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Review

Plants of the genus *Vitis*: Phenolic compounds, anticancer properties and clinical relevance

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ABSTRACT

Background: *Vitis* genus comprised about 70 species. Concerning its pharmacological properties, *V. vinifera* is the most studied one, but there are other species with interest.
Scope and approach: Therefore, this review aims to provide an updated overview on bioactive phytochemicals present in food products (grapes and wine) of *V. vinifera* and other *Vitis* species, as well as in different underused bioresources (stem, leaves, seeds, wine pomace, etc.). Moreover, due to their promising perspectives in the field of anticancer drug discovery, this bioactivity has been covered as well as the contribution that *Vitis* phenolic compounds has.
Findings and conclusions: Among the plant products reviewed, grape seed extracts was the most investigated at preclinical phase, hence exhibiting a promising potential as anticancer drugs. However, an evidence-based clinical efficacy is still lacking.

1. Introduction

The *Vitis* genus consists of about 70 species, which grow mostly in the temperate regions of the Northern hemisphere. It is divided into two subgenera: subgenus *Muscadinia* and subgenus *Vitis* (Ma, Wen, Ickert-Bond, Chen, & Liu, 2016). *Vitis vinifera* L. is one of the most widely cultivated and studied *Vitis* species and it is also an economically important crop worldwide. Moreover, various studies on the fruit composition and health benefits of muscadine grapes have been also reported (Xu et al., 2014, 2015, 2017). Muscadine grapes (*Vitis rotundifolia* Michx., *Vitis munsoniana* J.H. Simpson ex Planch., and *Vitis popenoei* J.L. Fennell) and wines are noted for nutritive values.

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Apart from the use of grapes as food, bioactive compounds from grapes and grape-derived products are associated with prevention of many pathophysiological processes, including cardiovascular and neurodegenerative diseases, cancers, diabetes and others. As an example, *Vitis* leaves are used in traditional medicine as laxative, stomachic, diuretic and cooling agents, as well as to treat chronic bronchitis, heart diseases and gout. Other *Vitis* species are also sources of tradictional medicines. This is the case of wild grape native to Taiwan *Vitis thunbergii* Sieb. and Zucc. var. *taiwaniana* Lu, which is applied as folk medicine for treating hepatitis, jaundice, stomachache and so on (K. T. Wang et al., 2011).

The chemical composition and biological activities of the fruits, leaves, stems and seeds of the *Vitis* species have been extensively investigated. The most health-protective biomolecules from grapes are proanthocyanidins, anthocyanins and other flavonoids, hydroxycinnamates and stilbenes (resveratrol) that possess antioxidant, antimicrobial, anti-cancer, anti-inflammatory properties and inhibit lipid peroxidation (Georgiev, Ananga, & Tsolova, 2014; Koyama, Kamigakiuchi, Iwashita, Mochioka, & Goto-Yamamoto, 2017). It has been also reported that grape phenolic compounds are directly associated with well-publicized “French paradox“. Namely, different epidemiological studies from several reports have linked the stilbene resveratrol from wines with reducing risk of myocardial infarction, atherosclerosis and other cardiovascular diseases (Catalgol, Batirel, Taga, & Ozer, 2012).

Apart from these and other medicinal properties, extracts from *Vitis* plants could be used for food preservation. The strong antioxidant potential of grapes has been described in various studies. The leaf extracts of *V. vinifera* exhibits high antioxidant activity; the IC_{50} in the DPPH assay was similar with synthetic BHT antioxidant (Aouey, Samet, Fetoui, Simmonds, & Bouaziz, 2016; Burin, Ferreira-Lima, Panceri, & Bordignon-Luiz, 2014). Other *Vitis* species such as *Vitis tiliifolia* Humb. & Bonpl. ex Schult . , a tropical grape with a purple colour, also showed a high antioxidant potential (Jiménez, Juárez, Jiménez-Fernández & And, 2018). Furthermore, other studies have reported that winery waste represent a novel feed additive. The feed which was supplemented with this waste decreased oxidative stress in broilers’ blood and tissues (Makri et al., 2017). In addition, grape extracts of different parts of the plant have exhibited antibacterial and antifungal activity against several pathogenic strains (*Staphylococcus aureus*, *Bacillus cereus*, *Escherichia coli*, *Salmonella infantis*, *Candida albicans*, etc.) (Corrales et al., 2010; Katalinić et al., 2010). As an example, the biomolecules presented in grape seed can be used to inhibit foodborne pathogens growth in cooked beef and thus are promising additives for maintaining the quality and safety of meat products (Tiwari et al., 2009).

Although some of these plant species are well investigated, there is a wide spectrum of unexplored species and underused bioresources. Therefore, this review firstly covers the phytochemical composition of different plant parts of *Vitis* species, including *V. vinifera,* and winery residues. Besides the aforementioned bioactivities and potential applications, these plant sources could have chemopreventive and therapeutic effects, thus studies *in vitro*, *in vivo* and in humans are described. This can help to understand the relationship between *Vitis* phytochemicals and their anticancer activity through several mechanisms.

2. Phenolic composition, occurrence and factors affecting their concentration in *V. vinifera*

2.1. Occurrence

V. vinifera is an important fruit crop cultivated across the globe, as commented before. Wines from *V. vinifera* contain a variety of phenolic compounds (Table 1), such as hydroxybenozic acis (e.g. dimer gallates), hydroxycinnamic acids (e.g. *trans*-caftaric acid), pyroanthocyanins (e.g. vitisin A), flavonols (e.g. quercetin and myricetin), flavones (e.g. luteolin), and flavanols and their polimeric forms (e.g. procyanidin dimers). Some of these phenolics come from grapes, while others such as vitisin A can be mainly generated during alcoholic fermentation when the concentrations of the precursors, malvidin-3-glucoside and pyruvic acid, are at higher levels (Asenstorfer, Markides, Iland, & Jones, 2003). A recent study has shown that the majority of flavanol hexosides detected in wines have a grape origin. Other flavanol hexosides are present in wine but not in grape; thus other biochemical pathways (production or degradations) from microorganisms should not be discarded (Zerbib et al., 2018).

The phenolic composition depends on the fruit part. Thus, Table 1 lists not only phenolic compounds reported from *V. vinifera* grapes, but also those found in other plant parts, including skin, seed, leaf, and root tissues. As an example, the phenolic composition of both grape pulp and skin of Garnacha Tintorera grapes (*V. vinifera* grape cv.) exhibited interesting findings. It was found that anthocyanins were asymmetrically distributed within grape pulp and skins. Malvidin derivatives were dominated in skin, followed by peonidin-type anthocyanins while peonidin 3-glucoside was exclusively found in the pulp. This in agreement with the results obtained in other cultivars (Chen et al., 2018). Further, analysis indicated the presence of small amounts of peonidin 3,5-diglucoside, peonidin dihexoside derivative followed by the occurrence of pelargonidin 3-glucoside and its acetyl and *p*-coumaroyl derivatives in *V. vinifera* grapes. Flavonols was also detected in the pulp of this cultivar, but lower contribution of myricetin, laricitrin, and syringetin as compared to the skin. The skin of Garnacha Tintorera grapes possesses higher amounts of hydroxycinnamic acids than in pulp. Caftaric acid was the main derivative detected and coutaric acid possess highest amount in the skin (Castillo-Munoz, Fernandez-Gonzalez, Gomez-Alonso, Garcia-Romero, & Hermosín-Gutiérrez, 2009b). Findings about skins from the red grape *V. vinifera* cv. Petit Verdot revealed that flavonols occur as 3-*O*-glycosides, 3-*O*-galactosides, 3-*O*-glucuronides and trace amounts of quercetin 3-*O*-(6″-rhamnosyl)-glucoside (rutin) was also recorded (Castillo-Munoz et al., 2009b). Moreover, acetylated and *p*-coumaroylated derivatives of the flavonol 3-*O*-glucosides of isorhamnetin, laricitrin and syringetin have been detected in skins and wines of *V. vinifera* grape. These results demonstrated the higher diversity of grape and wine flavonols (Favre et al., 2018).

In another work, the phenolic compounds present in the skin, pulp and seeds of hybrid grape cultivar ‘BRS Violeta’ (BRS Rubea × IAC 1398–21) were studied using solid-phase extraction (SPE) and liquid chromatograpy (LC)-mass spectrometry (MS) and MS/MS. The study showed that this cultivar has a very thick skin (46% of grape weight), accumulating most of grape phenolic compounds; maximum amounts of anthocyanins (3930 mg/kg, as malvidin 3,5-diglucoside), along with flavonols (150 mg/kg, as quercetin 3-glucoside), hydroxycinnamic acid derivatives (120 mg/kg, as caftaric acid), and proanthocyanidins (670 mg/kg, as (+)-catechin). On the contrary, a low resveratrol was detected in the skin samples. Further, seeds of the species accounted for similar proportions of low molecular weight flavan-3-ols; mainly monomers (345 mg/kg, as (+)-catechin) and proanthocyanidins (480 mg/kg, as (+)-catechin). However, traces of anthocyanins and low amounts of all the other phenolic types in its red-colored pulp were detected (Rebello et al., 2013). Alternatively, other works suggested that over all extractable phenolics in the grapes, around 10% are present in the pulp, 28–35% in the skin and 60–70% in the seeds (Fiume et al., 2014). In this regard, the phenolic substances concentration in seed, skin and peduncle extracts was ranged from 4.72 to 7.05, 2.72–3.55 g and 2.03–2.11 g catechin equivalents/kg fresh mass, respectively (Agustin-Salazar, Medina-Juárez, Soto-Valdez, Manzanares-López, & Gámez-Meza, 2014). Anyway, grape seeds and skins are good sources of phenolic compounds, including monomeric forms such as catechin, epicatechin, and gallic acid, and polymeric forms such as procyanidins (Monagas, Gómez-Cordovés, Bartolome, Laureano, & Ricardo da Silva, 2003). These authors found that the polymeric fraction represent 77–84% of total flavan-3-ols in wines and displayed a

Table 1
Example of phenolic compounds characterized in different cultivars and plant parts of *V. vinifera*.

