
Quercetin 3-glucoside	Teran, Plavac Mali, Merlot, Cabernet Sauvignon, Petit Verdot, Vranec, Tempranillo, Pinot Noir	0.34–8.11	Del-Castillo-Alonso et al., 2020; Ivanova-Petropulos et al., 2015; Lukić et al., 2019; Pérez-Navarro et al., 2018
Quercetin 3-glucuronide	Teran, Plavac Mali, Merlot, Cabernet Sauvignon, Syrah, Petit Verdot, Vranec, Tempranillo	0.34–171.54	Del-Castillo-Alonso et al., 2020; Ivanova-Petropulos et al., 2015; Lingua et al., 2018; Lukić et al., 2019; Pérez-Navarro et al., 2018;
Isorhamnetin	Syrah, Vranec, Cabernet Sauvignon, Merlot	0.5–4.15	Ivanova-Petropulos et al., 2015; Lingua et al., 2018
Kaempferol	Plavac Mali, Merlot, Cabernet Sauvignon, Carménère, Malbec, Syrah, Petit Verdot, Vranec, Tempranillo	0.26–6.38	Del-Castillo-Alonso et al., 2020; Ivanova-Petropulos et al., 2015; Lingua et al., 2018; Lukić et al., 2019; Panceri et al., 2015; Pérez-Navarro et al., 2018; Valentin et al., 2020
Kaempferol 3-glucoside	Petit Verdot, Vranec, Cabernet	0.01–3.97	Del-Castillo-Alonso et al.,

Table 1 (*continued*)

Phenolic compounds	Wine variety	Content range (mg/L)	References
	Sauvignon, Merlot, Vranec, Tempranillo		2020; Ivanova-Petropulos et al., 2015; Pérez-Navarro et al., 2018
Myricetin	Teran, Plavac Mali, Merlot, Cabernet Sauvignon, Carménère, Malbec, Syrah, Vranec, Tempranillo	0.09–16.80	Del-Castillo-Alonso et al., 2020; Ivanova-Petropulos et al., 2015; Lingua et al., 2018; Lukić et al., 2019; Panceri et al., 2015; Valentin et al., 2020
Myricetin 3-glucoside	Syrah, Petit Verdot, Vranec, Cabernet Sauvignon, Merlot, Tempranillo	0.95–44.93	Del-Castillo-Alonso et al., 2020; Ivanova-Petropulos et al., 2015; Lingua et al., 2018; Pérez-Navarro et al., 2018
Myricetin 3-glucuronide	Syrah, Vranec, Cabernet Sauvignon, Merlot, Tempranillo	1.00–4.33	Del-Castillo-Alonso et al., 2020; Ivanova-Petropulos et al., 2015; Lingua et al., 2018
Laricitrin	Teran, Plavac Mali, Merlot, Cabernet Sauvignon, Syrah, Petit Verdot, Vranec	0.47–9.10	Ivanova-Petropulos et al., 2015; Lingua et al., 2018; Lukić et al., 2019; Pérez-Navarro et al., 2018
Laricitrin 3-glucoside	Syrah, Petit Verdot, Vranec, Cabernet Sauvignon, Merlot, Tempranillo	0.65–31.18	Del-Castillo-Alonso et al., 2020; Ivanova-Petropulos et al., 2015; Lingua et al., 2018; Pérez-Navarro et al., 2018
Syringetin	Vranec, Cabernet Sauvignon, Merlot, Tempranillo	0.20–2.14	Del-Castillo-Alonso et al., 2020; Ivanova-Petropulos et al., 2015
Syringetin 3-glucoside	Syrah, Petit Verdot, Vranec, Cabernet Sauvignon, Merlot, Tempranillo	2.20–28.20	Del-Castillo-Alonso et al., 2020; Ivanova-Petropulos et al., 2015; Lingua et al., 2018; Pérez-Navarro et al., 2018
Anthocyanins			
Delphinidin 3-glucoside	Teran, Plavac Mali, Merlot, Cabernet Sauvignon, Carménère, Malbec, Syrah, Petit Verdot, Vranec, Crljenak kaštelanski, Tempranillo, Pinot Noir, Tannat	0.11–43.15	Del-Castillo-Alonso et al., 2020; Generalić Mekinić et al., 2019; Ivanova-Petropulos et al., 2015; Lingua et al., 2018; Lukić et al., 2019; Panceri et al., 2015; Pérez-Navarro et al., 2018; Rutan et al., 2018; Valentin et al., 2020; Vidal et al., 2018

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Table 1 (*continued*)

Phenolic compounds	Wine variety	Content range (mg/L)	References
Cyanidin 3-glucoside	Teran, Plavac Mali, Merlot, Cabernet Sauvignon, Carménère, Malbec, Petit Verdot, Vranec, Crljenak kaštelanski, Tempranillo, Pinot Noir, Tannat	0.48–8.29	Del-Castillo-Alonso et al., 2020; Generalić Mekinić et al., 2019; Ivanova-Petropulos et al., 2015; Lukić et al., 2019; Panceri et al., 2015; Pérez-Navarro et al., 2018; Rutan et al., 2018; Valentin et al., 2020; Vidal et al., 2018
Petunidin 3-glucoside	Teran, Plavac Mali, Merlot, Cabernet Sauvignon, Carménère, Malbec, Syrah, Petit Verdot, Vranec, Crljenak kaštelanski, Tempranillo, Pinot Noir, Tannat	3.04–50.2	Del-Castillo-Alonso et al., 2020; Generalić Mekinić et al., 2019; Ivanova-Petropulos et al., 2015; Lingua et al., 2018; Lukić et al., 2019; Pérez-Navarro et al., 2018; Rutan et al., 2018; Valentin et al., 2020; Vidal et al., 2018
Peonidin 3-glucoside	Teran, Plavac Mali, Merlot, Cabernet Sauvignon, Carménère, Malbec, Syrah, Petit Verdot, Vranec, Crljenak kaštelanski, Tempranillo, Tannat	1.73–37.00	Del-Castillo-Alonso et al., 2020; Generalić Mekinić et al., 2019; Ivanova-Petropulos et al., 2015; Lingua et al., 2018; Lukić et al., 2019; Panceri et al., 2015; Pérez-Navarro et al., 2018; Rutan et al., 2018; Valentin et al., 2020; Vidal et al., 2018
Malvidin 3-glucoside	Teran, Plavac Mali, Merlot, Cabernet Sauvignon, Carménère, Malbec, Syrah, Petit Verdot, Vranec, Crljenak kaštelanski, Tempranillo, Pinot Noir, Tannat	21.63–244.00	Del-Castillo-Alonso et al., 2020; Generalić Mekinić et al., 2019; Ivanova-Petropulos et al., 2015; Lingua et al., 2018; Lukić et al., 2019; Panceri et al., 2015; Pérez-Navarro et al., 2018; Rutan et al., 2018; Valentin et al., 2020; Vidal et al., 2018
Delphinidin 3-acetylglcusodide	Teran, Plavac Mali, Merlot, Cabernet Sauvignon, Syrah, Petit Verdot, Vranec, Crljenak kaštelanski, Tempranillo, Tannat	0.40–4.17	Del-Castillo-Alonso et al., 2020; Generalić Mekinić et al., 2019; Ivanova-Petropulos et al., 2015; Lingua et al., 2016; Lukić et al., 2019; Pérez-Navarro et al., 2018; Vidal et al., 2018
Cyanidin 3-acetylglucoside	Teran, Plavac Mali, Merlot, Cabernet Sauvignon, Petit Verdot, Crljenak kaštelanski, Tempranillo, Tannat	0.15–1.86	Del-Castillo-Alonso et al., 2020; Generalić Mekinić et al., 2019; Lukić et al., 2019; Pérez-Navarro et al., 2018; Vidal et al., 2018
Petunidin 3-acetylglucoside	Teran, Plavac Mali, Merlot, Cabernet Sauvignon, Syrah, Petit Verdot, Vranec, Crljenak kaštelanski, Tempranillo, Tannat	0.47–8.79	Del-Castillo-Alonso et al., 2020; Generalić Mekinić et al., 2019; Ivanova-Petropulos et al., 2015; Lingua et al., 2018; Lukić et al., 2019; Pérez-Navarro et al., 2018; Vidal et al., 2018
Peonidin 3-acetylglucoside	Teran, Plavac Mali, Merlot, Cabernet Sauvignon, Syrah, Petit Verdot, Vranec, Crljenak kaštelanski, Tempranillo, Tannat	0.58–11.89	Del-Castillo-Alonso et al., 2020; Generalić Mekinić et al., 2019; Ivanova-Petropulos et al., 2015; Lingua et al., 2018; Lukić et al., 2019; Pérez-Navarro et al., 2018; Vidal et al., 2018
Malvidin 3-acetylglucoside	Teran, Plavac Mali, Merlot, Cabernet Sauvignon, Syrah, Petit Verdot, Vranec, Crljenak kaštelanski, Tempranillo, Tannat	31.08	Del-Castillo-Alonso et al., 2020; Generalić Mekinić et al., 2019; Ivanova-Petropulos et al., 2015; Lingua et al., 2018; Lukić et al., 2019; Pérez-Navarro et al., 2018; Vidal et al., 2018
Delphinidin 3-p-coumaroyl-glucoside	Teran, Plavac Mali, Merlot, Cabernet Sauvignon, Petit Verdot, Vranec, Tempranillo, Tannat	1.04–166.35	Del-Castillo-Alonso et al., 2020; Ivanova-Petropulos et al., 2015; Lukić et al., 2019; Pérez-Navarro et al., 2018; Vidal et al., 2018
Cyanidin 3-p-coumaroyl-glucoside	Teran, Plavac Mali, Merlot, Cabernet Sauvignon, Petit Verdot, Vranec, Crljenak kaštelanski, Tempranillo, Tannat	0.26–11.00	Del-Castillo-Alonso et al., 2020; Generalić Mekinić et al., 2019; Ivanova-Petropulos et al., 2015; Lukić et al., 2019; Pérez-Navarro et al., 2018; Vidal et al., 2018
Petunidin 3-p-coumaroyl-glucoside	Teran, Plavac Mali, Merlot, Cabernet Sauvignon, Syrah, Petit Verdot, Vranec, Crljenak kaštelanski, Tempranillo, Tannat	0.26–5.32	Del-Castillo-Alonso et al., 2020; Generalić Mekinić et al., 2019; Ivanova-Petropulos et al., 2015; Lingua et al., 2018; Lukić

