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Unusual stilbene glucosides from *Vitis vinifera* roots

Iris Aja[1,2], Grégory Da Costa[2], Eric Pedrot[2], Marie-Laure Iglesias[2], Antonio Palos-Pinto[2], Josep Valls[2], Nassima Chaher[3], M. Begoña Ruiz-Larrea[1], Jean-Michel Mérillon[2], Djebbar Atmani[3], José Ignacio Ruiz-Sanz[1] and Tristan Richard[2]

[1]Department of Physiology, School of Medicine and Nursing, University of the Basque Country – UPV/EHU, 48940 Leioa, Spain
[2]University of Bordeaux, ISVV, EA 4577, USC 1366 INRA, Unité de Recherche Œnologie, 210 Chemin de Leysotte, F-33882 Villenave d'Ornon, France
[3]Laboratoire de Biochimie Appliquée, Faculté des Sciences de la Nature et de la Vie, Université de Bejaia, Bejaia 06000, Algeria

*Corresponding author: tristan.richard@u-bordeaux.fr

ABSTRACT

Aim: Stilbenes are well-known phytoalexins present in vine and wine. Stilbene glucosides have been identified in wine; however, other than piceid, these compounds have never been reported to be present in the woody parts of grapevine. The aims of this study were to investigate the presence of stilbene glucosides in the woody parts of the vine and to evaluate their cytotoxic activity, in comparison with that of resveratrol, in human hepatoma HepG2 cells.
Methods and results: Stilbene glucosides were isolated from a *Vitis vinifera* root extract. The extract was partitioned with ethyl acetate and fractionated by polyamide gel column chromatography. Pure compounds were obtained by semipreparative high-performance liquid chromatography. These were then identified by mass spectrometry and nuclear magnetic resonance (NMR) analyses, including analysis of two-dimensional NMR spectra. In addition to resveratrol, five stilbene glucosides were found: resveratroloside, resveratrol rutinoside, *trans*-ε-viniferin diglucoside, *cis*-ε-viniferin diglucoside and piceid. Of these, the first four showed cytotoxic effects against HepG2 cells when the crystal violet assay was used to determine cell viability.
Conclusion: In addition to resveratrol and piceid, this is the first report of the presence of four glucosylated derivatives of resveratrol (resveratroloside, resveratrol rutinoside, and *trans*- and *cis*-ε-viniferin diglucosides) in the woody parts of vine. These compounds showed significant cytotoxicity against HepG2 cells.
Significance and impact of the study: Stilbenes are well-known biological compounds. Grapevine is one of the main sources of this family of polyphenols. Other than piceid, stilbene glucosides have been identified in wine but never in the woody parts of vine. This is the first study in which five glucosylated derivatives of resveratrol were isolated from woody parts of vine. They were also shown to exert antiproliferative effects in human hepatoma HepG2 cells.

KEYWORDS

antiproliferative effects, cytotoxicity, HepG2 cells, phytoalexins, resveratrol, stilbene glucosides

INTRODUCTION

Stilbenes are natural compounds present in several plants (Rivière *et al.*, 2012). One of their main vegetal sources is grapevine. They are present throughout the plant; however, the woody parts (e.g. wood and roots) are significantly richer in stilbenes than the vegetative and generative parts (Gabaston *et al.*, 2017). Stilbenes are known particularly for their antimicrobial properties (Schnee *et al.*, 2013); they also act as grapevine phytoalexins (Langcake and Pryce, 1977; Jeandet *et al.*, 2002).

Members of the stilbene family are based on the resveratrol structure (3,5,4¢-trihydroxystilbene), differing in the number and position of hydroxyl groups, sugars, and methyl or methoxy groups. Furthermore, oxidation of resveratrol leads to the formation of various oligomers, including ε-viniferin, which is a dimer of resveratrol and one of the main stilbenes in grapevine stem extract (Biais *et al.*, 2017). In grapevine berries, stilbene glucosides are usually found in significantly higher concentrations than those of stilbene aglycones (Pawlus *et al.*, 2012). However, other than piceid, no stilbene glucoside has been reported in the woody parts of grapevine.