Nº	Variety/cultivar	Chemical constituent	Plant part/product	Reference
Phenylethanoids				
1	Pinot Noir	hydroxytyrosol	seed, skin	Casazza, Aliakbarian, Mantegna, Cravotto, & Perego, 2010;
2	Tannat, Syrah, Shiraz, Muscat of Alexandria	tyrosol	leaf, grape	Boido et al., 2003; Bureau, Baumes, & Razungles, 2000; Wirth, Guo, Baumes, & Günata, 2001
Coumarins				
3	Cabernet Sauvignon, Merlot and others	esculetin	leaf	Pintać et al. (2019)
4	Merlot and Sila	umbelliferone	leaf	Pintać et al. (2019)
5	Agiorgitiko	coumarin	grape	Dourtoglou, Yannovits, Tychopoulos, and Vamvakias (1994)
Hydroxybenzoic acids				
6	Pinot Noir, Feteasсă neagră, Cabernet Sauvignon, Merlot, and others	*p*-hydroxybenzoic acid	leaf, seed	Casazza et al., 2010; Cotea et al., 2018; Katalinic et al., 2009; Pintać et al., 2019
7	Cabernet Sauvignon, Merlot, and others	2,5–dihydroxybenzoic acid	leaf	Pintać et al. (2019)
8	Grenache noir and Airén, Pinot Noir, Merlot, Petit Verdot, Carmenere and Cabernet Sauvignon, Syrah, Tinta Cão, and others	gallic acid	red grape must, leaf, skin, seed, pomace	Casazza et al., 2010; Cotea et al., 2018; Obreque-Slier et al., 2010; Guchu et al., 2015; Kadouh, Sun, Zhu, & Zhou, 2016; Rózek et al., 2007; Katalinic et al., 2009; Obreque-Slier et al., 2010; Pintać et al., 2019
9	Pinot Noir, Feteasсă neagră, Cabernet Sauvignon, Merlot, and others	protocatechuic acid	seed, skin, leaf	Casazza et al., 2010; Cotea et al., 2018; Pintać et al., 2019
10	Feteasсă neagră, Merlot, and Frankovka	vanillic acid	seed, leaf	Cotea et al., 2018; Pintać et al., 2019
11	Pinot Noir, Cabernet Sauvignon, Merlot, and others	syringic acid	seed, skin, leaf	Casazza et al., 2010; Cotea et al., 2018; Pintać et al., 2019
12	Graciano, Tempranillo, Cabernet Sauvignon	dimer gallates (B2-3-*O*-gallate, B2-3'-*O*-gallate, and B1-3-*O*-gallate)	wine, seed, skin	Monagas et al. (2003)
13	Feteasсă neagră	*o*-hydroxybenzoic acid (salicylic acid)	seed	Cotea et al. (2018)
14	Feteasсă neagră, Cabernet Sauvignon, Merlot, and others	ellagic acid	seed, leaf	Cotea et al., 2018; Pintać et al., 2019
Hydroxycinnamic acids				
15	Garnacha Tintorera, Petit Verdot, Syrah, Tinta Cão, Hybrid cultivar (Violeta Rubea × IAC 1398–21), Cabernet Sauvignon, Merlot, and others	caffeic acid	leaf, red grape must, pulp, skin, pomace, seed	Rebello et al., 2013; Rózek et al., 2007; Katalinic et al., 2009; Castillo-Munoz et al., 2009b; Kadouh et al., 2016; Pintać et al., 2019
16	Hybrid cultivar (Violeta Rubea × IAC 1398–21), Cabernet Sauvignon, Merlot, and others	*p*-coumaric acid	leaf, skin, pulp, seed, red grape must, pomace	Rebello et al., 2013; Rózek et al., 2007; Kadouh et al., 2016; Pintać et al., 2019
17	Feteasсă neagră and red, Cabernet Sauvignon, Merlot, and others	ferulic acid	leaf, red grape must, seed	Cotea et al., 2018; Karacabey and Mazza, 2008; Pintać et al., 2019; Rózek et al., 2007
18	Twenty Portuguese varieties (white and red), Muscat Lefko, Garnacha Tintorera, Tannat	*trans*-caffeoyltartaric	wine, skin, red grape must, leaf, grape	Boido et al., 2003; Castillo-Munoz et al., 2009b; Dresch et al., 2014; Fernandes et al., 2013; Karagiannis, Economou, & Lanaridis, 2000; Rózek et al., 2007
19	Twenty Portuguese varieties (white and red), Grenache noir and Airén Muscat Lefko, and Garnacha Tintorera	*trans*-coumaroyltartaric acid	red grape must, skin	Fernandes et al., 2013; Karagiannis et al., 2000; Rózek et al., 2007; Castillo-Munoz et al., 2009b
20	Hybrid cultivar (Violeta Rubea × IAC 1398–21)	hydroxycinnamoyl-tartaric acid	skin, pulp, seed	Rebello et al. (2013)
21	Hybrid cultivar	hydroxycinnamic acid derivative of caftaric acid	skin, pulp, seed	Rebello et al. (2013)
22	Cabernet Sauvignon, Merlot, and others	caffeoylquinic acid	leaf	Pintać et al. (2019)
Flavonols				
23	Red cultivars, Maraština, Pošip, Lasin, Merlot, Syrah, Vranac, Merlot, and others	kaempferol	wine, grape, leaf, pomace	Castillo-Munoz, Gómez-Alonso, García-Romero, & Hermosín-Gutiérrez, 2007; Fang, Li, Pan, & Huang, 2007; Katalinic et al., 2013; Kadouh et al., 2016; Pintać et al., 2019
24	Twenty Portuguese varieties (white and red), Yan73 and Kolor, and others	kaempferol-3-*O*-glucoside	leaf, skin, pulp, pomace, stalk	Fernandes et al., 2013; Chen et al., 2018; Monagas, Hernández-Ledesma, Gómez-Cordovés, & Bartolome, 2006; Teixeira et al., 2018
25	Yan73, Kolor, others	kaempherol-3-*O*-galactoside	skin, pulp, pomace, leaf	Chen et al., 2018; Monagas et al., 2006; Pintać et al., 2019
26	Red cultivars, Yan73, Kolor	kaempferol-3-*O*-glucuronide	grape, skin, pulp	Castillo-Munoz et al., 2007; Chen et al., 2018
27	Grenache noir and Airén Maraština, Pošip, Lasin, Merlot, Syrah, Vranac, Pinot Noir, Merlot, others	Quercetin	wine, leaf, red grape must, skin, seed, peduncle, pomace	Agustin-Salazar et al., 2014; Casazza et al., 2010; Fang et al., 2007; Guchu et al., 2015; Monagas et al., 2006; Katalinic et al., 2009; Katalinic et al., 2013; Kadouh et al., 2016; Rózek et al., 2007; Pintać et al., 2019
28	Petit Verdot, Syrah, Tinta Cão	quercetin hydrate	pomace	Kadouh et al. (2016)
29	Twenty Portuguese varieties (white and red), Yan73, Kolor, Cabernet Sauvignon, Merlot and others	quercetin-3-*O*-galactoside	skin, pulp, pomace, leaf	Monagas et al., 2006; Fernandes et al., 2013; Dresch et al., 2014; Chen et al., 2018; Pintać et al., 2019

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Table 1 (*continued*)

Nº	Variety/cultivar	Chemical constituent	Plant part/product	Reference
30	Grenache noir and Airén, twenty Portuguese varieties (white and red), Yan73, Kolor, Hybrid cultivar (Violeta, BRS Rubea × IAC 1398–21), and others	quercetin-3-*O*-glucoside	skin, pulp, seed, pomace, leaf	Chen et al., 2018; Guchu et al., 2015; Fernandes et al., 2013; Dresch et al., 2014; Monagas et al., 2006; Rebello et al., 2013; Pintać et al., 2019
31	Maraština, Pošip, Lasin, Merlot, Syrah, and Vranac	quercetin-4'-glucoside	leaf	Katalinic et al., 2009; Katalinic et al., 2013
32	Yan73, Kolor, others	quercetin-3-*O*-glucuronide	leaf, pomace, peduncle, skin, seed, pulp, stalk	Chen et al., 2018; Teixeira et al., 2018
33	Marastina, Pošip, Lasin, Merlot, Syrah, Vranac, Petit Verdot, Syrah, Tinta Cão, Yan73, Kolor	quercetin-3-*O*-rutinoside	leaf, pomace, peduncle, skin, pulp, seed	Rózek et al., 2007; Katalinic et al., 2009; Dresch et al., 2014; Agustin-Salazar et al., 2014; Kadouh et al., 2016; Chen et al., 2018
34		quercetin-3-*O*-hexoside	peduncle, skin, seed	Agustin-Salazar et al. (2014)
35	Cabernet Sauvignon, Merlot and others	quercetin-3-*O*-rhamnoside	leaf	Pintać et al. (2019)
36	Garnacha Tintorera (also known as Alicante Bouschet, Maraština, Pošip, Lasin, Merlot, Syrah, Vranac, Petit Verdot, Syrah, Tinta Cão, others	myricetin	wine, pulp, pomace, peduncle, leaf, skin, seed	Agustin-Salazar et al., 2014; Castillo-Munoz et al., 2009b; Fang et al., 2007; Katalinic et al., 2009; Katalinic et al., 2013; Kadouh et al., 2016
37	Twenty Portuguese varieties (white and red), Yan73, Kolor	myricetin-3-*O*-glucoside	leaf, skin, pulp	Fernandes et al., 2013; Chen et al., 2018
38	Yan73, Kolor	myricetin-3-*O*-glucuronide	skin, pulp	Chen et al. (2018)
39	Yan73, Kolor	myricetin-3-*O*-galactoside	skin, pulp	Chen et al. (2018)
40	Cabernet Sauvignon, Merlot and others	isorhamnetin	wine, grape, leaf	Castillo-Munoz et al., 2007; Fang et al., 2007; Pintać et al., 2019
41	Yan73, Kolor	isorhamnetin-3-*O*-glucoside	skin, pulp	Chen et al. (2018)
42	Red cultivars Garnacha Tintorera (also known as Alicante Bouschet	laricitrin	grape, pulp skin	Castillo-Munoz et al., 2007; Castillo-Munoz et al., 2009b
43	Red cultivars, Yan73, Kolor	laricitrin-3-glucoside	grape, skin, pulp	Castillo-Munoz et al., 2007; Chen et al., 2018
44	Red cultivars	methoxylated trisubstituted flavonols	grape	Castillo-Munoz et al. (2007)
45	Red cultivars Garnacha Tintorera (also known as Alicante Bouschet	syringetin	grape, pulp, skin	Castillo-Munoz et al., 2007
46	Yan73, Kolor	syringetin-3-O-glucoside	skin, pulp	Chen et al. (2018)
Anthocyanins				
47	Hybrid cultivar (Violeta Rubea × IAC 1398–21)	anthocyanidin 3,5-diglucoside	skin, pulp seed	Rebello et al. (2013)
48	Pinot Noir, Grenache noir and Airén, Yan73 and Kolor	malvidin-3-*O*-glucoside	grape, pulp, pomace, skin,	Cortell, Halbleib, Gallagher, Righetti, & Kennedy, 2007a,b; Guchu. et al., 2015; Chen et al., 2018
49	Tannat	malvidin-3-glucoside	skin, pulp, seed, leaf	Boido et al., 2003; Monagas et al., 2006
50	Hybrid cultivar (Violeta Rubea × IAC 1398–21)	malvidin 3,5-diglucoside	skin, pulp, seed	Rebello et al. (2013)
51	Yan73 and Kolor	malvidin-3-*O*-acetylglucoside	skin, pulp	Chen et al. (2018)
52		malvidin 3-hexoside	peduncle, skin, seed	Agustin-Salazar et al. (2014)
53	Tannat	malvidin-3-acetylglucoside	seed, pomace	Boido et al., 2003; Guchu. et al., 2015
54	Merlot	malvidin chloride	pomace	Kadouh et al. (2016)
55	Pinot Noir vineyard, Malbec	peonidin	grape	Cortell, Halbleib, Gallagher, Righetti, & Kennedy, 2007b; Berli, Fanzone, Piccoli, & Bottini, 2011
56	Pinot Noir, Yan73, Kolor Tannat, Garnacha Tintorera	peonidin-3-*O*-glucoside	grape, skin, pulp, seed, leaf	Cortell et al., 2007a; Dresch et al., 2014; Chen et al., 2018
57	Tannat	peonidin-3-acetylglucoside	pulp, leaf	Boido et al., 2003; Monagas et al., 2006
58	Garnacha Tintorera (also known as Alicante Bouschet	peonidin dihexoside derivative	skin, pulp	Castillo-Munoz et al. (2009b)
59	Yan73, Kolor	peonidin-3-*O*-acetylglucoside	skin or pulp	Chen et al. (2018)
60	Yan73, Kolor	peonidin-3,7-*O*-diglucoside	skin or pulp	Chen et al. (2018)
61	Yan73, Kolor	peonidin pentoside	skin or pulp	Chen et al. (2018)
62	Garnacha Tintorera (also known as Alicante Bouschet), Yan73, Kolor	pelargonidin 3-glucoside	skin, pulp	Castillo-Munoz et al., 2009b; Chen et al., 2018
63	Merlot	delphinidin chloride	pomace	Kadouh et al. (2016)
64	Tannat, Yan73, Kolor	delphinidin-3-*O*-acetylglucoside	skin, pulp	Boido et al., 2003; Chen et al., 2018
65	Tannat Yan73, Kolor	delphinidin-3-*O*-glucoside	skin, pulp, seed, leaf	Boido et al., 2003; Monagas et al., 2006; Chen et al., 2018
66	Pinot Noir, Malbec	delphinidin	grape	Berli et al., 2011; Cortell et al., 2007a,b
67	Merlot	cyanidin chloride	pomace	Kadouh et al. (2016)
68	Pinot Noir, Malbec	cyanidin	grape	Berli et al., 2011; Cortell et al., 2007a,b
69	Tannat, Yan73, Kolor	cyanidin-3-*O*-glucoside	skin, pulp, seed, leaf	Boido et al., 2003; Chen et al., 2018; Dresch et al., 2014; Monagas et al., 2006
70	Yan73, Kolor	cyanidin-3-*O*-acetylglucoside	skin or pulp	Chen et al. (2018)
71	Pinot Noir, Malbec	petunidin	grape	Berli et al., 2011; Cortell et al., 2007a,b
72	Tannat, Yan73, Kolor	petunidin-3-*O*-glucoside	skin, pulp, seed, leaf	Boido et al., 2003; Monagas et al., 2006; Chen et al., 2018
73	Tannat,Yan73, Kolor	petunidin-3-*O*-acetylglucoside	seed, skin, pulp	Boido et al., 2003; Chen et al., 2018

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Table 1 (*continued*)