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Table 1 (*continued*)

Phenolic compounds	Wine variety	Content range (mg/L)	References
			et al., 2019; Pérez-Navarro et al., 2018; Vidal et al., 2018
Peonidin 3-p-coumaroyl-glucoside	Teran, Plavac Mali, Merlot, Cabernet Sauvignon, Syrah, Petit Verdot, Vranec, Crljenak kaštelanski, Tempranillo, Tannat	0.50–10.96	Del-Castillo-Alonso et al., 2020; Generalić Mekinić et al., 2019; Ivanova-Petropulos et al., 2015; Lingua et al., 2018; Lukić et al., 2019; Pérez-Navarro et al., 2018; Vidal et al., 2018
Malvidin 3-p-coumaroyl-glucoside	Teran, Plavac Mali, Merlot, Cabernet Sauvignon, Syrah, Petit Verdot, Vranec, Crljenak kaštelanski, Tempranillo, Tannat	2.24–86.47	Del-Castillo-Alonso et al., 2020; Generalić Mekinić et al., 2019; Ivanova-Petropulos et al., 2015; Lingua et al., 2018; Lukić et al., 2019; Pérez-Navarro et al., 2018; Vidal et al., 2018
Flavan 3-ols			
Catechin	Teran, Plavac Mali, Merlot, Cabernet Sauvignon, Carménère, Malbec, Syrah, Petit Verdot, Vranec, Crljenak kaštelanski, Tempranillo, Pinot Noir, Tannat	5.82–288.00	Del-Castillo-Alonso et al., 2020; Generalić Mekinić et al., 2019; Ivanova-Petropulos et al., 2015; Lingua et al., 2018; Lukić et al., 2019; Panceri et al., 2015; Pérez-Navarro et al., 2018; Rutan et al., 2018; Valentin et al., 2020; Vidal et al., 2018
Epicatechin	Teran, Plavac Mali, Merlot, Cabernet Sauvignon, Carménère, Malbec, Syrah, Petit Verdot, Crljenak kaštelanski, Tempranillo, Pinot Noir, Tannat	4.60–196.00	Del-Castillo-Alonso et al., 2020; Generalić Mekinić et al., 2019; Lingua et al., 2018; Lukić et al., 2019; Panceri et al., 2015; Pérez-Navarro et al., 2018; Rutan et al., 2018; Valentin et al., 2020; Vidal et al., 2018
Epigallocatechin	Teran, Plavac Mali, Merlot, Cabernet Sauvignon, Petit Verdot, Tempranillo, Tannat	1.16–12.80	Del-Castillo-Alonso et al., 2020; Lukić et al., 2019; Pérez-Navarro et al., 2018; Vidal et al., 2018
Gallocatechin	Teran, Plavac Mali, Merlot, Cabernet Sauvignon, Petit Verdot, Tannat	0.12–16.35	Del-Castillo-Alonso et al., 2020; Lukić et al., 2019; Pérez-Navarro et al., 2018; Vidal et al., 2018
Catechin gallate	Petit Verdot, Tempranillo	0.04–0.11	Del-Castillo-Alonso et al., 2020; Pérez-Navarro et al., 2018
Epicatechin gallate	Petit Verdot, Tempranillo, Tannat	0.32–4.70	Del-Castillo-Alonso et al., 2020; Pérez-Navarro et al., 2018; Vidal et al., 2018
Procyanidin B1	Teran, Plavac Mali, Merlot, Cabernet Sauvignon, Syrah, Petit Verdot, Vranec, Tempranillo	5.40–90.96	Del-Castillo-Alonso et al., 2020; Ivanova-Petropulos et al., 2015; Lingua et al., 2018; Lukić et al., 2019; Pérez-Navarro et al., 2018
Procyanidin B2	Teran, Plavac Mali, Merlot, Cabernet Sauvignon, Petit Verdot, Vranec, Tempranillo	0.90–46.78	Del-Castillo-Alonso et al., 2020; Ivanova-Petropulos et al., 2015; Lukić et al., 2019; Pérez-Navarro et al., 2018

delphinidin, cyanidin, petunidin, peonidin and malvidin. In the case of flavonols, the main reported forms are quercetin, kaempferol, rutin and myricetin and its glycosylated forms. Flavan-3-ols catechin, epicatechin, gallocatechin and epigallocatechin are usually reported in grapes and their derivatives as a good source of this type of flavonoids. The polymeric forms of catechin and epicatechin, procyanidins, are also found distributed throughout wine and grape pomace: procyanidin B1, B2, B4 and others.

3. Cardioprotective effect of wine

Table 3 summarizes the studies that have investigated the cardioprotective effect of wine. In spite of these studies, the cardioprotective effect of wine has not been fully disclosed yet. However, it has been proposed that this effect could the result of platelet aggregation inhibition, decrease in LDL-C oxidation, reduction of endothelin synthesis, and increase in endothelial-type NO-synthase expression and activity (de Moura et al., 2004).

Platelets play an important role in the healing process of sealing wounds by platelet plug and the arrest of bleeding (Adili et al., 2018). But their excessive activation is involved in pathological process like strokes and myocardial infarction. Platelets are also involved in the inflammatory process by releasing cytokines and prostanoids (Bonechi et al., 2017; Faggio et al., 2017). Several agonists and adhesion proteins mediate platelet reactivity. The cell membrane of platelets contains a large variety of receptors involved in activating platelets and adhesive receptors of damaged cells and other platelets to form a thrombus (Clemetson & Clemetson, 2019).

Platelet aggregation is activated by many factors such as thrombin, adenosine diphosphate (ADP), adenosine triphosphate (ATP) and collagen (Lee et al., 2019). G proteins are transmembrane receptors that mediate the response of platelets and are constituted by three subunits α, β and γ (Lee et al., 2019) G proteins cause an increase of calcium ($[Ca^{+2}]$), phospholipase C (PLC), and diacylglycerol (DAG). The increase of $[Ca^{+2}]$ in the cytosol can be generated by the production of inositol triphosphate (IP3) and DAG. Such increase releases arachidonic acid (AA) that is, in turn, converted into thromboxane A_2 (TXA_2) by cicloxygenase-1 (COX-1) in platelets, leading to platelet activation and

Table 2
Principal phenolic compounds identified in winemaking byproducts.