Resveratrol is a well-known bioactive polyphenol with many biological activities associated with life extension and some of the health benefits of wine (Vang *et al.*, 2011). Several studies have shown that resveratrol exerts, via diverse mechanisms, proapoptotic and antiproliferative effects in a number of different cancer cell lines (Ko *et al.*, 2017). Piceid is a resveratrol glucoside and the major resveratrol derivative in grape juices and wine (Neveu *et al.*, 2010). It may have similar beneficial actions against various pathologies to those of resveratrol (Fabris *et al.*, 2008). Su and colleagues have compared the antioxidant and antiproliferative effects of resveratrol and piceid in different cell lines (Su *et al.*, 2013). Their results have shown that piceid has stronger radical-scavenging activity than resveratrol and inhibits proliferation in the human hepatoma HepG2 and human breast cancer MDA-MB-231 and MCF-7 cell lines.

Our aims in carrying out the present study were to investigate the presence of stilbene glucosides in grapevine root extracts and to evaluate the antiproliferative activity of these compounds *in vitro*, using the hepatoma HepG2 cell line.

MATERIALS AND METHODS

1. Plant material and reagents

Grapevine roots were kindly provided by Actichem S.A. (Montauban, France). Healthy grapevine roots, namely SO4 rootstocks (*Vitis riparia ´ Vitis berlandieri*), were harvested in the *Saint Christoly de Blaye* vineyard in the Bordeaux area of France. The roots were dried at room temperature for 2 months under conditions of no light, and then crushed in powder. Extraction was carried out using an ethanol–water mixture (85:15, v/v) under agitation at 60 °C. The ethanol was removed by evaporation *in vacuo*. The aqueous phase was then lyophilized, producing a brown powder.

Analytical-grade methanol, formic acid and ethyl acetate were supplied by Fisher Scientific (Waltham, MA, USA) or Sigma–Aldrich (St Louis, MO, USA). Acetonitrile for ultra–high-performance liquid chromatography (UPLC)–mass spectroscopy (MS) was of high-purity grade and purchased from Sigma–Aldrich. Deuterated solvents were purchased from Eurisotop (Saint-Aubin, France).

2. Extraction and isolation procedures

The crude root extract (10 g) was partitioned with ethyl acetate (100 mL). After removal of the ethyl acetate, the precipitate (3 g) was reconstituted in water (30 mL). Column chromatography was carried out using a glass column loaded with polyamide gel. The sample solution was loaded at the top of the polyamide and eluted with 500 mL of methanol, at a flow rate of 10 mL/min; this was done eight times. The eight fractions thereby obtained were subjected to evaporation *in vacuo*. They were screened for the presence of stilbenes by reverse-phase high-performance liquid chromatography (HPLC) and ultra-performance liquid chromatography (UPLC)–MS in the negative-ion mode (Gabaston *et al.*, 2017). Fraction 3 (440 mg) was found to contain five stilbene glucosides.

This fraction was rechromatographed on a semipreparative HPLC Varian Pro Star equipped with an Agilent Zorbax C18 column (7 µm, 250 ´ 25 mm) (Agilent, Santa Clara, CA, USA). The solvent programme was a gradient system:

A, water with 0.1 % formic acid; B, acetonitrile with 0.1 % formic acid. The elution programme at 15 mL/min was as follows: 10 % B (0–5 min); 10–20 % B (5–10 min); 20–30 % B (10–20 min); 30–35 % B (20–25 min); 35–60 % B (25–35 min); 60–100 % B (35–45 min); and 100 % (45–50 min). Chromatograms were monitored at 280 and 306 nm. Final purification yielded resveratroloside (3 mg), resveratrol rutinoside (1 mg), piceid (4 mg), *trans*-viniferin diglucoside (2 mg) and *cis*-viniferin diglucoside (1 mg).