Nº	Variety/cultivar	Chemical constituent	Plant part/product	Reference
Anthocyanins conjugated with hydroxyccinamic acids				
73	Yan73, Kolor, Tannat	cyanidin-3-*O*-coumarylglucoside	skin, pulp, leaf	Chen et al., 2018; Monagas et al., 2006
74	Tannat	cyanidin-3-(p-coumaroyl)glucoside	skin	Boido et al. (2003)
75	Tannat	cyanidin-3-(*p*-coumaroyl) glucoside (cis)	skin, wine	Boido et al. (2003)
76	Yan73, Kolor	pelargonidin-3-*O*-coumarylglucoside	skin, pulp	Chen et al. (2018)
77	Yan73, Kolor, Tannat	peonidin-3-*O*-coumarylglucoside	skin, pulp, wine	Boido et al., 2003; Chen et al., 2018
78	Tannat	peonidin-3-(*p*-coumaroyl)glucoside (*cis*)	skin	Boido et al. (2003)
79	Yan73, Kolor	delphinidin-3-*O*-coumarylglucoside	skin, pulp	Chen et al. (2018)
80	Tannat	delphinidin-3-(6-*p*-coumaroyl)glucoside	leaf, skin, wine	Boido et al., 2003; Monagas et al., 2006
81	Tannat	delphinidin-3-(*p*-coumaroyl) glucoside (*cis*)	skin	Boido et al. (2003)
82	Tannat	petunidin-3-(*p*-coumaroyl)glucoside (*cis*)	skin	Boido et al. (2003)
83	Yan73, Kolor	petunidin-3-*O*-coumarylglucoside	skin, pulp, leaf, wine	(Boido et al., 2003); Chen et al., 2018; Monagas et al., 2006
84	Tannat, Portuguese cultivars	malvidin-3-*O*-coumarylglucoside	leaf, skin, pulp, seed, stalk	Boido et al., 2003; Chen et al., 2018; Monagas et al., 2006; Teixeira et al., 2018
85	Tannat	malvidin-3-caffeoylglucoside	skin, wine	Boido et al. (2003)
86	Tannat	malvidin-3-(*p*-coumaroyl)glucoside (*cis*)	skin, wine	Boido et al. (2003)
87	Tannat	malvidin-3-(*p*-coumaroyl)glucoside	skin, wine	Boido et al. (2003)
Pyranoanthocyanin				
88	Cabernet Sauvignon, Noir vineyard, Shiraz, others	vitisin A	grape, wine	Asenstorfer et al., 2003; Cortell et al., 2007b; Schwarz, Quast, Baer, & Winterhalter, 2003
89	Tannat	vitisin B	skin, wine	Boido et al. (2003)
90	Tannat	others	skin, wine	Boido et al. (2003)
Flavanols				
91	Pinot Noir, Carmenere and Cabernet Sauvignon, Petit Verdot, Syrah, Tinta Cão, Graciano, Tempranillo, Carmenere and Cabernet Sauvignon, Maraština, and others	catechin	seed, skin	Agustin-Salazar et al., 2014; Casazza et al., 2010; Cotea et al., 2018; Guchu. et al., 2015; Katalinic et al., 2009; Katalinic et al., 2013; Kadouh et al., 2016; Monagas et al., 2003; Obreque-Slier et al., 2010; Rebello et al., 2013; Rózek et al., 2007
92	Graciano, Tempranillo, and Cabernet Sauvignon, Maraština, Pošip, Lasin, Merlot, Syrah, Vranac, Grenache noir and Airén Carmenere, Cabernet Sauvignon	epicatechin	peduncle, skin, seed	Agustin-Salazar et al., 2014; Guchu et al., 2015; Katalinic et al., 2009, 2013; Monagas et al., 2003; Obreque-Slier et al., 2010; Rózek et al., 2007
93	Merlot	epicatechin gallate	pomace, peduncle, skin, seed	Agustin-Salazar et al., 2014; Kadouh et al., 2016
94	Carmenere, Cabernet Sauvignon	epicatechin-3-*O*-gallate	skin, seed	Obreque-Slier et al. (2010)
95	Carmenere, Cabernet Sauvignon	dimeric procyanidins esterified with gallic acid	skin, seed	Obreque-Slier et al. (2010)
96	Graciano, Tempranillo, Cabernet Sauvignon, Feteasc̆ă neagră	procyanidin dimer (B1)	wine, seed, skin	Cotea et al., 2018; Monagas et al., 2003
97	Graciano, Tempranillo, Cabernet Sauvignon, Feteasc̆ă neagră	procyanidin dimer (B2)	wine, seed, skin	Cotea et al., 2018; Monagas et al., 2003
98	Graciano, Tempranillo, Cabernet Sauvignon	procyanidin dimer (B3)	wine, seed, skin	Monagas et al. (2003)
99	Graciano, Tempranillo, Cabernet Sauvignon	procyanidin dimer (B4)	wine, seed, skin	Monagas et al. (2003)
100		procyanidin dimer (B5)	seed	Zhao, Wang, Chen, and Agarwal (1999)
101		procyanidin B2 3,3(″)-di-O-gallate	seed	Tyagi et al. (2014)
102		procyanidin B5–3′-gallate	seed	Zhao et al. (1999)
103	Graciano, Tempranillo, Cabernet Sauvignon	procyanidins trimer (T2)	wine, seed, skin	Monagas et al. (2003)
104	Graciano, Tempranillo, Cabernet Sauvignon	procyanidins trimer (C1)	wine, seed, skin	Monagas et al. (2003)
105		aminoethylthio − flavan-3-ol conjugates	pomace	Torres and Bobet (2001)
Flavones				
106	Maraština, Pošip, Lasin, Merlot, Syrah, Vranac	apigenin	leaf	Katalinic et al., 2009; Katalinic et al., 2013
107	Cabernet Sauvignon, Merlot and others	luteolin	wine, leaf	Fang et al., 2007; Pintać et al., 2019
108	Tinta Roriz and Touriga Nacional	fisetin	skin	Novak, Janeiro, Seruga, and Oliveira-Brett (2008)
109	Cabernet Sauvignon, Merlot and others	luteolin 7-*O*-glucoside	leaf	Pintać et al. (2019)
110	Cabernet Sauvignon, Merlot and others	amentoflavone	leaf	Pintać et al. (2019)
111	Cabernet Sauvignon, Merlot and others	baicalein	leaf	Pintać et al. (2019)
Flavanonols				
112	Portuguese cultivars	astilbin	stalk	Teixeira et al. (2018)
113	Portuguese cultivars	engeletin	stalk	Teixeira et al. (2018)
Flavanones				
114	Cabernet Sauvignon, Merlot and others	naringenin	leaf	Pintać et al. (2019)

(*continued on next page*)

Table 1 (*continued*)

N°	Variety/cultivar	Chemical constituent	Plant part/product	Reference
Stilbenes				
115	Milled canes, Pinot Noir, Hasaine Hasansky, sladki, Zilga, Yubilei Novgoroda, Cabernet Sauvignon, Merlot and others	*trans*-resveratrol	woody stems, pomace, skin, seed, stalk, leaf, red grape must, root	Casazza et al., 2010; Cotea et al., 2018; Esatbeyoglu et al., 2016; Kadouh et al., 2016; Karacabey and Mazza, 2008; Pintać et al., 2019; Pussa, Floren, Kuldkepp, & Raal, 2006
116	*Hasaine Hasansky, sladki, Zilga, Yubilei Novgoroda,*	*trans-resveratrol derivatives*	woody stems	Pussa et al. (2006)
117	Hasaine Hasansky, sladki, Zilga, Yubilei Novgoroda	piceatannol	woody stems, root	Esatbeyoglu et al., 2016; Pussa et al., 2006
118	Several cultivars	*trans*-ε-viniferin	milled grape canes, stalk, root	Esatbeyoglu et al., 2016; Karacabey and Mazza, 2008; Teixeira et al., 2018
119	Maraština, Pošip, Lasin, Merlot, Syrah, Vranac	astringin	leaf	Katalinic et al. (2013)
120		ampelopsin A	root	Esatbeyoglu et al. (2016)
121		miyabenol C	root	Esatbeyoglu et al. (2016)
122	Cabernet-Sauvignon, Chardonnay, Chardonnay	pterostilbene	leaf, grapes[a]	Adrian, Jeandet, Douillet-Breuil, Tesson, & Bessis, 2000; Langcake, Cornford, & Pryce, 1979

[a] With symptoms of *Botrytis cinerea* attack.

mean degree of polymerization value from 6.3 to 13. While in case of grapes seeds the polymeric fraction represented 75–81% of total flavan-3-ols and 94–98% in skins and displayed mean degree of polymerization values of 6.4–7.3 in seeds and 33.8–85.7 in skins. Similarly, proanthocyanidins were unequally distributed in the skin, pulp and seeds of other grape cultivars. Proanthocyanidin content, composition and mean degree of polymerisation varied distinctly in the three tissues, especially the profile of the proanthocyanidin terminal and extension subunits (Chen et al., 2018).

However, few reports on leaves, stems and roots of different cultivars are available, but these parts also present stilbenes, including *trans*-resveratrol. Moreover, the main anthocyanins isolated from leaf extracts were cyanidin-3-*O*-glucoside and peonidin-3-*O*-glucoside, while rutin, quercetin-3-*O*-galactoside, quercetin-3-*O*-glucoside, and quercetin-3-*O*-glucuronide were the predominant flavonoids. Other authors have described the presence of *trans*-caftaric acid, anthocyanins conjugated with hydroxyccinamic acids and several phenolic volatile compounds (Dresch et al., 2014) (Table 1). Concerning stems, González-Centeno et al. (2012) have profiled the flavanols composition in 10 different *V. vinifera* cultivars. Among them, the 'Callet' cultivar is promising polyphenol-rich source. Furthermore, a total of seven stilbenes, two monomeric (resveratrol and piceatannol), two dimeric (*trans*-ε-viniferin and ampelopsin A), one trimeric (miyabenol C), and two tetrameric compounds were detected in a root extract of *V. vinifera* using LC-MS/MS analyses (Esatbeyoglu et al., 2016).

It is also reported that waste products produced during wine and grape juice processing are phenolic compounds rich sources. Grape pomace (grape bagasse or grape marc) obtained as a byproduct of winemaking industries represents almost 20% by weight of the original grape. If the stalks are removed before processing of the grapes, the residue comprises of 60% skin and pulp and 40% seeds. Winery waste pressed with the stalks consists of 30% stalks, 40% skin and pulp, and 30% seeds, with slight differences depending on the grape cultivar (Domínguez, Sanchez Hernandez, & Lores, 2017). It also possesses significant amounts of substances that are not efficiently used. As an example, Baydar, Ozkan, and Sağdic (2004) extracted the powdered grape seeds and pomace with petroleum ether, being re-extracted with different solvent mixtures to determine their total phenolic content. It is observed that the total phenolic content depended on the solvent used and the byproduct type. The phenolic content varied from 627.98 to 667.87 mg gallic acid equivalent (GAE)/g in the grape seeds extract, while pomace extracts possessed 29.55–45.44 mg GAE/g, respectively. Seeds also contains higher content of total phenolic compounds (108.3 mg GAE/g), *o*-diphenols (47.0 mg GAE/g) and flavonoids (47.2 mg catechin catechin equivalents (CE)/g) compared to skins (34.2 mg GAE/g, 10.1 mg GAE/g, 21.6 mg CE/g, respectively). In another work, phenolic compounds were quantified in pre- and post-fermentation products obtained from the fermentation of *V. vinifera* cv. Grenache noir and Airén, including wine, pomace, lees, and rachises. Pomace was observed to be a rich source of all identified polyphenols. Over 90% of the total amount of gallic acid, catechin and epicatechin and ~50% of the quercetin-3-*O*-glucoside was found in the pomace. Lees possessed a significantly higher concentration of gallic acid, catechin, epicatechin, malvidin-3-*O*-glucoside, malvidin-3-acetylglucoside, quercetin-3-*O*-glucoside, and quercetin (Guchu, Ebeler, Lee, & Mitchell, 2015).

Grape stalks wastes from wine production was investigated for its chemical composition after milling and separation in three different size material fractions. The presence of lignin, polysaccharides and polyphenolic compounds was confirmed by Fourier transform infrared spectroscopy (Pujol et al., 2013). Moreover, the presence of phenolic compound in stalks (sample prepared by mixing several Portuguese cultivars) has been also confirmed using colorimetric methods, LC-UV-Vis and LC-MS (Teixeira, Mateus, de Freitas, & Oliveira, 2018), including dimeric and trimeric proanthocyanidin, flavonols (quercetin glucuronide, kaempferol glucoside), flavanonols (astilbin and

Table 2
Other phenolic compounds found in *V. vinifera*.