Phenolic compounds	Grape variety	Content Range (μg/g D. W.)	Content Range (μg/g Extract)	References
Hydroxybenzoic acids				
Gallic acid	Merlot[1], Cabernet Sauvignon[1], Tempranillo[1], Cabernet Franc[1], Malbec[1], Pinot Noir[1], Chambourcin[3], Norton[3], Petit Verdot[1], Tinta Cão[3]	1: 0.22–530.78	1: 2.86–12.24	Bender et al., 2020; Fontana et al., 2017; Gerardi et al., 2020; Gil-Sánchez et al., 2017; Kadouh et al., 2016; Lingua et al., 2016a; Reis et al., 2016; Wang et al., 2017
			3: 45.00–2420.00	
Methylgallic acid	Tempranillo [1]	1: 7.19		Gerardi et al., 2020
Ellagic acid	Tempranillo[1,3]	3: 335.45	1: 4130.00–8570.00	Gil-Sánchez et al., 2017; Wang et al., 2017
Ethyl gallate	Syrah[3], Merlot[3], Cabernet Sauvignon[3], Tempranillo[1]	1: 5.5		Lingua et al., 2016a; Syed et al., 2017
		3: 28.99–53.04		
Vanillic acid	Tempranillo[1,3], Tintilla de Rota[1], Cabernet Sauvignon[1], Petit Verdot[1], Syrah[1], Pinot Noir[1]	1: 0.72–53.31		Carmona-Jiménez et al., 2018; Gerardi et al., 2020; Reis et al., 2016; Wang et al., 2017
		3: 102.48		
Protocatechuic acid	Tempranillo[1], Tintilla de Rota[1], Cabernet Sauvignon[1], Petit Verdot [1], Syrah[1]	1: 18.10–598.55		Carmona-Jiménez et al., 2018; Gerardi et al., 2020; Wang et al., 2017
p-Hydroxybenzoic acid	Tempranillo[3],	3: 49.99		Wang et al., 2017
Gentisic acid	Tempranillo[1]	1: 27.90		Gerardi et al., 2020
Syringic acid	Tempranillo[1], Merlot[1,3], Cabernet Sauvignon[1,3], Cabernet Franc[1,3], Malbec[1,3], Tintilla de Rota[1], Petit Verdot[1], Syrah[1]	1: 0.24–202.53	1: 3.08	Bender et al., 2020; Carmona-Jiménez et al., 2018; Fontana et al., 2017; Gerardi et al., 2020; Wang et al., 2017
		3: 112.75	3: 697.00–6665.00	
Hydroxycinnamic acids				
Caftaric acid	Syrah[3], Merlot[3], Cabernet Sauvignon[3], Tempranillo[3]	3: 0.25–91.05		Lingua et al., 2016a; Wang et al., 2017
Coutaric acid	Syrah[3], Merlot[3], Cabernet Sauvignon[3]	3: 1.38–5.41		Lingua et al., 2016a
Fertaric acid	Tempranillo[3]	3: 120.06		Wang et al., 2017
Caffeic acid	Syrah[1], Merlot[1,3], Cabernet Sauvignon[1,3], Cabernet Franc[1,3], Malbec[1,3], Tempranillo[1], Tintilla de Rota[1], Petit Verdot[1], Chambourcin[3], Norton[3], Tinta Cão[3]	1: 7.70–57.82	3: 5.00–2000.00	Carmona-Jiménez et al., 2018; Fontana et al., 2017; Gerardi et al., 2020; Kadouh et al., 2016; Lingua et al., 2016a; Reis et al., 2016
***p*-Coumaric acid**	Merlot[3], Cabernet Sauvignon[3], Cabernet Franc[3], Malbec[3], Pinot Noir[1], Chambourcin[3], Norton[3], Petit Verdot[3], Syrah[3], Tinta Cão[3]	1: 0.40	3: 18.00–350.00	Fontana et al., 2017; Kadouh et al., 2016; Reis et al., 2016
Ferulic acid	Merlot[1,3], Cabernet Sauvignon[1,3], Cabernet Franc[1,3], Malbec[1,3], Tempranillo[1], Tintilla de Rota[1], Petit Verdot[1], Syrah[1], Pinot Noir [1]	1: 0.30–21.30	3: 12.00–41.00	Carmona-Jiménez et al., 2018; Fontana et al., 2017; Gerardi et al., 2020; Reis et al., 2016
Chlorogenic acid	Tempranillo[1], Tintilla de Rota[1], Petit Verdot[1], Syrah[1]	1: 20.05–30.79		Carmona-Jiménez et al., 2018
Stilbenes				
Resveratrol	Merlot[1,3], Cabernet Sauvignon[1,3], Cabernet Franc[1,3], Malbec[1,3], Feteasc̆a Neagr̆a[1], Pinot Noir[1], Chambourcin[3], Norton[3], Petit Verdot[3], Tinta Cão[3], Tempranillo[1]	1: 0.58–4.58	3: 0.07–328.00	Balea et al., 2018; Fontana et al., 2017; Gerardi et al., 2020; Kadouh et al., 2016; Reis et al., 2016
Piceid	Feteasc̆a Neagr̆a[1], Tempranillo[1]	1: 0.64–14.31		Balea et al., 2018; Gerardi et al., 2020
Phenylethanoids				
Hydroxytyrosol	Cabernet Sauvignon[3], Cabernet Franc[3], Malbec[3]		3: 4.00–328.00	Fontana et al., 2017
Tyrosol	Merlot[1,3], Cabernet Sauvignon[1,3], Cabernet Franc[1,3], Malbec[1,3], Tempranillo[1], Tintilla de Rota[1], Petit Verdot[1], Syrah[1]	1: 37.03–264.22	3: 17.00–285.00	Carmona-Jiménez et al., 2018; Fontana et al., 2017
Flavonols				
Quercetin	Syrah[2,3], Merlot[2,3], Cabernet Sauvignon[2,3], Tempranillo[1], Cabernet Franc[2,3], Malbec[2,3], Pinot Noir[1,2], Marselan[2,3], Chardonnay[2,3]	1: 0.30–2.60	3: 218.00–1695.00	El Achkar et al., 2017; Fontana et al., 2017; Gil-Sánchez et al., 2017; Lingua et al., 2016a; Reis et al., 2016; Wang et al., 2017
		2: 9.00–121.60		
		3: 87.53–251.06		
Quercetin 3-glucoside	Syrah[3], Merlot[3], Cabernet Sauvignon[3], Tempranillo[3], Chambourcin[3], Norton[3], Petit Verdot[3], Tinta Cão[3]	3:16.05–26.53	3: 0.09–3.90	Kadouh et al., 2016; Lingua et al., 2016a; Wang et al., 2017
Quercetin 3-glucuronide	Syrah[1,3], Merlot[1,3], Cabernet Sauvignon[1,3], Tempranillo[1,3], Tintilla de Rota[1], Petit Verdot[1]	1: 6.97–22.20	3: 230.00–240.00	Carmona-Jiménez et al., 2018; Lingua et al., 2016a; Wang et al., 2017
		3: 31.92–81.42		
Rutin	Tempranillo[3], Chambourcin[3], Merlot[2,3], Norton[3], Marselan[2], Petit Verdot[3], Syrah[2,3], Tinta Cão[3], Cabernet Sauvignon[2,3], Cabernet Franc[2], Tintilla de Rota[3]	2: 233.90–1218.30	3: 420.00–3850.00	Carmona-Jiménez et al., 2018; El Achkar et al., 2017; Kadouh et al., 2016; Wang et al., 2017
		3: 5.70		
Isorhamnetin	Syrah[3], Merlot[3], Cabernet Sauvignon[3], Tempranillo[3]	3: 12.46–20.52		Lingua et al., 2016a; Wang et al., 2017
Isohamnetin 3-glucoside	Syrah[3], Merlot[3], Cabernet Sauvignon[3], Tempranillo[3]	3: 1.96–5.29		Lingua et al., 2016a; Wang et al., 2017
Kaempferol		3: 9.83–34.23	1: 160.00–300.00	

(*continued on next page*)

Table 2 (*continued*)