3. NMR and mass spectrometry

Nuclear magnetic resonance spectra were recorded on a Bruker Avance III 600 NMR spectrometer (Bruker, Billerica, MA, USA). Mass spectra were recorded by an Agilent 1290 series UHPLC apparatus connected to an Esquire LC-ESI-MS/MS from Bruker Daltonics. Mass spectra were recorded in negative mode, with the capillary set at 1500 V, the end plate at –500 V, the capillary exit at –120.4 V, dry gas at 330 °C, gas flow at 11 L/min, the nebulizer at 60 p.s.i., target mass at *m*/*z* 500, scan range from *m*/*z* 100 to 3000, helium as the collision gas, and MS/MS fragmentation amplitude at 1.0 V. An analytical C18 column (Zorbax C18, 100 ´ 2.1 mm, 1.8 µm, Agilent) was used, with a flow rate of 0.4 mL/min (solvent system: 0.1 % [v/v] formic acid [A], acetonitrile [B]). Gradient started over 0 min at 5 % B, 1.7 min at 10 % B, 3.4 min at 20 % B, 5.1 min at 30 % B, 6.8 min at 30 % B, 8.5 min at 35 % B, 11.9 min at 60 % B, 15.3 min at 100 % B and 17.0 min at 100 % B, and resulted in 17.3 min at 10% B.

4. Cell culture and cell viability assay

The human hepatoma cell line HepG2 was purchased from the American Type Culture Collection (Manassas, VA, USA). The HepG2 cells were cultured in Eagle's Minimum Essential Medium (Sigma-Aldrich) supplemented with 10 % heat-inactivated fetal bovine serum, 2 mM L-glutamine, 0.1 mg/mL streptomycin and 100 U/mL penicillin (Sigma-Aldrich). The cells were grown at 37 °C in a humidified 5 % CO_2 atmosphere, with the medium replaced every 2–3 days. When the culture reached approximately 80 % confluence, the cells were detached by a solution of 0.1 % trypsin–0.04 % EDTA and harvested for use in the cell viability assays.

The HepG2 cells were seeded onto 96-well plates (5 ´ 10^3 cells/well), 24 h before treatment. Solutions of stilbenes (dissolved in culture medium) were added to the wells at increasing concentrations. After at least 72 h, the viability of the cells was determined using the crystal violet assay. The assay procedure was as follows. First, the medium was removed. The cells were then washed once with phosphate-buffered saline (PBS), before being fixed by exposure to a 3.7 % formaldehyde solution for 15 min at room temperature. Next, the cells were washed twice with PBS, before being stained by exposure to a 0.25 % crystal violet solution (Merck, Darmstadt, Germany) for 20 min in the dark. The microplates were then washed with running water and dried at 37 °C. After the crystal violet had been dissolved by adding 150 µL of a 33 % acetic acid solution, a Synergy HT microplate reader (BioTek, Winooski, VT, USA) was used to measure absorbance at 590 nm.

5. Statistical analysis

Means (± standard error, SE) were calculated from data yielded from at least three independent experiments. Means of related groups were compared by paired-samples Student's *t*-test, using the SPSS 17.0 statistical package (SPSS Inc., Chicago, IL, USA).

RESULTS AND DISCUSSION

The main stilbenes in different grapevine extracts have been identified and quantified by previous studies (Biais *et al.*, 2017; Gabaston *et al.*, 2017). Thirteen stilbenes have been identified: ampelopsin A, hopeaphenol, isohopeaphenol, myabenol C, pallidol, piceatannol, resveratrol, δ-viniferin, ε-viniferin, ω-viniferin, vitisin A, vitisin B and vitisinol C. Additionally, their antioxidant and cytotoxic activities in PC12 cells have been evaluated using oxygen radical absorbance capacity (Biais *et al.*, 2017).

Surprisingly, liquid chromatography–MS analyses of extracts from different parts of grapevine, including canes, wood and roots, showed the presence of stilbene glucosides mainly in the root extracts. In an effort to isolate and identify these compounds, the grapevine root extract was fractionated further. First, the extract was partitioned with ethyl acetate. The precipitate was then subjected to column chromatography on a polyamide gel. Subsequent elution with methanol yielded eight fractions.

Each fraction was subjected to evaporation, reconstituted in water–methanol (1:1, v/v), and analysed by UPLC-MS or MS spectroscopy in negative mode. In addition to resveratrol, five putative glycosylated stilbenes were found to be present in fractions 3 and 4. These compounds were isolated and purified to enable elucidation of their structures. Purification was carried out using reverse-phase semipreparative HPLC. The structures were deduced from two-dimensional NMR experiments. Assignments of proton and carbon resonances were based on homonuclear and heteronuclear experiments, including COSY, HSQC, HMBC and ROESY experiments. The five stilbenes were identified as resveratroloside, resveratrol rutinoside, piceid, *trans*-viniferin diglucoside and *cis*-viniferin diglucoside. Their structures are shown in Figure 1.