Nº	Variety/cultivar	Chemical constituent	Plant part/ product	Reference
1	Syrah, Tannat, Riesling Shiraz, Muscat of Alexandria, Aglianico	4-vinylguaiacol and derivatives	Grape, leaf, skin, pulp juice, wine	Boido et al., 2003; Bureau, Baumes, & Razungles, 2000; Keyzers & Boss, 2010; Ugliano & Moio, 2008; Wirth et al., 2001
2	Syrah, Shiraz, Muscat of Alex,ria, Tannat, Aglianico	4-vinylphenol and derivatives	Grape, leaf, skin, pulp juice, wine	Boido et al., 2003; Bureau et al., 2000; Genovese, Lamorte, Gambuti, & Moio, 2013; Wirth et al., 2001
3	Syrah, Shiraz, Muscat of Alex,ria,Tannat, Aglianico	methyl vanillate	Grape, leaf, skin, pulp juice	Bureau et al., 2000; Genovese et al., 2013; Wirth et al., 2001
4	Syrah, Shiraz, Muscat of Alex,ria, Tannat	zingerone	Grape, leaf	Bureau et al., 2000; Wirth et al., 2001
5	Shiraz, Muscat of Alexandria	3,4,5-trimethoxyphenol	Grape, leaf	Wirth et al. (2001)
6	Syrah, Shiraz, Muscat of Alexandria, and Aglianico	guaiacol	Grape, skin, juice	Bureau et al., 2000; Genovese et al., 2013; Wirth et al., 2001
7	Shiraz, Muscat of Alexandria	alcohol methyl benzylic	Grape	Wirth et al. (2001)
8	Agiorgitiko, Shiraz, Muscat of Alexandria, Yan73 & Kolor teinturier	phenol	Leaf, grape, juice	Chen et al., 2018; Dourtoglou et al., 1994; Wirth et al., 2001
9	Agiorgitiko, Syrah, Shiraz, Muscat of Alexandria, Aglianico, Yan73 & Kolor teinturier	eugenol	Leaf, grape, skin, juice	Chen et al., 2018; Bureau et al., 2000; Dourtoglou et al., 1994; Wirth et al., 2001; Genovese et al., 2013
10	Shiraz, Muscat of Alexandria	4-methoxybenzene methanol	Grape	Wirth et al. (2001)
11	Syrah, Shiraz, Muscat of Alexandria	acetovanillone	Grape	Bureau et al., 2000; Wirth et al., 2001
12	Agiorgitiko, Shiraz, Muscat of Alexandria, Aglianico	vanillin	Leaf, grape, skin, juice	Dourtoglou et al., 1994; Genovese et al., 2013; Wirth et al., 2001
13	Syrah, Shiraz, Muscat of Alexandria	3,4-dimethoxyphenol	Grape	Bureau et al., 2000; Wirth et al., 2001
14	Shiraz, Muscat of Alexandria	ethyl homovanilate	Grape	Wirth et al. (2001)
15	Syrah, Shiraz, Muscat of Alexandria	benzyl salicylate	Grape	Bureau et al., 2000; Wirth et al., 2001
16	Syrah, Shiraz, Muscat of Alexandria	vanillol	Grape	Bureau et al., 2000; Wirth et al., 2001
17	Syrah, Shiraz, Muscat of Alexandria	vanilloyl methyl ketone	Grape	Bureau et al., 2000; Wirth et al., 2001
18	Syrah, Shiraz, Muscat of Alexandria	2-(4-guaiacyl)-ethanol	Leaf, grape,	Bureau et al., 2000; Wirth et al., 2001
19	Syrah, Shiraz, Muscat of Alexandria	3,5-dimethoxyphenol	Grape	Wirth et al. (2001)
20	Shiraz	zingerol	Grape	Wirth et al. (2001)
21	Syrah, Shiraz, Muscat of Alexandria	4-hydroxybenzaldehyde	Grape	Wirth et al. (2001)
22	Syrah, Shiraz, Muscat of Alexandria	4-hydroxybenzaldehyde + methyl 4-hydroxybenzoate	Grape	Wirth et al. (2001)
23	Syrah, Shiraz, Muscat of Alexandria	syringaldehyde + methyl 4-hydroxybenzoate	Leaf, grape	Bureau et al., 2000; Wirth et al., 2001
24	Syrah, Shiraz, Muscat of Alexandria	methyl syringoate	Leaf, grape	Bureau et al., 2000; Wirth et al., 2001
25	Syrah, Shiraz, Muscat of Alexandria	3-(4-guaiacyl)propanol	Leaf, grape	Bureau et al., 2000; Wirth et al., 2001
26	Agiorgitiko	phenylethyl alcohol	Grape	Dourtoglou et al. (1994)
27	Agiorgitiko	phenyl ethyl hexanoate	Grape	Dourtoglou et al. (1994)
28	Agiorgitiko	phenyl ethyl propionate	Grape	Dourtoglou et al. (1994)
29	Agiorgitiko	phenyl ethyl butyrate	Grape	Dourtoglou et al. (1994)
30	Agiorgitiko	hexyl benzoate	Grape	Dourtoglou et al. (1994)
31	Agiorgitiko	benzyl hexanoate	Grape	Dourtoglou et al. (1994)
32	Agiorgitiko	benzyl benzoate	Grape	Dourtoglou et al. (1994)

engeletin), the anthocynin malvidin-3-*O*-(6-*p*-coumaroyl)glucoside and the stilbene viniferin (Table 1).

Moreover, other phenolic compounds, which are characteristic of aroma of grape and leaf tissues, have been characterized and are listed in Table 2.

2.2. Phenolic compounds in other Vitis species

The phytochemical composition of other *Vitis* species and hybrids is shown in Table 3. The presence of *trans*-caftaric acid, quercetin derivatives and anthocyanins has been found in leaf extracts of *Vitis labrusca* L. (Dresch et al., 2014). By means of nuclear magnetic resonace, Pacifico et al. (2011) showed that *Vitis* × *labruscana* 'Isabella', known in Italy as "fragola" (strawberry) grape, presented catechins in both stalk and seed, whereas caffeic acid and quercetin were the main phenolic compounds of leaf. These authors also found three isomers of hydroxycinnamoyl tartaric acid, isoquercitrin, and five flavonol glucuronides in leaf (Pacifico et al., 2013). Notably, some of the latter metabolites were characterized by glucuronic or galacturonic acid methyl ester, which was described in the genus *Vitis* for the first time in this work. Furthermore, four new resveratrol derivatives, vitisinols A-D, together with (+)-ε-viniferin, (−)-viniferal, ampelopsin C, miyabenol A, (+)-vitisin A, and (+)-vitisin C were isolated in the roots of *V. thunbergii* (*V. ficifolia*) (Huang, Tsai, Shen, & Chen, 2005). While *V. rotundifolia* (muscadine) seeds and grape pomace may contain ellagic acid, resveratrol, flavonols, flavanols, and anthocyainins. Furthermore, by means of LC-MS^n 17, 28 and 43 phenolic compounds were tentatively identified in the pulp, skin and seed of this plant (Sandhu & Gu, 2010). Several anthocyanins have also been characterized in the fruits of *Vitis coignetiae* Pulliat, a folk medicine in Korea known as meoru (Yun et al., 2010).

2.3. Variation due to cultivar

The phenolic profile of *Vitis* plant parts, including grapes, depends on the cultivar (Perestrelo, Silva, Silva, & Câmara, 2018; Sagdic, Ozkan, Yetim, Ekici, & Yilmaz, 2011), but flavonoids, phenolic acids and stilbenes are generally the most important phenolic classes. Moreover, the variation of the phenolic composition in wine (Zerbib et al., 2018) and wine byproducts also depends on the cultivar (Kammerer, Claus, Carle, & Schieber, 2004). This is importance in order to standardize extracts when looking for formulating functional ingredients. As an example, several flavonoid compounds have been reported from seven widespread *V. vinifera* red grape cultivars. Among them, 3-glucosides and 3-glucuronides of myricetin and quercetin and the 3-glucosides of kaempferol and isorhamnetin were the main flavonols. Further, 3-glucosides have the methoxylated trisubstituted flavonols, laricitrin and syringetin, as predominant. Nonetheless, minor flavonols were detected

Table 3
Example of phenolic compounds present in other *Vitis* species.

Nº	Species	Variety/cultivar	Chemical constituent	Plant part/culture/ extract	Reference
1	*V. labrusca*		*trans*-caftaric acid	leaf	Dresch et al. (2014)
2	*V. labrusca*		rutin	leaf	Dresch et al. (2014)
3	*V. labrusca*		quercetin-3-*O*-galactoside	leaf	Dresch et al., 2014;
4	*V. labrusca*		quercetin-3-*O*-glucoside	leaf	Dresch et al. (2014)
5	*V. labrusca*		quercetin-3-*O*-glucuronide	leaf	Dresch et al. (2014)
6	*V. labrusca; V. coignetiae*		peonidin-3-*O*-glucoside	leaf, fruit	Dresch et al., 2014; Yun et al., 2010
7	*V. labrusca; V. coignetiae*		cyanidin-3-*O*-glucoside	leaf, fruit	Dresch et al., 2014; Yun et al., 2010
8	*Vitis* × *labruscana*	Isabella	catechin	seed, stalk	Pacifico et al. (2011)
9	*Vitis* × *labruscana*	Isabella, Noble	epicatechin	seed, stalk, pomace	Luo et al., 207; Pacifico et al., 2011
10	*Vitis* × *labruscana; V. rotundifolia*	Isabella, Noble, other	quercetin[ab]	leaf, pomace, skin	Luo et al., 2017; Pacifico et al., 2011; Paller et al., 2015; Sandhu & Gu, 2010
11	*Vitis* × *labruscana*	Isabella	caffeic acid	leaf	Pacifico et al. (2011)
12	*V. thunbergii*		vitisinol A	root	Huang et al. (2005)
13	*V. thunbergii*		vitisinol B	root	Huang et al. (2005)
14	*V. thunbergii*		vitisinol C	root	Huang et al. (2005)
15	*V. thunbergii*		vitisinol D	root	Huang et al. (2005)
16	*V. thunbergii*		(+)-ε-viniferin	root	Huang et al. (2005)
17	*V. thunbergii*		(−)-viniferal	root	Huang et al. (2005)
18	*V. thunbergii*		ampelopsin C	root	Huang et al. (2005)
19	*V. thunbergii*		miyabenol A	root	Huang et al. (2005)
20	*V. thunbergii*		(+)-vitisin A	root	Huang et al. (2005)
21	*V. thunbergii*		(+)-vitisin C	root	Huang et al. (2005)
22	*V. rotundifolia*	Noble, others	ellagic acid	pomace, skin	Luo et al., 2017; Paller et al., 2015
23	*V. rotundifolia*	Noble	gallic acid[a]	pomace	Luo et al. (2017)
24	*V. rotundifolia*	Noble	kaempferol[ab]	pomace	Luo et al., 2017; Sandhu & Gu, 2010
25	*V. rotundifolia*	Noble	myricetin[ab]	pomace, skin	Luo et al., 2017; Sandhu & Gu, 2010
26	*V. rotundifolia*	Noble	isorhamentin[a]	pomace	Luo et al. (2017)
27	*V. rotundifolia*	Noble	syringetin[a]	pomace	Luo et al. (2017)
28	*V. rotundifolia*	Noble	procyanidin	pomace	Luo et al. (2017)
29	*V. rotundifolia*	Noble	delphinidin	pomace	Luo et al. (2017)
30	*V. rotundifolia*	Noble	cyanidin	pomace	Luo et al. (2017)
31	*V. rotundifolia*	Noble	petunidin	pomace	Luo et al. (2017)
32	*V. rotundifolia*	Noble	malvidin	pomace	Luo et al. (2017)
33	*V. rotundifolia*		resveratrol	skin	Paller et al. (2015)
34	*V. rotundifolia*		hydrolyzable tannins	seed, skin	Sandhu and Gu (2010)
35	*V. rotundifolia*		flavan-3-ols	seed	Sandhu and Gu (2010)
36	*V. rotundifolia*		ellagic acid derivatives	seed	Sandhu and Gu (2010)
37	*V. rotundifolia*		quercetin rhamnoside	seed	Sandhu and Gu (2010)
38	*V. rotundifolia*		anthocyanin 3,5-diglucoside	skin	Sandhu and Gu (2010)
39	*V. coignetiae*		delphinidin-3,5-diglucoside	grape	Yun et al. (2010)
40	*V. coignetiae*		cyanidin-3,5-diglucoside	grape	Yun et al. (2010)
41	*V. coignetiae*		petunidin-3,5-diglucoside	grape	Yun et al. (2010)
42	*V. coignetiae*		delphinidin-3-glucoside	grape	Yun et al. (2010)
43	*V. coignetiae*		malvidin-3,5-diglucoside	grape	Yun et al. (2010)
44	*V. coignetiae*		peonidin-3,5-diglucoside	grape	Yun et al. (2010)
45	*V. coignetiae*		petunidin-3-glucoside	grape	Yun et al. (2010)
46	*V. coignetiae*		malvidin-3-glucoside	grape	Yun et al. (2010)
47	*V. riparia*		pterostilbene	leaf	Langcake (1981)
48	*V. riparia/V. amurensis*		resveratrol	leaf	Kiselev, Aleynova, Grigorchuk, & Dubrovina, 2017; Langcake, 1981
49	*V. riparia/V. amurensis*		ε-viniferin	leaf	Kiselev et al., 2017; Langcake, 1981
50	*V. riparia*		α-viniferin	leaf	Langcake (1981)

[a]Phenolic compounds and derivatives in the case of grape pomace (Luo et al., 2017).
[b]Glycosides (Sandhu & Gu, 2010).

and could be used a differentiation markers; i.e. 3-galactosides of kaempferol and laricitrin, 3-glucuronide of kaempferol, and 3-(6"-acetyl)glucosides of quercetin and syringetin (Castillo-Munoz et al., 2007).