Phenolic compounds	Grape variety	Content Range (μg/g D. W.)	Content Range (μg/g Extract)	References
	Syrah[1,3], Merlot[1,3], Cabernet Sauvignon[1,3], Tempranillo[1,3], Chambourcin[3], Norton[3], Petit Verdot[3], Tinta Cão[3]			Gil-Sánchez et al., 2017; Kadouh et al., 2016; Lingua et al., 2016a; Wang et al., 2017
			3: 120.00–360.00	
Kaempferol 3-glucoside	Syrah[1], Merlot[1], Cabernet Sauvignon[1,3], Tempranillo[1], Cabernet Franc[3], Malbec[3], Tintilla de Rota[3], Petit Verdot[1]	1: 11.10–133.13	3: 36.00–45.00	Carmona-Jiménez et al., 2018; Fontana et al., 2017; Gerardi et al., 2020; Lingua et al., 2016a; Wang et al., 2017
		3: 28.43		
Myricetin	Syrah[1], Merlot[1], Cabernet Sauvignon[1], Tempranillo[1], Pinot Noir[1], Chambourcin[3], Norton[3], Petit Verdot[3], Tinta Cão[3]	1: 2.17–7.25	1: 0.25–0.37	Gil-Sánchez et al., 2017; Kadouh et al., 2016; Lingua et al., 2016a; Reis et al., 2016; Wang et al., 2017
		3: 25.27	3: 0.17–0.78	
Myricetin 3-glucoside	Syrah[1,3], Merlot[1,3], Cabernet Sauvignon[1,3], Tempranillo[1,3], Tintilla de Rota[1], Petit Verdot[1]	1: 14.74–47.77		Carmona-Jiménez et al., 2018; Lingua et al., 2016a; Wang et al., 2017
		3: 1.90–11.37		
Myricetin 3-glucuronide	Syrah[1,3], Merlot[1,3], Cabernet Sauvignon[1,3], Tempranillo[1], Tintilla de Rota[1], Petit Verdot[1]	1: 2.22–87.69		Carmona-Jiménez et al., 2018; Lingua et al., 2016a
		0.47–1.80		
Laricitrin	Syrah[3], Merlot[3], Cabernet Sauvignon[3], Tempranillo[3]	3: 0.14–19.09		Lingua et al., 2016a; Wang et al., 2017
Laricitrin 3-glucoside	Syrah[3], Merlot[3], Cabernet Sauvignon[3]	3: 2.91–6.37		Lingua et al., 2016a
Syringetin	Syrah[3], Merlot[3], Cabernet Sauvignon[3]	3: 0.20–0.49		Lingua et al., 2016a
Syringetin 3-glucoside	Syrah[3], Merlot[3], Cabernet Sauvignon[3], Tempranillo[3]	3: 4.17–11.97		Lingua et al., 2016a; Wang et al., 2017
Flavanone				
Astilbin	Syrah[3], Merlot[3], Cabernet Sauvignon[3]	3: 2.46–7.57		Lingua et al., 2016a
Anthocyanins				
Delphinidin 3-glucoside	Merlot[3], Cabernet Sauvignon[3], Tempranillo[1], Cabernet Franc[3], Malbec[3], Tintilla de Rota[1], Petit Verdot[3], Barbera[2]	1: 2.29–244.00	3: 748.00–7023.00	Carmona-Jiménez et al., 2018; Fontana et al., 2017; Gerardi et al., 2020; MohdMaidin et al., 2019; Wang et al., 2017
		2: 580.00		
		3: 4.82		
Cyanidin 3-glucoside	Syrah[1], Merlot[3], Cabernet Sauvignon[1,3], Tempranillo[1,3], Cabernet Franc[3], Malbec[3]	1: 2.92–14.90	3: 674.00–1131.00	Carmona-Jiménez et al., 2018; Fontana et al., 2017; Gerardi et al., 2020; Wang et al., 2017
		3: 1.99		
Petunidin 3-glucoside	Syrah[1,3], Merlot[1,3], Cabernet Sauvignon[1,3], Tempranillo[1,3], Cabernet Franc[1,3], Malbec[1,3], Tintilla de Rota[1], Petit Verdot[1]	1: 0.09–263.00	3: 263.00–9454.00	Carmona-Jiménez et al., 2018; Fontana et al., 2017; Gerardi et al., 2020; Lingua et al., 2016a; Wang et al., 2017
		3: 4.55		
Peonidin 3-glucoside	Syrah[1,3], Merlot[1,3], Cabernet Sauvignon[1,3], Tempranillo[1,3], Cabernet Franc[1,3], Malbec[1,3], Tintilla de Rota[1], Petit Verdot[1]	1: 0.86–146.47	3: 749.00–4201.00	Carmona-Jiménez et al., 2018; Fontana et al., 2017; Gerardi et al., 2020; Lingua et al., 2016a; Wang et al., 2017
		3: 2.87		
Malvidin 3-glucoside	Syrah[1], Merlot[1,3], Cabernet Sauvignon[1,3], Tempranillo[1,3], Cabernet Franc[1,3], Malbec[1,3], Tintilla de Rota[1], Petit Verdot[1], Barbera[2]	1: 151.21–1597.24	3: 3525.00–32056.00	Carmona-Jiménez et al., 2018; Fontana et al., 2017; Gerardi et al., 2020; Lingua et al., 2016a; MohdMaidin et al., 2019; Wang et al., 2017
		2: 680.00		
		3: 12.33–954.00		
Delphinidin 3-acetylglucoside	Merlot[3], Cabernet Sauvignon[3], Cabernet Franc[3], Malbec[3]		3: 716.00–1024.00	Fontana et al., 2017
Petunidin 3-acetylglucoside	Syrah[3], Merlot[3], Cabernet Sauvignon[3], Cabernet Franc[3], Malbec[3]	3: 0.03–0.86	3: 706.00–1866.00	Fontana et al., 2017; Lingua et al., 2016a
Peonidin 3-acetylglucoside	Syrah[3], Merlot[3], Cabernet Sauvignon[3], Cabernet Franc[3], Malbec[3]	3: 0.25–3.31	3: 674.00–2401.00	Fontana et al., 2017; Lingua et al., 2016a
Malvidin 3-acetylglucoside	Syrah[1,3], Merlot[1,3], Cabernet Sauvignon[1,3], Cabernet Franc[3], Malbec[1,3], Tempranillo[1], Tintilla de Rota[1], Petit Verdot[1]	1: 82.43–849.58	3: 1120.00–4136.00	Carmona-Jiménez et al., 2018; Fontana et al., 2017; Lingua et al., 2016a
		3: 28.37–195.01		
Delphinidin 3-*p*-coumaroyl-glucoside	Syrah[3], Merlot[3], Cabernet Sauvignon[3]	3: 0.26–43.95		Lingua et al., 2016a
Cyanidin 3-*p*-coumaroyl-glucoside	Merlot[3], Cabernet Sauvignon[3], Cabernet Franc[3], Malbec[3]		3: 754.00–2430.00	Fontana et al., 2017
Petunidin 3-*p*-coumaroyl-glucoside	Syrah[1,3], Merlot[1,3], Cabernet Sauvignon[1,3], Cabernet Franc[3], Malbec[1,3], Tempranillo[1], Tintilla de Rota[1], Petit Verdot[1]	1: 6.40–169.74	3: 708.00–2767.00	Carmona-Jiménez et al., 2018; Fontana et al., 2017; Lingua et al., 2016a
		3: 1.40–72.95		
Peonidin 3-*p*-coumaroyl-glucoside	Syrah[3], Merlot[3], Cabernet Sauvignon[3], Cabernet Franc[3], Malbec[3]	3: 1.62–42.71	3: 722.00–2198.00	Fontana et al., 2017; Lingua et al., 2016a
Malvidin 3-*p*-coumaroyl-glucoside	Syrah[3], Merlot[3], Cabernet Sauvignon[3], Cabernet Franc[3], Malbec[3]	3: 67.54–238.94	3: 1135.00–18626.00	Fontana et al., 2017; Lingua et al., 2016a
Flavan 3-ols				

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Table 2 (*continued*)

Phenolic compounds	Grape variety	Content Range (μg/g D. W.)	Content Range (μg/g Extract)	References
Catechin	Syrah[1,3], Merlot[1,3], Cabernet Sauvignon[1,3], Tempranillo[1], Cabernet Franc[1,3], Malbec[1,3], Tintilla de Rota[1], Petit Verdot[1,3], Feteasc̆ă Neagră[1], Pinot Noir[1], Chambourcin[3], Norton[3], Tinta Cão[3], Tempranillo[1]	1: 0.87–9778.25 3: 19.62–2178.00	1: 190.00–1720.00 3: 120.00–6450.00	Balea et al., 2018; Bender et al., 2020; Carmona-Jiménez et al., 2018; Fontana et al., 2017; Gerardi et al., 2020; Gil-Sánchez et al., 2017; Kadouh et al., 2016; Lingua et al., 2016a; Reis et al., 2016; Syed et al., 2017
Epicatechin	Syrah[1], Merlot[1,3], Cabernet Sauvignon[1,3], Tempranillo[1], Cabernet Franc[3], Malbec[3], Tintilla de Rota[1], Petit Verdot[1], Feteasc̆ă Neagră[1]	1: 0.61–2050.00 3: 17.29–112.76	1: 1030.00–570.00 3: 25.00–5518.00	Balea et al., 2018; Bender et al., 2020; Carmona-Jiménez et al., 2018; Fontana et al., 2017; Gerardi et al., 2020; Gil-Sánchez et al., 2017; Lingua et al., 2016a
Gallocatechin	Merlot[3], Cabernet Sauvignon[3], Cabernet Franc[3], Malbec[3]		3: 168.00–848.00	Fontana et al., 2017
Gallocatechin gallate	Cabernet Sauvignon[3], Cabernet Franc[3], Malbec[3]		3: 97.00–362.00	Fontana et al., 2017
Epicatechin gallate	Merlot[1,3], Cabernet Sauvignon[3], Cabernet Franc[3], Malbec[1], Syrah[1], Feteasc̆ă Neagră[1], Chambourcin[3], Norton[3], Petit Verdot[3], Tinta Cão[3], Tempranillo[1]	1: 700.00–800.00 3: 10.49–45.62	3: 12.00–1720.00	Balea et al., 2018; Bender et al., 2020; Fontana et al., 2017; Gerardi et al., 2020; Kadouh et al., 2016; Lingua et al., 2016a; Syed et al., 2017
Procyanidin dimer	Cabernet Sauvignon[3], Syrah[3], Merlot[3], Tempranillo[3]	3: 3.35–10.95	3: 24.62	Gil-Sánchez et al., 2017; Lingua et al., 2016a
Procyyanidin dimer monogallate	Cabernet Sauvignon[3], Syrah[3], Merlot[3]	3: 2.59–17.25		Lingua et al., 2016a
Procyanidin B1	Merlot[3], Cabernet Sauvignon[3], Cabernet Franc[3], Malbec[3], Tempranillo[1]	1: 13.30–1400.00	3: 44.00–1820.00	Fontana et al., 2017; Gerardi et al., 2020; Syed et al., 2017
Procyanidin B2	Cabernet Sauvignon[3], Cabernet Franc[3], Malbec[3], Tempranillo[1]	1: 0.34–400.00	3: 15.00–1378.00	Bender et al., 2020; Fontana et al., 2017; Gerardi et al., 2020; Syed et al., 2017
Procyanidin B4	Tempranillo[1]	1: 230.00		Syed et al., 2017

Each phenolic compound is presented in micrograms per gram od dry weight (μg/ g D.W.) and/or micrograms per gram of extract (μg/ g extract). Grape variety with the following superscript numbers determine the source of the phenolic compound[1] Whole grape pomace; [2] Skins [3] Skins and seeds.

aggregation (Faggio et al., 2017; Lee et al., 2019). Platelet activation can produce many molecules such as serotonin and lipoxygenase metabolites that may provoke the progression of atherosclerotic lesions. Some drugs, like aspirin, block the COX-1 action to inhibit platelet aggregation by reducing production of TXA_2 (Lutz et al., 2019).

According to Lutz et al. (2019), phenolic compounds are natural inhibitors of platelet activation, and some phenolics can inhibit platelet aggregation via AA pathway. Flavonoids have shown to inhibit the activation of platelets mediated by ADP, collagen and AA, nevertheless, such an inhibiting mechanism seems to be specific to each flavonoid (Bonechi et al., 2017; Faggio et al., 2017; Fragopoulou et al., 2009). The inhibition of platelet aggregation by consumption of wine has been investigated using *in vitro*, *ex vivo*, laboratory animals and, clinical trials (Giuliana et al., 2011).

De Lange et al., (2003) evaluated the effect of dealcoholized red wine compared with an extract of grape pomace and ethanol. They detected that the principal phenolic compounds in grapes and wine were quercetin, catechin, epicatechin and gallic acid. In this study, ADP was used as agonist at different concentrations (10, 5 and 1 μg/mL). Wine was prepared at different percentage of alcohol (0.015 to 0.48%). Results show that the 0.48 and 0.24% dilutions had a phenolic content of 2.29 and 1.15 mg/L, respectively. These wine samples presented better platelet aggregation than those with less alcohol and phenolic content. The grape extract was used at different concentrations from 11.25 to 180 mg/L. The higher concentration inhibited platelet aggregation completely. Finally, different alcohol solutions from 0.015 to 0.24% were tested, to compare the effect of alcohol against that of the red wine. Results showed no platelet inhibition by alcohol. On the other hand, rape extract presented better platelet inhibition compared with wine, nevertheless such phenomena could be explained due to the higher concentration of phenolic compounds present in the extract. These results suggest that the inhibition of platelet aggregation is produced by the phenolic compounds present in wine and grapes and not by the alcohol content.