1. Determination of the structure of the compounds

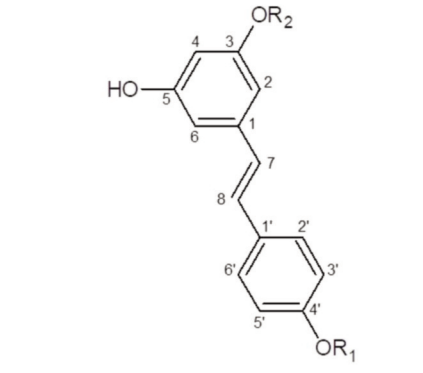
The structures of the stilbenes isolated are as follows:

• *Resveratroloside (3,5,4'-trihydroxystilbene-4'-O-b-glucoside)*: ESI-MS *m/z* 389 [M – H]$^-$; ^{1}H-NMR (DMSO-d_6) δ 7.49 (2H, d, *J* = 8.7 Hz, H-2′,6′), 7.00 (2H, d, *J* = 8.6 Hz, H-3′,5′), 6.98 (1H, d, *J* = 16.3 Hz, H-8), 6.91 (1H, d, *J* = 16.3 Hz, H-7), 6.39 (2H, d, *J* = 2.0 Hz, H-2,6), 6.11 (1H, brs, H-4), 4.86 (1H, d, *J* = 7.6 Hz, H-1″), 4.01 (1H, dd, *J* = 11.1, 4.0 Hz, H-6″a), 3.87 (1H, dd, *J* = 11.1, 6.5 Hz, H-6″b), 3.60–3.40 (4H, m, H-2″,3″,4″,5″) (Jayatilake *et al.*, 1993).

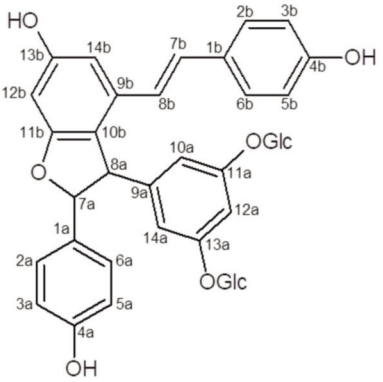
• *Resveratrol rutinoside (3,5,4'-trihydroxystilbene-3-O-b-rutinoside)*: ESI-MS *m/z* 578 [M – H]$^-$; ^{1}H-NMR (DMSO-d_6): δ 7.38 (2H, d, *J* = 8.6 Hz, H-2′,6′), 7.01 (1H, d, *J* = 16.3 Hz, H-8), 6.82 (1H, d, *J* = 16.3 Hz, H-7), 6.75 (2H, d, *J* = 8.6 Hz, H-3′,5′), 6.70 (1H, d, brs, H-2′), 6.53 (1H, d, brs, H-6′), 6.29 (1H, t, *J* = 2.1 Hz, H-4′), 5.12 (1H, d, *J* = 1.1 Hz, H-1'), 4.91 (1H, d, *J* = 7.4 Hz, H-1″), 3.90–3.20 (10 sugar protons), 1.19 (d, *J* = 6.2 Hz, OCH_3) (Joseph *et al.*, 2007).

• *Piceid (3,5,4'-trihydroxystilbene-3-O-b-glucoside)*: ESI-MS *m/z* 389 [M – H]$^-$; ^{1}H-NMR (DMSO-d_6): δ 7.36 (2H, d, *J* = 8.6 Hz, H-2′,6′), 7.02 (1H, d, *J* = 16.3 Hz, H-8), 6.85 (1H, d, *J* = 16.3 Hz, H-7), 6.79 (1H, br s, H-2), 6.77 (2H, d, *J* = 8.6 Hz, H-3′,5′), 6.62 (1H, brs, H-6), 6.46 (1H, t, *J* = 2.1 Hz, H-4), 4.89 (1H, d, *J* = 7.3 Hz, H-1″), 3.93 (1H, dd, *J* = 12.1, 2.5 Hz, H-6″a), 3.72 (1H, dd, *J* = 12.1, 5.6 Hz, H-6″b), 3.50–3.35 (4 sugar protons).