Concerning other *Vitis* parts and flavonoids, Monagas et al. (2003) showed that the content of monomers ((+)-catechin and (−)-epicatechin), procyanidin dimers (B1–B4), trimers (T2 and C1), and dimer gallates (B1-3-*O*-gallate, B2-3-*O*-gallate and B2-3'-*O*-gallate) also varied depending on the cultivar; seed (2.30–8.21 mg/g), skin (0.14–0.38 mg/g) and wine (76.93–133.18 mg/L). This means that the total anthocyanins content, monomeric flavan-3-ols, and total flavonoids, the mean degree of polymerization, and the percentage of galloylation of the skin and seed is highly dependent on the cultivar (Obreque-Slier et al., 2010). Another study also suggested that the phenolic composition of seeds and skins from pomace depend on the cultivar. In this case, a total of 13 anthocyanins, 11 hydroxybenzoic and hydroxycinnamic acids, 13 catechins and flavonols and 2 stilbenes were quantified. A large variation was observed among all individual phenolic compounds studied, depending on cultivar and vintage, red or white (Kammerer et al., 2004).

Likewise, phenolic compounds were evaluated in grapevine stems of three frost-hardy grapevine varieties. While the total phenolic content of the grapevine stems depended on the cultivar, the qualitative profile was similar. The methanolic extracts contained *trans*-resveratrol and its derivatives as major components (Pussa et al., 2006). In another study, leaf aqueous extracts from twenty Portuguese varieties (white and red)

of *V. vinifera* were evaluated for their phenolic composition. Again the content of these phenolic compounds varied from 14909.9 to 43199.3 mg/kg extract (dry basis) in white cultivars and from to 19227.1–67600.4 mg/kg extract (dry basis) in red cultivars. (Fernandes et al., 2013). Qualitatively, quercetin-3-*O*-galactoside and kaempferol-3-*O*-glucoside were the most predominant among studied varieties. Alternatively, González-Centeno et al. (2012) evaluated stems from 10 different cultivars and showed not only differences in the total phenolic content but also in the phenolic composition. However, the authors also suggested that there were no significant differences when stems from red and white varieties were evaluated separately.

2.4. Growth conditions, ripening and picking-time

The soil and climatic conditions affects the phenolic composition of grapes since these factors influence their biochemical synthesis and consequently their biological properties (Burin et al., 2014).

The phenolic composition of *V. vinifera* cv. Pinot noir was assessed in relation to the variations in its growth and resulting fruit and wine. For that, a commercial vineyard comprising the same clone, rootstock, age, and vineyard management practices was used for study. Flavanols were studied to analyse patterns in growth and development on a geo referenced grid pattern, but no significant influence of vine vigor was observed on the concentration per seed and slight differences were observed in proanthocyanidin composition of seed. However, it seems that in skins the content of proanthocyanidin (mg/grape) was increased in fruit from zones with a decrease in vine vigor, while minor changes were observed in seed proanthocyanidin composition (Cortell, Halbleib, Gallagher, Righetti, & Kennedy, 2005). These authors also evaluated the anthocyanin accumulation and composition in two vineyard sites based upon differences in vine growth and two periods. High vigor zones in both years were related with the lower anthocyanin concentration. Furthermore, there was a higher proportion of malvidin-3-*O*-glucoside and lower proportions of the other four anthocyanins (delphinidin-, cyanidin-, petunidin-, and peonidin-3-*O*-glucosides) detected in 'Pinot Noir' in 2004 as compared to 2003 (Cortell et al., 2007a). Another study has shown that water insufficiency had no significant effects on composition and polymerization of procyanidins in seeds (Geny, Saucier, Bracco, Daviaud, & Glories, 2003). Concerning stilbenes, high resveratrol glucoside levels and low free isomer content can be considered characteristics of the Monastrell cultivars as it happens to red wines deriving from other varieties grown at warm climates, e.g. some French and Portuguese red cultivars (Moreno-Labanda et al., 2004).

Ripening is another factor that affects the phenolic content as in other fruits. Perestrelo et al. (2018) studied different grape cultivars ('Malvasia', 'Sercial' and 'Tinta Negra') during ripening used to produce Madeira wine. Their outcomes suggested that grape ripening stages significantly influenced the phenolic content and antioxidant capacity in grapes. Nevertheless, it depends on the phenolic compound type. For example, quercetin 3-glucuronide seems to predominate at véraison, followed by quercetin 3-glucoside, and only trace amounts of trisubstituted flavonols are found. However, the proportion of quercetin 3-glucoside remained stable during grape ripening, while the proportion of other flavonols, such as myricetin 3-glucoside, increased and quercetin 3-glucuronide decreased (Castillo-Munoz et al., 2007). Moreover, monomeric and dimeric flavan-3-ol monohexosides was measured in several cultivars and harvested from three different developmental stages, showing differences in their levels, which might be a result of different genetic expressions of some glycosyl transferase genes (Zerbib et al., 2018). Furthermore, proanthocyanidin composition in the cell walls isolated from seeds of *V. vinifera* was measured during ripening for different levels of vine water status. A more significant difference was observed at maturity than at veraison due to an increased mean degree of polymerized procyanidins in the cell wall (Geny et al., 2003). Concerning wine, there are also changes in total phenolic content during the ripening of wine grapes depending on the harvesting period and cultivar (Kral and Ostadalova, 2018; Zerbib et al., 2018).

Leaves extracts from six grape varieties of *V. vinifera* collected during May, August, and September was investigated for their phenolic composition. It was observed that the phenolic potential of the extracts was dependent on variety and picking-time. Extracts of leaves collected in September were the richest in total phenols, flavonoids, flavonols, and stilbenes (Katalinic et al., 2013).

2.5. Effect of the extraction method and drying

The phenolic content and composition depends on the extraction method applied. As an example, Casaza et al. (2010) evaluated the effect of non-conventional extraction methods (ultrasound-assisted extraction, UAE, microwave-assisted extraction, MAE, and high pressure and temperature extraction, HPTE) *vs* classic solid–liquid extraction (SLE) to obtain phenolic compounds from 'Pinot Noir' grape seeds and skins. The highest content in total phenolic compounds, *o*-diphenols and flavonoids was provided by HPTE at 110 °C, 200 bar, using methanol as solvent and during 30–90 min. The main phenolic compounds were catechin, vanillic acid isomers and quercetin, which were at 151.0 mg/100 g, 334.3 mg/100 g, and124.8 mg/100 g in seeds, respectively, and 58.3 mg/100 g, 20.5 mg/100 g, and 66.1 mg/100 g in skins, respectively. In this work, methanol had better extraction abilitites than ethanol. However, in other work, the phenolic substances from the 'Carignan' grape (*V. vinifera*) pomace, as well as from the peduncle, skin and seeds were extracted using different solvent mixtures with water. The maximum phenolic substances and flavonoids were extracted using EtOH: water and MeOH:water:acetone followed by MeOH:water (Agustin-Salazar et al., 2014). Similarly, a mixture of acetone:ethanol:water (1:1:1) was found to be the extractive agents for grape stalk phenolic compounds using a pre-wash treatment with deionized water (Teixeira et al., 2018). Ethanol/water (80:20 v/v) was also demonstrated good extractive potential for resveratrol and piceid isomers from dry skin samples (Romero-Perez, Lamuela-Raventos, Andres-Lacueva, & de la Torre-Boronat, 2001). Likewise, SLE conditions for *trans*-resveratrol, *trans*-ε-viniferin, ferulic acid, and total phenolics was optimized using solid − liquid extraction for milled grape canes. For all responses the temperature and ethanol concentration were detected as major process variables, while ratio of solvent to solid was non-significant for any of the studied compounds (Karacabey & Mazza, 2008).

In another work, agiorgitico red grape pomace byproducts were dehydrated followed by sequential exraction in water, water:ethanol (1:1) and ethanol as solvents in three different extraction methods: MAE, UAE and the conventional Soxhlet extraction. In this case, water:ethanol extracts obtained by UAE were found to possess higher amount of phenolic compounds (up to 438984 ppm GAE in dry extract). Moreover, these extracts were analysed using LC-MS and revealed that anthocyanins, flavonols and flavan-3-ols level were also affected significantly by the drying procedure. Air dried extracts of grape pomace demonstrated the highest total phenolic content (Drosou, Kyriakopoulou, Bimpilas, Tsimogiannis, & Krokid, 2015).

Osmotic treatment is applied to produce high quality intermediate moisture products supplemenated with particular solutes (Rózek, Achaerandio, Güell, López, & Ferrando, 2009). The effect of osmotic dehydration was evaluated as an operation for impregnating a gel foodstuff (food model) with grape phenolics from a concentrated red grape must. Under optimized conditions the total phenolics in the gel was close to the values reported in some rich-in-phenolic fruits and vegetables. Moreover, the individual phenolics analysed significantly explain the antioxidant capacity of the osmo-dehydrated food (Rózek et al., 2007).

2.6. Other factors

The effects of exogenous melatonin administration of pre-veraison

grapes on phenolic compounds of grape berries and wine were evaluated by Meng et al. (2017). This study demonstrated that exogenous melatonin has an effect on grape development, and thus melatonin could be utilized as a plant growth regulator. Moreover, an enhancement in the amount of cyanin-*3-O*-glucoside, peonidin derivatives, and flavonols was found in both grapes and wine on application of melatonin. These compounds are the derivatives of the flavonoid 3'-hydroxylase produced through catalysate in the flavonoid synthesis pathway. Thus, the treatment of melatonin enhanced flavonoid 3′-hydroxylase activity or expression during grape maturation. Moreover, UV-C irradiation affects the content of stilbenes (Douillet-Breuil, Jeandet, Adrian, & Bessis, 1999).

3. Anticancer activities of *Vitis* plants (*in vitro* studies/*in vivo* studies)

3.1. Grape and wine phenolic compounds

Several authors have confirmed that various grape phenolic compounds derived from the family *Vitaceae* possess various anticancer effects, which include anti-invasive, anti-angiogenic, anti-proliferative, pro-apoptotic, antioxidant, etc. (Asensi et al., 2002; Hakimuddin, Tiwari, Paliyath, & Meckling, 2008; Kaur, Velmurugan, Rajamanickam, Agarwal, & Agarwal, 2009; Kim et al., 2004; Morré & Morré, 2006). Furthermore, some specific phenolic compounds obtained from grapevines has been confirmed to exhibit a high level of anti-cancer and anti-metastatic attributes, most especially when tested against breast cancer cells during various *in vitro* and *in vivo* trials (Hakimuddin et al., 2004; Singh, Sharma, & Katiyar, 2011; Schlachterman et al., 2008; Singletary et al., 2003). The mechanism of action can be related to the antioxidant, anti-inflammatory, and antiproliferative activity of grape phenolic compounds, which could prevent tumor initiation (Yang, Landau, Huang, & Newmark, 2001).

Interestingly, Schlachterman et al. (2008) higlighted that combined grape polyphenols at physiologically relevant concentrations (at 0.5, 5, or 20 μM each resveratrol, quercetin, and catechin) are more effective than individual compounds at inhibition of ERbeta(+), ERalpha(−) MDA-MB-231 breast cancer cell proliferation, cell cycle progression, and primary mammary tumor. Moreover, this combination at 0.5, 5, or 25 mg/kg reduced primary tumor growth of breast cancer xenografts in a nude mouse model, indicating that grape polyphenols can inhibit breast cancer progression. Following this study, Castillo-Pichardo et al. (2009) discovered the anticancer potential of grape phenolic compounds when tested at lower concentrations (5 mg/kg each resveratrol, quercetin, and catechin) by exhibiting an inhibitory effect on mammary tumor development *in vivo* and preventing the process of cancer initiation, particularly metastases precisely from bone and liver.