According to Castaldo et al. (2019), moderate consumption of alcohol is associated with higher levels of HDL-C and diminishing lipid oxidation stress. Tverdal et al. (2017), studied the effect of alcohol consumption and CVD. They observed an HDL-C increase as alcohol consumption increase. They also reported higher mortality by CVD in non-alcohol drinkers compared with alcohol drinkers. Finally, they observed a high relationship between wine consumption and low presence of CVD. Similar results were observed by Torres et al. (2015), who compared the effect of consumption of wine with other alcoholic beverages on antioxidant capacity and proinflammatory factors, since inflammation and oxidative stress have an important role in atherosclerotic process that leads to CVD. In this clinical trial, they used red wine, vodka, rum and brandy and a high-fat diet. Quantification of phenolic compounds in these beverages showed that wine has the highest phenolic content, while vodka lacked phenolic compounds. They observed that red wine intake decreased IL-6 and TNFα levels compared with other alcoholic beverages. They also reported an increase of total antioxidant capacity after comparing red wine intake with other beverages. These results indicate that the beneficial effect of wine can be attributed mainly to its phenolic compounds and not to alcohol content, since vodka presented the lowest total antioxidant capacity and highest content of pro-inflammatory markers. A critical factor observing the effect against platelet aggregation seems to be the phenolic content and phenolic profile. Moreover, to observe the cardioprotective effect from wine, phenolic compounds concentration in red wines is a relevant factor.

As previously mentioned, red wine contains a large variety of phenolic compounds at different concentrations depending on the grape variety, growth region and winemaking. Different authors have evaluated the cardioprotective effect of the main phenolic compounds found in wine in their pure form to clarify which phenolic compound can be responsible for the cardioprotective effect. Resveratrol, a stilbene present in wine, has been labeled as one of the main compounds with cardioprotective effect (Sham et al., 2017). Riccioni et al. (2015) reported that resveratrol shows anti-platelet aggregation effects. Even though its mechanism is still unknown, it can be related to the inhibition of platelet adhesion stimulated by thrombin, collagen and fibrinogen. To elucidate the action of resveratrol against platelet aggregation, Gresele

Table 3
Cardioprotective effect of red wine studies.

Grape product	Extraction method	Model	Results	Comments	Reference
Red wine	Chromatographic extraction acetone 70%	*In vitro*	Inhibition of endothelin-1 synthesis Induction of endothelium-dependent vasodilation No cytotoxic effect	Dose dependent	Khan et al., 2015
Red wine		*In vitro*	↑ eNOS mRNA expression ↑ eNOS protein expression ↑ NO production ↑ activity of eNOS promoter	Dose and time dependent	Wallerath et al., 2003
Red wine		*In vitro*	↑Inhibition of platelet aggregation by red wine compared with ethanol 12%		de Lange et al., 2003
Red wine and white wine/ Resveratrol		*In vitro/ ex vivo*	Increase of resveratrol in plasma from 0.72 to 1.32 μM for white wine and from 0.71 to 1.72 for red wine ↑ NO produced by platelets in presence of resveratrol ↑Inhibition of platelet aggregation with resveratrol 0.5 μM	Dose dependent	Gresele et al., 2008
Red wine	Dealcoholized sample lyophilized	*ex vivo/ in vitro*	NO and EDHF-mediated relaxations induced in arteries ↑ increase phosphorylation of Akt and activates eNOS phosphorylation		Ziberna et al., 2013
Red wine	Dealcoholized sample lyophilized	*ex vivo*	Akt phosphorylation and eNOS on endothelial cells Petunidin-3-glucoside response of phosphorylation of Akt and eNOS	Dose dependent	Auger et al., 2010
Red wine	Dealcoholized sample lyophilized	*ex vivo* porcine coronary arteries	Relaxion on coronary artery rings (endothelium dependent relaxation)	Dose dependent	Ndiaye et al., 2003
Red wine	Dealcoholized sample lyophilized	Wistar rats *ex vivo*	Relaxation of rings contracted with endothelium Minimum effect of relaxation in arteries without endothelium ↑ Formation of NO	Dose dependent	Ribeiro et al., 2016
Red wine	Dealcoholized sample lyophilized	Wistar rats / (*ex vivo*)	↑Vasodilation by induction of NO in endothelium cells	Dose dependent	de Moura et al., 2004
Red wine		Pigs	↓Reduction in total protein oxidation compared to control ↓Decrease in expression of NOX2 ↓Decrease in eNOS and p-eNOS Improvement in micro-vessel function		Lassaletta et al., 2012
Polyphenolic enriched white wine (PEWW) Sparkling red wine (SRW)		Golden Syrian hamsters (force feed)	↓TC compared to control ↔TG no change ↔ HDL no change ↑APO A tendency ↓APO B tendency ↑Antioxidant activity in plasma (PEWW) compared to control ↓Lipoperoxidation (SRW) compared to PEWW and control ↑SOD and CAT in liver with SRW and PEWW		Auger et al., 2005
Red wine (RW) Red wine enriched 3% (RW1) Red wine enriched 30% (RW2)		Golden Syrian hamsters (force feed)	↓TC ↔HDLC ↓LDLC ↓TG ↔Glucose ↓Insulin ↔Leptin ↑Adiponectin ↓NADPH oxidase activity with RW1 and RW2 in liver and cardiac ventricle ↓SOD and GPx activities with RW2 and RW2 ↓TNF α with RW2 ↓IL-6 with RW2 and RW2		Romain et al., 2014
Red wine		Clinical trial	↔LDL-Ox ↔Total antioxidants ↔Platelet aggregation		Giuliana et al., 2011
Red wine		Clinical trial	↑Coronary flow velocity reserve ↑Plasma antioxidant capacity	Dose dependent	Kiviniemi et al., 2007
Red wine White wine Grape juice Enriched grape juice (4 mg/L resveratrol)		Clinical trial	↑ Red and white wine platelet aggregation inhibition compared with grape juices using ADP as agonist ↑ Grape juice ↓Enriched grape juice ↑White and red wines platelet inhibition with thrombin as agonist		Pace-Asciak et al., 1996

et al., (2008) studied the effect of resveratrol on the stimulation of platelet NO derived production and platelet aggregation. In this study, resveratrol was used at two different concentrations (0.2 and 0.5 μM). Measuring resveratrol was decided upon a previous study that used high performance liquid chromatography (HPLC) reporting that volunteers who ingested red wine for 15 days presented similar resveratrol concentration in their plasma. Their results showed that NO production was dose dependent and that the activity of platelet nitric oxide synthase increased at the highest resveratrol concentration. Platelet aggregation inhibition also showed a dose-dependent pattern. These results suggest

that resveratrol may inhibit platelet aggregation by increasing NO production. Similar results were found by Bonechi et al. (2017), who evaluated the effect of resveratrol and ethanol at 15 mM against platelet aggregation using epinephrine as agonist. The concentration used was higher compared with that used by Gresele et al. (2008), and found that concentration in wines is far from those found in red wines.

Resveratrol content in wines varies from 0.43 to 62.65 μM, and depends on several factors such as grape variety, climate and winemaking process (Artero et al., 2015). According to Pannu & Bhatnagar (2019), resveratrol is highly absorbed in the intestine, presents low bioavailability and is rapidly excreted. It has been reported that consumption of pure resveratrol at doses higher than those present in wines results in a low content of this compound in plasma (Artero et al., 2015; Pannu & Bhatnagar, 2019; Szkudelska & Szkudelski, 2010). These findings may challenge the common idea that resveratrol is the main phenolic compound associated with cardioprotective effect. Consequently, other phenolic compounds present in wines such as flavonoids, have been studied.

For example, Pace-Asciak et al. (1995) tested the anti-platelet aggregation effect of phenolic compounds like resveratrol, quercetin, catechin, and epicatechin that are present in wine. These compounds were compared against two synthetic antioxidants: butylated hydroxytoluene (BHT) and hydroxyquinone (HQ). According to their results, resveratrol was the best platelet aggregation inhibitor. Quercetin, catechin, and epicatechin also demonstrated inhibitory activity against platelet aggregation whereas, BHT and HQ were ineffective. In this study, concentrations from 10 to 1000 μM of each compound were evaluated. These concentrations are high compared with those found in plasma by Gresele et al. (2008) (between 0.2 and 0.5 μM). Results provided by Pace-Asciak et al. (1995) demonstrated that compounds present in wines may be involved in the inhibition of platelet aggregation and its cardioprotective effects. The concentration of each compound present in red wine is crucial when studying its effects against platelet aggregation.

Moreover, the phenolic profile of wine should also be considered, since compounds such as catechin and epicatechin presented lower values compared with resveratrol. This may suggest that the mixture of phenolic compounds present in wines shows synergic, additive, even antagonic effects. Further studies are needed to evaluate the behavior of a mixture of phenolic compounds against platelet aggregation.

The surface of platelets has different receptors that initiate platelet responsiveness. Molecules known as agonists initiate different biochemical pathways that end in platelet aggregation. According to Cattaneo (2019), ADP causes a rapidly reversible aggregation. ADP induces platelet aggregation by binding to $P2Y_1$ and $P2Y_{12}$ receptors and activating PLC through a β-subunit from a G protein, leading the formation of IP3 and then the signaling for platelet aggregation. On the other hand, the most powerful agonist involved in platelet aggregation is thrombin (Han et al., 2019). Thrombin initiates platelet aggregation by binding to protease activation receptors 1 (PAR1) and PAR4, an important family of transmembrane receptors (Clemetson & Clemetson, 2019). PAR1 and PAR4 have structural differences but they activate the same signaling pathway by releasing granules, and activating G proteins, which in turn trigger the platelet aggregation process for (Han et al., 2019).

Different agonists have been employed to study how phenolic compounds in red wine inhibit platelet aggregation. In a study by Pace-Asciak et al. (1996), red wine, white wine, commercial grape, juice and enriched grape juice with resveratrol were given to volunteers in a crossover experiment. Participants consumed both types of grape juices and the different wines for 4 weeks without interruption, with wash out periods of 2 weeks between each intake. Blood samples were taken before intake and after the 4 weeks of consumption of each sample to measure platelet aggregation using ADP and thrombin as agonists. No significant changes were reported in platelet aggregation induced by ADP after consumption of grape juice and enriched grape juice.

In contrast, consumption of white and red wines showed platelet aggregation inhibitory effect. When thrombin was used as agonist, the commercial grape juice exhibited a significant reduction on platelet aggregation; however, platelet aggregation values increased after the intake of the enriched grape juice whereas consumption of white and red wine decreased platelet aggregation. These differences in the inhibition of platelet aggregation can be attributed to the pathway each agonist follows (Cattaneo, 2019a, 2019b). In this study, the action of phenolic compounds against two agonist showed higher platelet aggregation inhibition when ADP was used compared with thrombin. This may suggest that inhibitory activity can be set off by inhibiting secondary messengers like AA or TXA_2 or COX-1.

Pace-Asciak et al. (1996) studied the effect of grape juices and wines on the production of thromboxane B (TXB_2) and hydroxyheptadecatrienote (HHT) by platelets. TXB and HHT are stable metabolites produced during transformation of AA into TXA_2. Their presence indicates whether grape juice or wine modulate or block the AA pathway. Authors reported that red wine inhibited the TBX_2 synthesis 30% more than the control did whereas grape juice o increased TBX_2 by 50%. In contrast, enriched grape juice with resveratrol showed the same levels as control.

Regarding HHT synthesis, grape juice also showed an increase of 50% when compared with control, enriched grape juice reduced the synthesis by 25%, and red wine presented the best inhibition at around 50 to 70%. These findings indicate that not only resveratrol but also other phenolic components in wine can initiate platelet aggregation inhibition and that it can happen via blockage of the AA pathway, possibly by ADP induction.

Another important agonist involved in platelet activation is the activating platelet factor (PAF). PAF is a phosphoglycerylether lipid involved in several signaling processes (Lordan et al., 2019). The effect of wine consumption on platelet aggregation induced by PAF was studied by Xanthopoulou et al. (2017). In this clinical trial, participants were given a standardized meal accompanied by 4 different treatments: red wine, white wine, 12% ethanol, and water. A blood sample was taken before the meal (baseline) and six hours afterwards. Red wine showed higher effect against platelet aggregation and kept lower levels of TAG when compared with water and alcohol. Results also showed that individual given red wine presented lower PAF-induced platelet aggregation compared with those who took white wine. The study found that ethanol (12.5%) did not induce platelet aggregation inhibition when PAF was used as an agonist. Results also indicated that phenolic compounds found in wines with the same alcohol content were involved in platelet aggregation inhibition. Total phenolic content of red and white wine was 2875 and 213 mg equivalents of gallic acid, respectively. The higher phenolic content in red wine may explain why it showed higher anti-platelet aggregation than white wine.

Schmatz et al. (2013), studied a complex of ectoenzymes that regulate platelet aggregation induced by ADP. The ectoenzymes evaluated were ectonucleoside triphosphate phosphohydrolase (NTPDase), which hydrolyses ATP and ADP into AMP; ectonucleoside pyrophosphatase/phosphodiesterase (E-NPP) which hydrolyses 5′-phosphodiester bonds; ecto-5′nucelotidase, which hydrolyses AMP into adenosine; and ectoadenosine deaminase (ADA) which catalyzes the irreversible deamination of adenosine. For this purpose, they used diabetes-induced Wistar rats supplemented with red wine, grape juice, and ethanol solution to differentiate the effect of alcohol and phenolic compounds. Each animal received 4.28 mL/kg, equivalent to 300 mL of wine or juice per day in an adult person of 70 kg. The subjects were in treatment for 45 days and blood samples were collected for platelet aggregation tests and to evaluate enzymatic activity. Results showed that ethanol had no effect ither on enzymatic activity or on platelet aggregation. Administering wine increases the activity of NTPDase, increasing the hydrolysis of ADP and ATP compared with the control and grape juice groups. The same trend was observed in the activity of ecto-5′nucleotidase and E-NPP in those groups supplemented with red wine. ADA activity decreased equally after wine and juice administration. Both wine and grape juice

treatments resulted in a platelet aggregation inhibition. Authors attributed this effect to phenolic compounds present in wine and grape juice, which may inhibit platelet aggregation by decreasing the level of ADP and increasing adenosine levels. These results may support the findings of Pace-Asciak et al. (1996), who observed better inhibition of phenolic compounds in wine using ADP as agonist in contrast with that observed for thrombin.

It is well known that CVD risk factors like hypertension, hypercholesterolemia and smoking lead to the increase of reactive oxygen species (ROS). Such increase in ROS promotes oxidative stress (Apostolidou et al., 2015; Li et al., 2014). Phenolic compounds present in wine are natural antioxidants and provide protection against oxidative stress. Phenolic compounds can neutralize free radicals by donating an electron or hydrogen atom (Zhang & Tsao, 2016). The antioxidant capacity of wines has been widely reported (Atanacković et al., 2012; Ivanova-Petropulos et al., 2015; Lingua et al., 2016a) and depends on phenolic content. In a study performed by Atanacković et al. (2012), authors observed that antioxidant activity of wine is not attributed to specific compound like resveratrol, but to a mix of different phenolic compounds present in wines. On the other hand, Lingua et al. (2016a), malvidin and its derivatives acetylglucoside and p-coumaroylglucoside, pigment A and isorhamnetin are the principal compounds associated with antioxidant activity.

Oxidation of LDL-C seems to play a relevant role in the risk of developing CVD. Oxidation promotes endothelial cells to produce chemokines and other molecules that stimulate monocytes to adhere to endothelium. oxidized LDL-C is transformed into “foam cells” by macrophages inducing atherosclerotic lesions (Di Renzo et al., 2015; Leifert & Abeywardena, 2008). Phenolic compounds are related to preventing LDL-C oxidation and reducing oxidized phospholipids (Fragopoulou et al., 2009), reducing the formation of foam cells and preventing CVD and atherosclerotic process (da Luz et al., 2018).

Previous studies have attributed antioxidant properties to phenolic compounds from red wine. Such properties are: inhibition of LDL-C oxidation and modulation of cholesterol absorption, VLDL-C and triglycerides. In a study conducted by Apostolidou et al. (2015), consumption of wine increased the antioxidant capacity in plasma of patients with normal cholesterol and asymptomatic hypercholesterolemics. Authors reported that lipid profile was modified after consumption of red wine in asymptomatic hypercholesterolemics by decreasing total cholesterol, LDL-C, and HDL-C. Meanwhile, no changes were observed in HDL and LDL levels in the group with normal cholesterol levels. Nevertheless, the decrease in LDL and HDL values in asymptomatic hypercholesterolemic subjects was non-significant, which can be attributed to the time of consumption since only one month was evaluated. Besides, the sample size could have affected the results. No specific phenolic compound from wine was related to the activity observed. These findings can be compared with those reported by Giuliana et al., (2011) who evaluated the effect of daily consumption of 250 mL of red wine in 15 volunteers. After four weeks of treatment, no significant changes in glucose level, lipid profile and alcoholic liver damage markers were observed. Authors observed no changes in platelet aggregation induced by ADP and collagen after wine consumption. They reported that oxidative stress did not change after wine consumption intervention. d no change in LDL-C and HDL-C levels was observed compared with the initial values. Although these two studies involved different populations, biomarkers were not modified by consumption of wine, which may be related to the bioavailability of phenolic compounds since during gastrointestinal digestion, a portion of phenolic compounds cannot reach the target, express their bioactivity as antioxidant, and diminish the levels of LDL, HDL or triglycerides.

In a study by Taborsky et al. (2017), the authors compared the effect of a red and white wine in asymptomatic CVD subjects. They evaluated the effect of one-year wine consumption on LDL-C, HDL-C, LDL-c oxidized and triglycerides. After 1-year consumption of red and white wine, no changes were observed in values of HDL-C and triglycerides. Nevertheless, reduction on LDL-C and total cholesterol was observed in the treatments that involved red and white wine consumption. In this study, the time of consumption was longer compared with the one used by Apostolidou et al. (2015) and Giuliana et al. (2011). Such a difference may help either observe differences in acute and long terms or the protective effect of wine consumption during prolonged periods. These results have to take carefully since they may lead to conclude that consumption of red win slightly improves lipid profile. However, there are several other factors that must be observed, such as the initial subjects’ lipid condition; the dose of wine; and the phenolic content of wine. This last factor crucial since several of the cardioprotective effects of wines are dose-dependent.