Corinthian raisins (Currants) and Sultanas are dried grapes from *V. vinifera* with many culinary uses. Kountouri et al. (2013) evaluated the anticancer effect of methanol extracts of these raisins against human colon cancer cells. Their mechanism of action from these two extracts might be linked to their anti-inflammatory and antioxidant activity demonstrated against the human colon cancer cells. Furthermore, an ethyl acetate fraction from methanol extraction of *V. thunbergii* (var. *taiwaniana*), a Taiwan wild grape, induced G0/G1 phase arrest through the inhibition of cyclins D and E and the induction of apoptosis in human prostate carcinoma DU145 cells (Lin et al., 2018).

3.2. Grapevine, grape and winery byproducts

3.2.1. Grape seed and skin extract

Several studies have reported the anticancer effect of phenolic compounds from grape skins and seeds (Zhou & Raffoul, 2012), revealing a potential as chemopreventive or therapeutic agents (Gao et al., 2009). As an example, Alia, Badr El-Din, and Abou-El-magd (2015) described the antineoplastic effect of *V. vinifera* grape seed and skin on Ehrlich solid tumor-induced oxidative stress, hepatic dysfunction and pathological changes in the liver of mice. Compared to untreated mice, these authors found that grape seed and skin mixed with a standard diet at 10% (w/w) were able to recover liver function enzymes, reduce MDA level, enhance antioxidant parameters, normalize liver protein and DNA contents as well as improve hepatic lesions. Grape seed and skin enhanced the antioxidant defense system, defending the liver against oxidative stress prompted by Ehrlich solid carcinoma tumors. In another work, Hamza et al. (2018) showed the anti-cancer efficacy of grape seed extract in the human liver cancer cell line HepG2 and against chemically induced liver cancer *in vivo*. The grape seed extract was tested at 25, 50 and 100 mg/kg every day for a period of 14 weeks. They observed that grape seed extract repressed pre-neoplastic foci development, reduced the quantity of glutathione-S-transferase in livers of rats treated with diethylnitrosamine and 2-acetyl aminofluorene between 4 and 10 fold. In this case, the mode of action could be mediated via the inhibition of cell proliferation, modulating oxidative damage, induction of apoptosis, and suppressing inflammatory response.

Prostate cancer has been highlighted as one type of cancer responsible for the high death rate of men globally. In view of that, several scientists have intensified significant efforts towards the utilization of grape seed extracts for the management of prostate cancer. Park, Lee, Choi, and Yoon (2011), Dhanalakshmi, Agarwal, and Agarwal (2003), and Agarwal, Singh, and Agarwal (2002) confirmed the inhibitory activity of grape seed extracts against human prostate cancer cell lines, LNCaP cells and DU145 cells. Some of these studies emphasized the role of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) pathway, while caspases activation, dissipation of mitochondrial membrane potential and cytochrome c release could be also key molecular mechanisms. Moreover, Singh, Tyagi, Dhanalakshmi, Agarwal, and Agarwal (2004) revealed the anticancer activity of the seed extract obtained from grape against human prostate tumor growth that has reached an advanced stage and angiogenesis by up-regulating the activity of insulin-like growth factor binding protein-3. Raina, Singh, Agarwal, and Agarwal (2007) also reported the anti-neoplastic effect of grape seed extract on TRAMP mice, a model for prostate cancer, by inducing cell death and inhibition of cell cycle, whle Kaur, Agarwal, and Agarwal (2006) suggested that anoikis and caspase-mediated cell death could be related to this effect.

Besides the latter studies, grape seed extracts from *V. vinifera* has been reported to have anticancer activity against other cancer cells: skin cancer cell lines A431 (Mohansrinivasan, Subathra Devi, Deori, Biswas, & Naine, 2015), oral cancer cells Ca9-22 (Yen et al., 2015), Jurkat, U937 and HL-60 human leukemia cells (Gao et al., 2009), colon carcinoma HT-29 cells (Kaur et al., 2011). The mechanism of action includes oxidative stress, DNA impairment, apoptosis, inducing cell death through JNK activation and Cip1/p21 up-regulation, generating caspase activation, impairment of EGFR-ERK1/2-Elk1-AP1-mediated mitogenic signaling causing growth inhibition and activation of JNK causing apoptosis, up-regulation of p21 (Cip1) via redox-mediated stimulation of ERK1/2, etc. *In vivo* the application of grape seed phenolic compounds inhibited 12-*O*-tetradecanoylphorbol-13-acetate-induced tumor promotion in CD-1 mouse epidermis via inhibition of the activity of ornithine decarboxylase and myeloperoxidase (Bomser, Singletary, Wallig, & Smith, 1999, 2000). Velmurugan, Singh, Agarwal, and Agarwal (2010) showed that the administration of grape seed extract (0.5%, w/w, mixed in the diet for 6 weeks) prevented intestinal tumorigenesis in $APC^{min/+}$ mice. It was also observed a reduction of cell proliferation, an increase of apoptosis together with down-regulation in iNOS, COX-2, β-catenin, c-Myc, cyclin D1 expression, and an increase of Cip1/p21. Moreover, grape seed extract could be combined with doxorubicin in a synergic way for the prevention of estrogen-receptor–-activities against estrogen-receptor negative MDA-MB468 and MCF-7 cells (Sharma, Tyagi, Singh, Chan, & Agarwal, 2004). Alternatively, Kim et al. (2004) revealed the synergetic anticancer effect between the

isoflavone genistein and grape seed extract in an *in vivo* assay using a carcinogen-induced mammary cancer on female rats.

As commented before, grape skin could have a role as anticancer agent alone or combined with seeds and other phytochemicals. Radhakrishnan, Reddivari, Sclafani, Das, and Vanamala (2011) demonstrated the synergetic effect of grape seed extract together with grape skin resveratrol and their capability to induce cell death on colon cancer cells. This might also be linked to their interrelationship connected with Bax: Bcl-2 ratio and p53 levels. Furthermore, Sun, Chen, Wu, Yao, and Sun (2012) reported the anticancer effect of grape skin extract; when it was included in the drinking water caused a drastic reduction of lung metastasis occurrence. The experiment was carried out using BALB/c 4T1 mammary xenograft mouse model. In another work, Morré and Morré (2006) reported the anticancer effect of grape and grape skin extracts alone and combined with green tea infusions against human cervical carcinoma cells and mouse mammary 4T1 cells in culture and transplanted tumors *in vivo*. Grape skins were more active than other sources (grape pulp, juice, and seeds). Moreover, grape extracts interacted, often synergistically, with decaffeinated green tea extracts. Among other mechanisms of action, they could prevent the tNOX activity and induce cell death.

3.2.2. Stems

A major part of the wineries' wastes (*V. vinifera*) is composed of grape stems, which can cause environmental problems when this residue is discarded into the soil (Sahpazidou et al., 2014). However, grape stems have exhibited a great antioxidant and anticancer potential and could be useful as nutraceutical/pharmaceutical agent. As an example, phenolic compounds found in them modulated oxidative stress induced by H_2O_2 in HaCaT cells (Domínguez-Perles, Guedes, Queiroz, Silva, & Barros, 2016). This plant part also possessess ability to inhibit proliferation of different cancer cell lines such as colon (HT29), breast (MCF-7 and MDA-MB-23), renal (786–0 and Caki-1) and thyroid (K1), through the induction of apoptosis (Sahpazidou et al., 2014). In this work, the IC_{50} values ranged from 121 (MCF-7) to > 400 μg/mL (Caki-1), depending on the cell line and cultivar. For example, the 'Voidomato' (red) cultivar extract was the most active against the aforementioned cancer cell lines, except for 786–0, and presented high content of gallic acid and *trans*-resveratrol. Moreover, the stems protect cells and DNA of oxidative damage (Apostolou et al., 2013).

3.2.3. Leaves

The chemical composition and the cytotoxicity of leaf extracts from eight *V. vinifera* varieties from Serbia was recently studied by Pintać et al. (2019). Among them, 'Chardonnay' extract was the most cytotoxic towards the tumor cell lines tested (HeLa, MCF7 and HT-29), followed by 'Merlot'; IC_{50} ranged from 317 to 1682 μg/mL. The activity could be explained by the presence of high amounts of ursolic acid, although phenolic compounds could contribute. In another study, leaves from *V. vinifera* obtained in two different climatic regions of Palestine were screened as an anticancer agent against lung cancer cells *in vitro* (Abed, Harb, Khasib, & Saad, 2015). They observed that the cytotoxic activity of leaves depended on the region.

Besides the influence of the cultivar and agroclimatic conditions on the citotoxicity results, the health status of leaves can also affect. As an example, the methanolic extracts of leaves and fruits of *V. vinifera* from both virus free and virus (Grapevine fanleaf virus) infected cultivars exhibited limited to moderate cytotoxic activity. Alternatively, the methanolic extract of leaves belonged to virus infected cultivars had strong cytotoxic effect against breast cancer cell line MDA-MB-231 (Esfahanian, Behbahani, Shanehsaz, Hessami, & Nejatian, 2013).

3.2.4. Grape pomace

A purified pomace extract from white grapes (100 μg/mL), containing phenolic acids (6.01 mg/g), flavanols (92.6 mg/g), and flavonols (43.3 mg/g), have shown antiproliferative activity against Caco-2 colon cancer cells, inhibiting 52.1% at 48 h (Jara-Palacios et al., 2015). These authors also revealed that this extract induced apoptosis in human leukemia Jurkat cells via mitochondrial depolarization and caspase-3 cleavage, related to reactive oxygen species (ROS) generation and regulation of epigenetic gene silencing (León-González, Jara-Palacios, Abbas, Heredia, & Schini-Kerth, 2017). In another work, phenolic fractions from Muscadine grape 'Noble' pomace showed higher potencty to ihhibit breast cancer cell MDA-MB-231 than those from European grape 'Cabernet Sauvignon' via induction of S-phase arrest and apoptosis (Luo et al., 2017).

3.3. The role of some phenolic compounds

The efficacy of products made from grapes of *V. vinifera* and its raw extracts could be linked to the presence of phenolic compounds (Ali, Maltese, Choi, & Verpoorte, 2010; Nassiri-Asl and Hosseinzadeh, 2009; Xia, Deng, Guo, & Li, 2010; Zhou & Raffoul, 2012). Thus, in this section the anticancer properties of some phenolic classes and particular phenolic compounds are described and the mechanism of action reported. Their action can contribute to the activity of the aforementioned *V. vinifera* plant parts and winery residues.

3.3.1. Stilbenes

Stilbenes, including resveratrol (Fig. 1), have a lot of pharmacological properties, such as antioxidant, anti-inflammatory, and anticancer activity (Roupe, Remsberg, Yáñez, & Davies, 2017). The latter review highlighted the potential of resveratrol and other structurally related stilbenes as phytochemical constituent that could be used for the treatment of various cancer-related diseases.

3.3.1.1. Resveratrol. Dandawate, Subramaniam, Jensen, and Anant (2016) recapitulated the recent understanding of breast cancer stem cells and the signaling pathways induced by several phytochemicals, including resveratrol. They were able to induce cell cycle arrest and cell death, to reduce cell proliferation, to decrease tumor xenograft growth and the number of stem cells in the tumor. In particular, the inhibitory effects of resveratrol against, mainly, breast cancer cells could be through: stimulation of cell death, tumor cell proliferation inhibition, prevention of tumor cell movement, and inhibition of tumor-derived nitric oxide synthase initiation (Busquets et al., 2007; Castillo-Munoz et al., 2009a; Delmas, Lançon, Colin, Jannin, & Latruffe, 2006; Garvin, Ollinger, & Dabrosin, 2006; Nakagawa et al., 2001). Resveratrol can also modulates estrogen through several ways (Bowers et al., 2000, Eng et al., 2002; Harris, Besselink, Henning, Go, & Heber, 2005), such as aromatase and estrogen receptor-positive inhibition. Moreover, the results by Provinciali et al. (2005) showed that resveratrol could prevent the development of mammary tumors associated with the lung metastases incidence when it was administered orally in female FVB/N HER2/*neu* transgenic mice. Resveratrol is a strong antioxidant able to reduce lipid peroxidation and prevent DNA damage in carcinogen-challenged rat mammary tissue, while an increase of the transforming growth factor beta 1 (TGF-β1) expression in resveratrol treated rats could induce apoptosis to suppress mammary carcinogenesis (Chatterjee, Das, Janarthan, Ramachandran, & Chatterjee, 2011).