Di Renzo et al. (2015), evaluated the effect of a resveratrol-enriched wine on LDL-C oxidation. In this crossover clinical trial, volunteers were divided into three groups: one group consumed a high-fat meal; the second group consumed high-fat meal and 250 mL of wine; and finally; the third group consumed only 250 mL of wine. Blood samples were taken at baseline and three hours after treatment consumption. After a three-week washout period, the groups were shifted and received a different treatment. Authors reported that consumption of high-fat meal increased LDL-C oxidation by15% compared with the baseline, while a 20% LDL-C oxidation decrease was observed when wine was consumed together with a high-fat meal. Consumption of high-fat meal plus wine or only wine reported similar values than those of the baselines. These results indicate that red wine can keep LDL-C oxidation levels at basal stage even after a high-fat meal consumption. During postprandial stage, there is a process that generates an oxidative environment by producing ROS. Phenolic compounds and their antioxidant activity may be involved in preventing the damages associated with ROS.

Chassot et al. (2018) compared the effect of wine, dealcoholized wine, and commercial capsules of resveratrol administration in mice. This study used two protocols. The first to demonstrate prevention of atherosclerotic effect, for which mice were fed each treatment for eight weeks followed by an eight weeks period of an atherogenic diet. The second protocol was designed to demonstrate atherosclerosis regression, for which mice were fed an atherogenic diet for eight weeks and switched to the treatment mentioned above for another eight weeks. The results showed that dealcoholized wine and resveratrol reduced plasmatic LDL-C, VLDL-C and HDL-C levels when compared with control and wine groups. These effects were observed in both protective and regressive protocols. In histological analyses of the aorta artery, authors observed that consumption of red wine, dealcoholized red wine and resveratrol capsules, prevented the formation of fat streaks caused by the atherogenic diet. The concentration of phenolic compounds for the prevention and protective protocols were 18.35 and 16.42 μg phenolic compounds/day for wine, 20.45 and 18.49 μg phenolic compounds/day of dealcoholized wine and 0.82 and 83 mg resveratrol/day. In both experiments, resveratrol was used at a higher content than phenolic compounds from wine. This may explain why resveratrol showed better results than wine. Interestingly, dealcoholized wine showed similar results than resveratrol, which may indicate that other phenolic compounds apart of resveratrol are involved in the decrease of HDL-C, LDL-C and VLDL-C.

The effect of red wine consumption on the vasodilatation process has also been studied. de Moura et al. (2004), studied the vasodilatory effect of dealcoholized red wine using an *ex vivo* model, using isolated mesenteric vascular bed from rats. Red wine produced an endothelial-dependent dilatation. This effect was attributed to the release of endothelial-derived relaxation factors (EDRF) such as NO and endothelial-derived hyperpolarizing factor (EDHF) since red wine can be involved in activation of potassium/calcium channels. EDHF is a major endothelium-derived relaxing factor in the coronary artery and the coronary microcirculation (Ndiaye et al., 2003). de Moura et al. (2004) observed that vasorelaxation produced by red wine decreased when NG-nitro-L-arginine methyl ester (L-NAME) and oxodiazoloquinoxlin-1-one (ODQ) were used. L-NAME is a NO synthase inhibitor,

while ODQ is a guanylyl cyclase (GC) inhibitor. GC plays a major role in the signaling pathway of endothelium-dependent vasodilator effect by reducing intracellular calcium concentration. This may explain why phenolic compounds from red wine can induce NO synthase and GC activity.

In another study Ndiaye et al. (2003), evaluated the effect of red wine phenolic compounds on the EDHF mediated relaxation. In order to evaluate the effect of phenolic compounds without the interference of alcohol, red wine was lyophilized. Authors used porcine arteries to observe the effect of lyophilized wine on NO generation and coronary arteries relaxation. A dose-dependent relaxation effect of red wine extract on porcine coronary artery rings with endothelium was observed, while a minimum relaxation effect was observed without endothelium. This relaxation was attributed to a formation of NO and EDHF by endothelial cells, mediated by red wine phenolic compounds. Since tthe alcohol was removed from the samples, results suggest it is not involved in the increase of NO. These results are in agreement with those found by de Moura et al. (2004), both studies demonstrated that phenolic compounds stimulate EDHF-relaxations by redox-sensitive events that occur in the endothelial cells since phenolic compounds are known for their antioxidant capacity.

The endothelium-dependent relaxation effect was also reported by Ribeiro et al., (2016), who used a lyophilized wine, and performed *in vivo*, *ex vivo* and *in vitro* models. In the first experiment, lyophilized red wine was injected into the femoral artery of rats in three doses (10, 30 and 90 mg/kg), changes in blood pressure were further measured. In the second experiment, L-NAME hypertensive rats were given 100 mg/kg/day, the equivalent to a glass of wine taken by an adult, person) of further measuring epinephrine-induced contraction of the mesenteric artery. In the third experiment, cultured cells of porcine arteries were treated with red wine at two different concentrations (100 and 300 μg/mL) to measure the presence of e-NOS by Western blot. Authors reported that injecting red wine extract reduced blood pressure caused by NO production. Oral administration of phenolic compounds in hypertensive rats resulted in blood pressure decrease. Authors attributed this protective effect to phenolic compounds, considering that they might restore an optimal endothelium-derived NO formation. It was also reported that phenolic compounds produced relaxation in the mesenteric artery rings by the formation of NO. They found that red wine causes relaxation in mesenteric arteries even when inhibitors of calcium/potassium channels were used, indicating that the phenolic compounds from wines are also involved in EDHF-relaxation processes. These results are in agreement with those found by de Moura et al. (2004) and Ndiaye et al. (2003), who attributed the vasodilatory effect to phenolic compounds. Nevertheless, all the studies use either *ex vivo* or *in vitro* models. In those models, the phenolic content of wines can be higher than expected in a *in vivo* model, where the bioavailability of the phenolic compounds decreases its concentration in the circulatory system.

Khan et al. (2015) evaluated the vasodilatory effect of proanthocyanins, an essential fraction of phenolic compounds present in wines using a red wine enriched with oligomeric proanthocyanins, pure resveratrol and grape seed extract in concentrations ranging from 5 to 100 μM to evaluate the effect on endothelin-1 (ET-1) release in bovine aortic endothelial cells in an *in vitro* model. They observed a dose-dependent effect of treatments against ET-1, the effect was higher with enriched red wine and grape seed extracts than with pure resveratrol. Authors proposed that procyanidins from wine and grape extract may be acting as agonist or receptors in the cell surface of endothelium that lead to the inhibition of ET-1, promoting vasorelaxation. Considering that receptors involved in this process are not well established and concentrations used were higher than those that can be present in plasma after absorption, further research is need to observe if real plasma concentration of phenolic compounds from wine present the same effect observed in this work.

Lassaletta et al. (2012) evaluated the cardioprotective effect of wine and compared it with ethanol and vodka. In this study, an *ex vivo* model was used. Pigs were induced into endothelial dysfunction with a high-fat diet and supplemented with red wine. No difference on myocardial perfusion was found. In contrast, a reduction in total protein oxidation was observed with red wine treatment, compared with the control. Red wine also decreased the expression of NOX2, which synthesizes superoxide and is involved in the development of atherosclerosis. A decrease of superoxide dismutase (SOD) on mitochondria and cytoplasm was observed compared with control. An improvement in microvessel function was observed only in the subjects with red wine treatment. This effect was attributed to the phenolic compounds present in wine, which may confer a cardioprotective effect by normalizing endothelial disfunction. These results highlight that the antioxidant capacity of phenolic compounds from red wine can inhibit protein oxidation and also modulate the expression of enzymes involved in increasing ROS in the environment. Ventricular arrhythmias can be caused by an unbalance between ROS and antioxidants. Arrhythmias may cause death by ischemic heart disease. Phenolic compounds present in red wines may prevent reperfusion-induced arrythmias and improve the recovery of the myocardium (Leifert & Abeywardena, 2008).

Mosca & Cingolani, (2002), evaluated a mechanism in which a red wine phenolic compounds extract can prevent ischemia/reperfusion injury. Hearts from Wistar rats were used for this purpose. Red wine was dealcoholized to evaluate the effect of its phenolic compounds at different dosages (0.1, 0.2 and 0.5 mg/min). Results showed that red wine induces a recovery of function after the ischemia/reperfusion, although in a dose-dependent manner. Since there is a large variety of phenolic compounds in the extract, the cardioprotective mechanism remains elusive.

4. Cardioprotective effect of grape pomace

Grape pomace is the main byproduct of the winemaking process and large quantities are produced annually. Pomace is composed by seeds, stalks, and skins (Muñoz-Bernal et al., 2018). This byproduct is an important source of phenolic compounds, and many effects on health such as free radicals scavenging activity, anti-inflammatory properties, anticancer, and cardioprotective activity have been reported (Tournour et al., 2015). Though the use of by-products is becoming more relevant, the number of studies regarding the use of grape pomace as CVD prevention is scarce. Table 4 offers a summary of such studies.

Research has demonstrated that plant food byproducts may serve as better source of phenolic compounds than their product (wine compared with grape pomace). de Oliveira et al. (2017) compared the phenolic content of red wine and grape pomace and observed that grape pomace presented higher content of total phenolic compounds (4290 mg GAE/kg and 5450 GAE/kg, respectively) and anthocyanin content (304 and 715 mg equivalents of malvidin per kilogram (mg MGE/kg) respectively) than red wine.