Furthermore, Tessitore, Davit, Sarotto, and Caderni (2000) reported the utilization of resveratrol as an antitumor agent in colon carcinogenesis, when applied at a lower concentration (200 μg/kg/day in drinking water) to rats, by a mechanism involving changes in bax and p21 expression. The antiproliferative and apoptotic effects in human prostate cancer cells may be mediated by the inhibition NF-κB activity, which could lead to the regulate genes and the process of metastasis and tumor development (Benitez, Hermoso, Pozo-Guisado, Fernández-Salguero, & Castellón, 2009). When it was tested in a renal tumor model, Chen, Yang, Liao, and Xiong (2015) also confirmed that this compound could regulate the microenvronment around tumor by

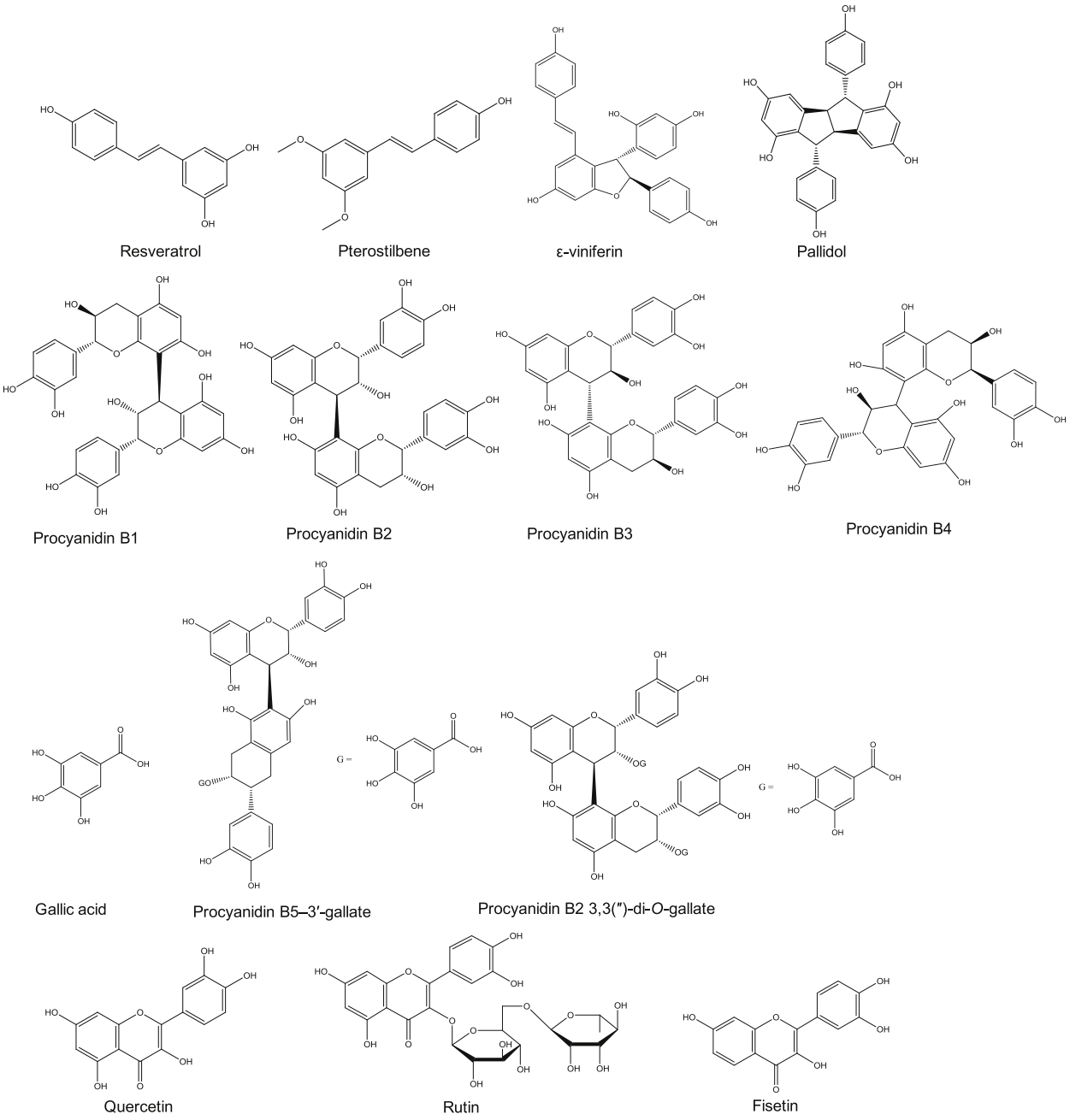

Fig. 1. Examples of phenolic compounds from *V. vinifera* with anticancer properties.

stimulating $CD8^+$ T cells, which are responsible for the initiation of antitumor immunity, reducing Tregs available in tumors, rising the stages of interferon-gamma and reducing interleukins-6 and -10, and the vascular endothelial growth factor (VEGF). Moreover, it can prevent oxidative stress by a direct action as scavenger of ROS, preventing NADPH oxidase and xanthine oxidase activities, and upregulating sirtuin 1 action (Xu et al., 2012).

It is also suggested that resveratrol could have a promising role to counteract multidrug resistance: in adjuvant therapy resveratrol had additive and/or synergistic effects increasing the chemosensitization of cancer cells. This compound can act through diverse mechanisms simultaneously, and thus it could be a multi-target anticancer agent, as recently suggested the review by (Varoni, Lo Faro, Sharifi-Rad, & Iriti, 2016). However, a lot of factors have been highlighted as a limitation impeding its health benefits and application. Among them, a rapid metabolism and poor bioavailability are major problems affecting the effectiveness of resveratrol (Berman, Motechin, Wiesenfeld, & Holz, 2017). Moreover, in order to break this limitation, it has been suggested that leaving resveratrol in the mouth for prolonged periods may enhance a higher occurrence of resveratrol in the plasma levels. In order to validate this hypothesis, Leifer and Barberio (2016) tested various parameters from that could enhance the bioactivity of resveratrol and pterostilbene *in vitro* and in animal studies. They observed that uninterrupted consumption might lead to another technique for attaining these clinically valuable doses.

3.3.1.2. Pterostilbene. Besides resveratrol, *V. vinifera* contains other interesting stilbenes, such as pterostilbene, a dimethyl ether analog of resveratrol (Fig. 1). This phenolic compound could play a protective role against various diseases, most especially cancer (Chakraborty et al., 2012; Tippani et al., 2014). Notably, the greater *in vivo* bioavailability of pterostilbene, as compared to resveratrol, is advantageous for its use

as potential drug with pleiotropic health applications (Kosuru, Rai, Prakash, Singh, & Singh, 2016), while it is considered generally safe for use in humans up to 250 mg/day (Riche et al., 2013). As an example, Tippani et al. (2014) evaluated the anticancer effects of pterostilbene, with the aids of molecular docking studies involving the crystal structure of telomerase. Moreover, the effect of pterostilbene against breast (MCF7) and lung cancer (NCI H-460) cell lines, telomerase activity, antimitotic activity were evaluated in an *in vitro* assay, while curcumin serves as the standard. Bear in mind that telomerase plays an active role in cellular immortalization and tumor stimulation and hence it is a molecular target in cancer therapy. The result obtained from the docking study showed that there is a considerable interaction between the active site of telomerase and pterostilbene. Moreover, an inhibitory effect was observed on cell development and *in vitro* telomerase activity of the pterostilbene-treated cancer cells in a concentration dependent manner, especially at 80 μM after 72 h. Pterostilbene had also an inhibitory effect on MCF-7 cells, which might be linked to the separation of the mammary carcinoma cells into a regular epithelial cell in term of morphology and autophagy initiation (Chakraborty et al., 2012). Moreover, the efficacy of pterostilbene against other breast cancer cells (MDA-MB-231) has been also reported (Ko et al., 2014). In this case, it prevented cancer cell movement and attack by NF-κB-stimulated uPA action and Rac1/WAVE/Arp2/3 pathway.

The anticancer effects of pterostilbene against adenocarcinoma cervical cancer cell line HeLa and endometrial cancer cell lines HTB-111 and Ishikawa have also been reported (Wang et al., 2017; Zhang, Wang, Chen, & Liu, 2014). There was a dose-response relationship between this compound and the characteristics of HeLa apoptosis as well as pterostilbene triggered endoplasmic reticulum stress (ERS) by redox homeostasis imbalance, negatively regulated by a subsequent activation of Nrf2, while in the second case a down-regulating miR-663b was observed. Moreover, Paul et al. (2009) evidenced that pterostilbene could initiate p38 mitogen-activating protein kinase cascade, which plays a significant part in the transduction pathway, whenever it exhibits its anti-inflammatory activity against HT-29 colon cancer cells. In this regard, Remsberg et al. (2008) validated in an *in vitro* trial using a colitis model, which shows that pterostilbene could prevent the PGE (2) production in the media of HT-29 cells. There was a reduction in the level of TNF-alpha, sGAG, and MMP-3 in comparison to the cell serving as a control.

In another work, Ma et al. (2017) reported the anticarcinogen effects of pterostilbene against non-small-cell lung cancer *in vitro* and *in vivo*. This is an interesting finding since non-small-cell lung cancer has been recognized as one of the main causes of lung cancer and normally results in death (Singh et al., 2011). The study by Ma et al. (2017) showed that, depending on the concentration and time of application of pterostilbene, it has the capability to stimulate the ERS signaling. This could reduce the cell viability and stimulates cell death in human lung carcinoma cell lines PC9 and A549s. The mechanism of action includes: reducing the adhesive and migratory abilities, increasing the levels of ROS, downregulating the intracellular glutathione level, enhancing Caspase 3 activity and mitochondrial membrane depolarization on the treated cancerous cells. These effects were overturned by CHOP siRNA, which repressed the ERS signaling pathway. Moreover, the *in vivo* trial confirmed that this stilbene had anticancer effect by activating ERS signaling and apoptosis-related proteins, which was boosted by thapsigargin (an ERS inducer). In this regard, pterostilbene and piceatannol exhibited the highest potentials to induce ERS from 1726 molecules screened by Papandreou, Verras, McNeil, Koong, and Denko (2015). Their toxicity is more pronounced in cancer cells expressing Wnt growth factors and can be potentiated by the addition of autophagy inhibitors (e.g. chloroquine), suggesting a potential therapeutic application.

3.3.1.3. Others. Concerning other stilbenes, Nivelle et al. (2017) reported the anticancer activity of four stilbenes (ε-viniferin, resveratrol, pallidol and a novel dimer) (Fig. 1), which were produced inside a 14 L bioreactor culture of grapevine cell suspensions (*V. labrusca*). These compounds were tested on two human skin malignant melanoma cancer cell lines (HT-144 and SKMEL-28) and a healthy human dermal fibroblast HDF line. The result revealed that ε-viniferin and the stilbene dimer shows a lesser activity when compared to resveratrol and pallidol.

3.3.2. Proanthocyanidins

3.3.2.1. Grape seed proanthocyanidins. Several studies have evaluated the *in vitro* and *in vivo* effects of grape seed proanthocyanidins against breast cancer. Ye, Krohn, Liu, and Bagchi (1999) confirmed the cytotoxic activity of this pool of compounds on MCF-7 human breast cancer cells and A-427 human lung cancer cells, while no inhibitory effect on a normal cell was found. Mantena, Baliga, and Katiyar (2006) reported that grape seed proanthocyanidins could prompt cell death *in vitro* (4T1, MCF-7 and MDA-MB-468), and hence these compounds could possess chemotherapeutic efficacy against breast cancer *in vivo* and prevent metastasis. Agarwal, Sharma, Zhao, and Agarwal (2000) also showed the anticancer influence of this phenolic fraction. The high level of apoptosis was mediated by preventing the stimulation of MAPK/p38 and MAPK/ERK1/2, reduction of CDK4, stimulation of CDKI Cip1/p21, available in MDA-MB-468 cancer cells. Additionally, it has been revealed that grape seed proanthocyanidins could lead to the arrest of the cell cycle most especially G1, preventing cancer cell development.