It is well known that red wine has a higher phenolic content compared with white wine and this is attributed to the maceration process red wines go through. To compare the phenolic content of white and red grapes, Moschona & Liakopoulou-Kyriakides (2018) took ethanol extracts from red grape pomace and white grape pomace. They found a higher phenolic content in red grape pomace (22 mg/g DM) than in white grape pomace (18 mg/g DM). They reported that the phenolic profile from both extracts was similar and mainly contained ellagic and caffeic acids, quercetin, and kaempferol. This study also evaluated platelet aggregation activity using ADP as agonist. Both extracts were used at the same concentration of phenolic compounds (0.65 mg/ g DM) and an inhibition of 51 and 84% was observed respectively. Nevertheless, this study does not provide information about the concentration of individual compounds and no specific phenolic content is attributed to inhibiting platelet aggregation. In the same manner, the study does not explain the reason for using only one concentration of both grape pomace extracts.

Ferri et al. (2016) evaluated the effect of grape pomace enzymatic

Table 4
Cardioprotective effect of grape pomace extracts.

Grape product	Extraction method	Model	Results	Comments	Reference
Grape pomace	Enzymatic (pectinase, α-amylase, xylanase, cellulase)	*In vitro*	Extracts modulates the transcription of cholesterol 7α-hydroxylase and sterol 27-hydroxylase	Dose dependent	Ferri et al., 2016
Grape pomace	Enzymatic (trypsin-chymotrypsin)	*ex vivo*	Relaxation of arteries by extract with endothelium Endothelium relaxation by NO release	Dose dependent	Rodriguez-Rodriguez et al., 2012
Grape pomace	Methanol 50% Acetone 70%	Wistar rats	↔Glucose ↔TC ↔LDLC ↓VLDL ↓TG		de Oliveira et al., 2017
Grape seeds	Commercial extract	Golden Syrian Hamsters	↔Glucose ↔Insulin ↔Leptin ↔TG ↓TC		Caimari et al., 2013
Red grape seeds	Capsule	Clinical trial	↔TG ↓TC ↔HDL-C ↓LDL-C ↔VLDL-C ↓Ox-LDL		Razavi et al., 2013

phenolic extracts on 7 α-hydroxylase and sterol 27-hydroxylase using an *in vitro* model. These two enzymes are related to bile acid biosynthesis and cholesterol homeostasis in the organism. Grape pomace was obtained by enzymatic hydrolysis with pectinase, α-amylase, xylanase and cellulase after treatment with enzymes, an ethanolic extraction was performed. The authors reported that extraction with cellulase and ethanolic extract (control) presented more phenolic content compared with other treatments. These extracts contained mainly quercetin, rutin, catechin and epicatechin. The study reported that control and cellulase-treated extracts induced transcription of 7 α-hydrolase while, no effect was observed in the transcription of 27-hydroxylase. Upregulation in transcription of 7 α-hydrolase can be related to the increase of bile acid synthesis and may also be related to LDL-C uptake. This effect in upregulation of 7 α-hydroxylase is attributed to catechin, epicatechin, and quercetin present in the extracts. Phenolic content in extracts from wine byproducts depends on several factors like the method used (enzymatic, microwave or ultrasound assisted), solvent election (methanol, ethanol or water), and time. These factors affect the concentration and phenolic profile of the extracts. So far, a standardized method for optimizing the extraction of phenolic compounds from wine byproducts is not available.

Rodriguez-Rodriguez et al. (2012) tested the cardioprotective effect of a grape pomace enzymatic phenolic extract in an *ex-vitro* model, using male Wistar rats' arteries. Rats arteries were treated with phenolic compound extract at concentrations from 0.0001 to 0.03 g/L. Extracts induced a relaxation in aortic rings in a dose-dependent manner. Authors attributed this relaxation to activation of eNOS through a NO-dependent mechanism. Arteries were treated with ET-1, which is known to provoke a contraction in the arteries, producing superoxide anion O_2^-, treatment with phenolic compounds extract produced an inhibition in the contraction of aortic rings, probably because of the antioxidant activity of the phenolic compounds present in the extract. These results agree with those found by Khan et al. (2015), who used a procyanidin-enriched red wine in an *in vitro* model. These results may indicate that the same effect against ET-1 can be observed when using wine or grape pomace, probably caused by the antioxidant properties of phenolic compounds present in both samples.

de Oliveira et al. (2017) evaluated a grape pomace phenolic extract and a red wine extract in an *in vivo* model using male Wistar rats. Grape pomace extract was obtained with methanol and acetone and red wine was dealcoholized to avoid interferences from alcohol. Rats were separated into 3 groups, a control group, a red wine group, and a grape pomace group. Rats were supplemented with 100 mg/kg/day of grape pomace or dealcoholized wine for 30 days. Results showed that grape pomace presented higher concentration of phenolic compounds than red wine, being malvidin, quercetin, gallic acid, and a procyanidin dimer type B the main compounds identified. At the end of the experiment, results showed that glucose, total cholesterol, HDL-C and LDL-C levels were not affected by the consumption of red wine or phenolic extract compared with the control. Nevertheless, VLDL-C and triacylglycerols levels decreased with grape pomace treatment, probably due to a higher phenolic content. LDL-C and HDL-C are considered biomarkers for the risk of CVD, in this case the results obtained cannot prove that the consumption of phenolic compounds from grape pomace or red wine reduces the levels of these biomarkers, however; VLDL-C and triacyl glycerides also contribute to the development of coronary heart disease, and a reduction of these molecules in this study may contribute to elucidate the mechanism by which phenolic compounds from red wine and grape pomace to prevent CVD.

These results are similar to those of Caimari et al. (2013), who tested the effect of a commercial grape seed extract on male Syrian golden hamsters fed with a high-fat diet. According to these authors, the commercial grape seeds extract contained mainly monomeric, dimeric, and oligomeric procyanidins, and phenolic acids. Four experimental groups were tested: standard diet; standard diet supplemented with 25 mg/kg of commercial grape seeds extract; high-fat diet; and high-fat diet supplemented with 25 mg/kg of extract. Free fatty acids decreased in those hamsters treated with grape seeds extract in both diets. However, neither triacylglycerol nor glucose levels were modified by consumption of this extract. In contrast, leptin level diminished in the diets supplemented with the extract, compared with the high-fat diet treatment. These results showed that the phenolic compounds from commercial grape seeds extract, at the concentration tested, could not prevent hypertriglyceridemia and hypercholesteremia. The negative results observed in this study can be explained by the dose used to feed the subjects. Also, the phenolic extract only contain procyanidins. Compared with the study performed by de Oliveira et al. (2017) whose extract contained other compounds like gallic acid, quercetin, malvidin and procyanidin B. Such mixture of phenolic compounds could be presented a higher cardioprotective effect that only an extract of rich in procyanidins.

Razavi et al. (2013) evaluated a commercial grape pomace phenolic compounds extract over the hyperlipidemic response. For this, a clinical trial was performed with hyperlipidemia patients (21–64 years old) using a randomized crossover design. Patients were separated into two groups, one received grape pomace phenolic extract (100 mg twice a

day) and the other group received a placebo. Results showed a decrease in total cholesterol compared with initial values due to grape pomace phenolic extract. The treatment with phenolic extract also presented a decrease in LDL-C and the Ox-LDL-C levels. Triacyclglycerols, HDL-C and VLDL-C levels were not modified by the consumption of the extract. These results differ from those found by de Oliveira et al. (2017). Differences may be explained first by considering that de Oliveira used rats as models, and second, the amount supplemented, because higher dosages were given to the rats compared with those given to the hyperlipidemia patients.

5. Conclusions

Consumption of red wine is related to low prevalence of CVD. Several studies have demonstrated the effect of phenolic compounds from red wine against platelet aggregation, increased NO production, modification of some important enzymes related to vasorelaxation such as eNOS and that can be related to causing vasorelaxation by EDHF. Nevertheless, other studies proved that modification of lipidic profile, HDL-C, LDL-C and triacylglycerols levels, is not altered after consumption of red wine. Most of those studies have proved that beneficial effects of red wine are dependent of phenolic compounds concentration and type of phenolic compounds such as flavonoids and proanthocyanins (monomeric or oligomeric forms). Since phenolic compounds, concentration and type in red wine are affected by the harvesting and winemaking process, the effects observed can be different depending on the analyzed wine. Considering that grape pomace presents a higher phenolic content than red wine, grape pomace seems to be a great source of phenolic compounds with potential cardioprotective effect. However, the number of studies regarding the cardioprotective effect of grape pomace are scarce. No conclusive results have been obtained with grape pomace extracts, mainly because the phenolic content of the extracts has not been well quantified and characterized. Some studies used enzymatic extraction while other used different solvents such methanol, ethanol or acetone. Different results have been obtained by using *in vitro*, *ex vivo,* and clinical trials. Yet, the mechanisms by which phenolic compounds from red wine and grape pomace can prevent CVD remain elusive. Further studies must be done to clarify the receptors or pathways that can be altered after red wine or grape pomace consumption.

CRediT authorship contribution statement

Óscar A. Muñoz-Bernal: Investigation, Writing - original draft. **Alma J. Coria-Oliveros:** Investigation, Writing - original draft. **Laura A. Rosa:** Conceptualization, Writing - review & editing. **Joaquín Rodrigo-García:** Writing - review & editing. **Nina del Rocío Martínez-Ruiz:** Conceptualization, Writing - review & editing. **Sonia G. Sayago-Ayerdi:** Funding acquisition, Conceptualization, Writing - review & editing. **Emilio Alvarez-Parrilla:** Supervision, Conceptualization, Writing - review & editing.

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