Moreover, the results obtained from *in vitro* and *in vivo* (after administration of 50–200 mg grape seed proanthocyanidins to mice for 5 weeks) experiments revealed that these compounds exhibited anticancer activity on human non-small cell lung cancer (Singh et al., 2011). The anticancer activity was tested on non-small cell lung cancer cells A549 and H1299 and the mode of action involves: capability to break the membrane surrounding the mitochondrial, stimulation of caspases 9, 3, and poly(ADP-ribose) polymerase, improved initiation of proapoptotic protein Bax, reduction in the activities of Bcl2 and Bcl-xl proteins responsible for cell death. Sharma, Meeran, and Katiyar (2010) also confirmed the anticancer activities of grape seed proanthocyanidins on human non-small cell lung cancer cells by the upregulation of COX-2, prevention of prostaglandin E2 and their receptors.

Furthermore, *V. vinifera* grape seed proanthocyanidins possess anticancer properties on a pancreatic cancer cells, deactivating the inflammatory transcription factor NF-κB (Prasad & Katiyar, 2013), and colon cancer cells Caco2 and HCT-8 (Simona Dinicola et al., 2012). Some authors have evidenced the anticancer effect of grape seed proanthocyanidins in an *in vivo* trial using UV-B induced skin carcinogenesis in mice. The mechanisms of action might be linked to the reduced fat and lipid peroxidation (Mittal, Elmets, & Katiyar, 2003) and stimulation of mitogen-induced protein kinases and NF-kB signaling (Sharma, Meeran, & Katiyar, 2007). Zhang, Bai, Wu, Li, and Liu (2005) reported the anticancer effect of grape seed proanthocyanidins on doxorubicin-induced toxicity in tumour-bearing mice. The intragastric administration of these compounds (200 mg/kg daily) inhibited tumour growth, and increased NK cell cytotoxicity, lymphocyte proliferation, CD4 + /CD8 + ratio, INF-gamma and IL-2 production. This ameliorated doxorubicin-induced myocardial oxidative stress and immunosuppression. However, an *in vitro* study on colon cancer cells by Dinicola et al. (2012) suggested that besides epigallocatechin and procyanidins, other compounds present in the grape seed extracts could contribute to enhance the anticancer effects observed by the whole seed extracts.

Procyanidins from wild grape (*Vitis amurensis Rupr.*) seeds could be other chemopreventive agent through Nrf2/ARE-mediated phase II detoxifying/antioxidant enzymes induction through p38 and PI3K/Akt pathway. However, this effect was only tested *in vitro* on HepG2 human hepatocarcinoma cells (Bak, Jun, & Jeong, 2012).

3.3.2.2. Procyanidin B dimers. Procyanidin B dimers (Fig. 1), which are

found in a larger amount in grape seeds and wine, could deactivate the expression of aromatase. This enzyme is responsible for the conversion of androgen substrates into estrogens, which play a major role in promoting tumor growth (Eng et al., 2003). Red wine extracts inhibited aromatase activity *in vitro* and avorturned aromatase-induced hyperplasia and other neoplastic changes in mammary tissue *in vivo* (Eng et al., 2002). Later, Eng et al. (2003) demonstrated that procyanidin B dimers could be used as chemopreventive agents against breast cancer via suppressing *in situ* estrogen biosynthesis. In fact, procyanidin B dimers reduced androgen-dependent tumor growth in an aromatase-transfected MCF-7 breast cancer xenograft model.

Moreover, another work by Cheah, Howarth, Bindon, Kennedy, and Bastian (2014) suggested the anticancer acitivity of low molecular weight procyanidins from *V. vinifera* grape seeds against Caco-2 human colon cancer cells. The author observed that procyanidins, which include dimers, improved the action of 5-fluorouracil chemotherapy in this cancer cell line.

3.3.2.3. Procyanidins linked to gallic acid. Zhao et al. (1999) evaluated the antitumor stimulation influence of grape seed extract in topical applications. The authors performed an *in vivo* trial using a SENCAR mouse skin carcinogenesis model. The mouse was induced chemically with tumor-initiating agents which entail, 12-*O*-tetradecanoylphorbol 13-acetate and 12-dimethylbenz[*a*]anthracene. Their study reveals that procyanidin B5–3′-gallate (Fig. 1) was the most active antioxidant among all other phenolic compounds isolated (i.e. catechin, procyanidin B2, procyanidin B5, and procyanidin C1). Moreover, it was observed that procyanidin B5–3′-gallate significantly prevented the antitumor activity of 12-*O*-tetradecanoylphorbol 13-acetate and cause a significant decrease in tumor occurrence, tumor multiplicity, and tumor capacity. In another study, Tyagi et al. (2014) evidenced that procyanidin B2 3,3″-di-*O*-gallate (Fig. 1) was the most active compound from grape seed extract against human prostate cancer cells. The mode of action of this compound includes stimulation of the cell cycle arrest, cell death, reduced clonogenicity, and repressed cell growth via targeting Stat3, NF-κB, and AP1 transcription factors.

3.3.2.4. Gallic acid. Gallic acid (Fig. 1) from grape seeds has shown anticancer effects when tested in an androgen-independent DU145 and androgen-dependent-22Rv1 from human prostate cancer cells (Kaur et al., 2009). It induced cell death and exhibited anti-proliferative and anti-tumorigenic attributes. This hydroxybenzoic acid is also found in other dietary food products and herbs and several *in vitro* and *in vivo* studies suggest that the anticancer activity of this compound is related to the induction of apoptosis through different mechanisms, including regulation of apoptotic and anti-apoptotic proteins, generation of ROS, suppression of oncogenes, etc. (Subramanian et al., 2015). Besides its anticancer properties, this compound enhanced the antitumor activities of cisplatin (chemotherapy drug) via the ROS-dependent mitochondrial apoptotic pathway in small cell lung cancer H446 cells (Wang et al., 2016).

3.3.3. Other phenolic compounds

The anti-proliferative effect of anthocyanins such as cyanidin, malvidin, and peonidin derivatives has been tested in several studies (see review by Singh, Siddiqui, El-Abd, Mukhtar, & Ahmad, 2016). In particular, a muscadine grape skin extract and a purple grape juice rich in anthocyanins have shown anticancer activity in *vitro* in prostate and breast cancer cells and *in vivo* in 7,12-dimethylbenz[a]anthracene-induced rat mammary tumorigenesis, respetively (Burton et al., 2015; Jung, Wallig, & Singletary, 2006). In another study, anthocyanins isolated from fruits of *V. coignetiae* Pulliat showed anticancer activity through the modulation of NF-κB activation in colon cancer cells HT-29 (Yun et al., 2010).

In another study the effect of a red wine concentrate, its total phenolic pool, and some major phenolic compounds (catechin, epicatechin, quercetin, and resveratrol), which are also present in other *Vitis* plant parts (Table 1), have decreased cell proliferation in a dose- and a time-dependant manner on hormone sensitive (MCF7, T47D) and resistant (MDA-MB-231) breast cancer cell lines. Thus, besides flavanols and stilbenes, the flavonol quercetin was also able to inhibit the latter cancer cell lines at pM levels (Damianaki et al., 2000). Quercetin and rutin (Fig. 1) have also shown inhibition properties against aromatase as resveratrol (Eng et al., 2002), while Harris et al. (2005) highlighted the potential of quercetin, resveratrol, and catechin as a selective estrogen receptor modulators via inhibition of the estrogen receptor-positive breast tumors. Moreover, Del Follo-Martinez, Banerjee, Li, Safe, and Mertens-Talcott (2013) suggested a synergetic effect of resveratrol and quercetin when mixed in an equal proportion of 1:1 ratio against colon cancer cells.

There are other molecules that could contribute to the anticancer effects of *Vitis*. Lim and Park (2009) reported the anticancer effect of fisetin, a flavone presents in the skin of grapes of some cultivars (Novak et al., 2008), against HT-29 and HCT-116 human colon cancer cells. At 20–60 μmol/L fisetin inhibited cyclin-dependent kinase activities, resulting in cell cycle arrest in HT-29 cells (Lu et al., 2005). After that, this group characterized the mechanisms by which fisetin induced apoptosis in HCT-116 cells, i.e. via activation of the death receptor- and mitochondrial-dependent pathway and following activation of the caspase cascade, while the induction of p53 protein levels contributed to apoptosis (Lim & Park, 2009). Moreover, several studies support that fisetin could be a promising agent for cancer treatment, through targeting the growth signaling pathways (see review by Rengarajan & Yaacob, 2016).

4. Clinical effectiveness of *Vitis* plants in human

Since ancient times, grapes have been used both for nourishment and medicinal purposes, particularly in the European countries. A number of historic Greek philosophers have claimed the curative property of grapes, particularly in the form of wine. Epidemiological studies have associated the consumption of grapes and their products, wine and grape juice, with several health-promoting effects, including a reduction of the risk of cancer (Dinicola, Cucina, Antonacci, & Bizzarri, 2014). As shown clinical studies, wine drinking has a protective effect in adenocarcinoma of the lung (De Stefani et al., 2002) and had an inverse association with the development of lung cancer (Ruano-Ravina, Figueiras, & Barros-Dios, 2004). A meta-analysis by Chao (2007) suggested that modest wine consumption could be inversely associated with lung cancer risk.

Furthermore, the intake of an antioxidant-rich plant-based diet is associated with a decrease of the risk of cancer (Amiano et al., 2018). In this context, Park, Park, Kim, and Kang (2003) suggested that a nutritional inclusion of grape juice containing 480 mL/day for a period of 8 weeks might decrease lymphocyte DNA impairment by reducing the development of ROS up to 15%. Moreover, the effect of the administration of procyanidins from *V. vinifera* seeds (a daily dose of 110 mg) on oxidative stress was studied in ten healthy volunteers for one month. This study suggested that procyanidins possess antioxidant activity *in vivo* (Simonetti, Ciappellano, Gardana, Bramati, & Pietta, 2002). Therefore, if the antioxidant properties of *V. vinifera* phenolic constituents could be beneficial to prevent cancer, it requires further evidence *in vivo*.

Notably, it seems that Muscadine grape skin extract could be useful to treat men who have received an initial therapy for prostate cancer and show a rise in the prostate-specific antigens (PSA) level. Although no significant difference in PSA was observed between placebo and the dose of the extract (Muscadine Plus), there was a signal of benefit in the subgroup of men with the Alanine/Alanine superoxide dismutase 2 genotype receiving high dose (4000 mg) (https://clinicaltrials.gov/ct2/show/NCT01317199?term=%22muscadine+plus%22&rank=2; accesed on January 2019). This quantity seems to be safe (Paller et al.,

2015), but the consumption of grape seed extract supplement could have undesired effects and controlled trials detailing the adverse effect profile of this type of supplements are required (Berry et al., 2016).

Concerning resveratrol and pterostilbene, other interesting *Vitis* molecules, there are few clinical trials conducted (https://clinicaltrials.gov; accesed on January 2019). In this sense, Smoliga, Baur, and Hausenblas (2011) suggested that resveratrol should be considered as a therapeutic agent for cancer, but depending on the characteristics of the tumors to be treated, since pro-oxidant effects should not be avoided. Therefore, the efficacy of resveratrol depends on the type and stage of cancer, treatment period and dosage, but more clinical studies are still required to stablish them (Berman et al., 2017). In another context, the anti-tumor activity of megestrol acetate drug against endometrial cancer *in vitro* can be enhanced by combining with pterostilbene. It was also suggested in a xenograft mouse model (Wen et al., 2017). This is the basis of the clinical trial, which is currently under recruiting stage (https://clinicaltrials.gov/ct2/show/NCT03671811?term=pterostilbene&rank=1; accesed on January 2019).

5. Conclusions

This review describes the richness of phenolic structures in plant parts of *V. vinifera* and other *Vitis* species, specially underused parts, as well as winery byproducts. Genetic, environmental, agricultural, extraction and other factors affect the phenolic composition of these bioresources. All of them should be considered for futher standardization of the raw material for future food and pharmaceutical applications.

There are few reports on leaves, stems and root concerning both their phytochemical composition and anticancer activity; most studies were peformed *in vitro*. Alternatively, seeds and skins were the most studied parts in preclicnical studies, with a potential role as chemopreventive and chemotherapeutic agents, especially in lung, breast, liver and prostate cancers. Procyanidins and stilbenes could be active molecules, but a synergism between these phenolic compounds and others compounds present in the whole extracts should not be avoided. Moreover, some studies have also suggested that *Vitis* phenolic compounds, when used in combination with other agents/drugs, could impart a synergistic action, being promising to manage cancer. However, future clinical trials are required to support these *in vitro* and *in vivo* findings in order to provide a better profile for the potential benefit of these extracts and their active molecules in cancer patients, to stablish safe dosage, the type of cancer to be treated, etc.

Conflicts of interest

There are no conflicts of interest to declare.

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