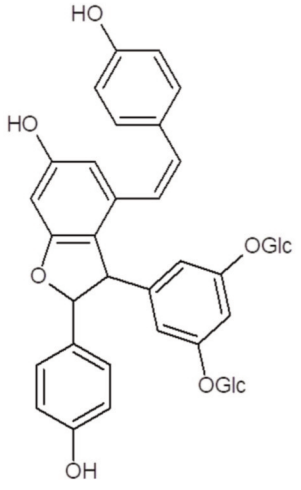
• *Trans-ε-viniferin-diglucoside*: ESI-MS *m/z* 777 [M – H]$^-$; ^{1}H-NMR (DMSO-d_6): δ 7.16 (2H, d, *J* = 8.6 Hz, H-2a,6a), 7.14 (2H, d, *J* = 8.6 Hz, H-2b,6b), 6.85 (1H, d, *J* = 16.3 Hz, H-8b), 6.74 (2H, d, *J* = 8.6 Hz, H-3a,5a), 6.68 (2H, d, *J* = 8.6 Hz, H-3b,5b), 6.61 (1H, t, *J* = 1.9 Hz, H-14b), 6.59 (1H, d, *J* = 1.9 Hz, H-12a), 6.61 (1H, t, *J* = 1.9 Hz, H-14b), 6.56 (1H, d, *J* = 16.3 Hz,



	R_1	R_2
piceid	OH	Glc
resveratrol	OH	OH
resveratrol rutinoside	OH	Rut
resveratroloside	Glc	OH



trans-ε-viniferin diglucoside



cis-ε-viniferin diglucoside

FIGURE 1. Structures of resveratrol glucosides isolated from grapevine root extract.

H-7b), 6.41 (2H, d, J = 1.9 Hz, H-10a,14a), 6.26 (1H, t, J = 1.9 Hz, H-12b), 5.34 (1H, t, J = 4.2 Hz, H-8a), 4.77 (2H, d, J = 7.5 Hz, H-1′,1″), 4.58 (1H, d, J = 4.2 Hz, H-7a), 3.64 (2H, dd, J = 11.4, 5.8 Hz, H-6a′,6a″), 3.43 (2H, m, H-6b′,6b″), 3.30–310 (8 sugar protons) (Baderschneider and Winterhalter, 2000).

• *Cis-ε-viniferin-diglucoside*: ESI-MS *m/z* 777 $[M - H]^-$; ^{1}H-NMR (DMSO-d_6): δ 6.97 (2H, d, J = 8.6 Hz, H-2a,6a), 6.93 (2H, d, J = 8.6 Hz, H-2b,6b) , 6.70 (2H, d, J = 8.6 Hz, H-3a,5a), 6.60 (2H, d, J = 8.6 Hz, H-3b,5b), 6.57 (1H, d, J = 1.9 Hz, H-12a), 6.21 (2H, d, J = 1.9 Hz, H-10a,14a), 6.20 (1H, d, J = 12.2 Hz, H-8b), 6.19 (2H, brs, H-12b,14b), 5.94 (1H, d, J = 12.2 Hz, H-7b), 5.17 (1H, t, J = 5.3 Hz, H-8a), 4.77 (2H, d, J = 7.5 Hz, H-1′, 1″), 4.00 (1H, d, J = 5.3 Hz, H-7a), 3.66 (2H, dd, J = 11.4, 5.8 Hz, H-6a′,6a″), 3.44 (2H, m, H-6b′,6b″), 3.30–310 (8 sugar protons) (Baderschneider and Winterhalter, 2000).

Resveratroloside has previously been isolated from roots of *Polygonum cuspidatum* (Jayatilake *et al.*, 1993) and in cell cultures of *Vitis vinifera* (Waffo Teguo *et al.*, 1998). However, to the best of our knowledge, the present study is the first to find resveratroloside in the woody parts of grapevine. Resveratrol-3-*O*-b-rutinoside has previously been described in root bark of *Terminalia sericea* (Joseph *et al.*, 2007); this is the first report of the presence of resveratrol-rutinoside in the *Vitis* genus. Piceid has been identified in different parts of grapevine, including stems and berries (Pawlus *et al.*, 2012). Both the *trans-* and *cis-*ε-viniferin diglucosides have previously been identified in wine (Baderschneider and Winterhalter, 2000), but this is the first report of their presence in grapevine extract.

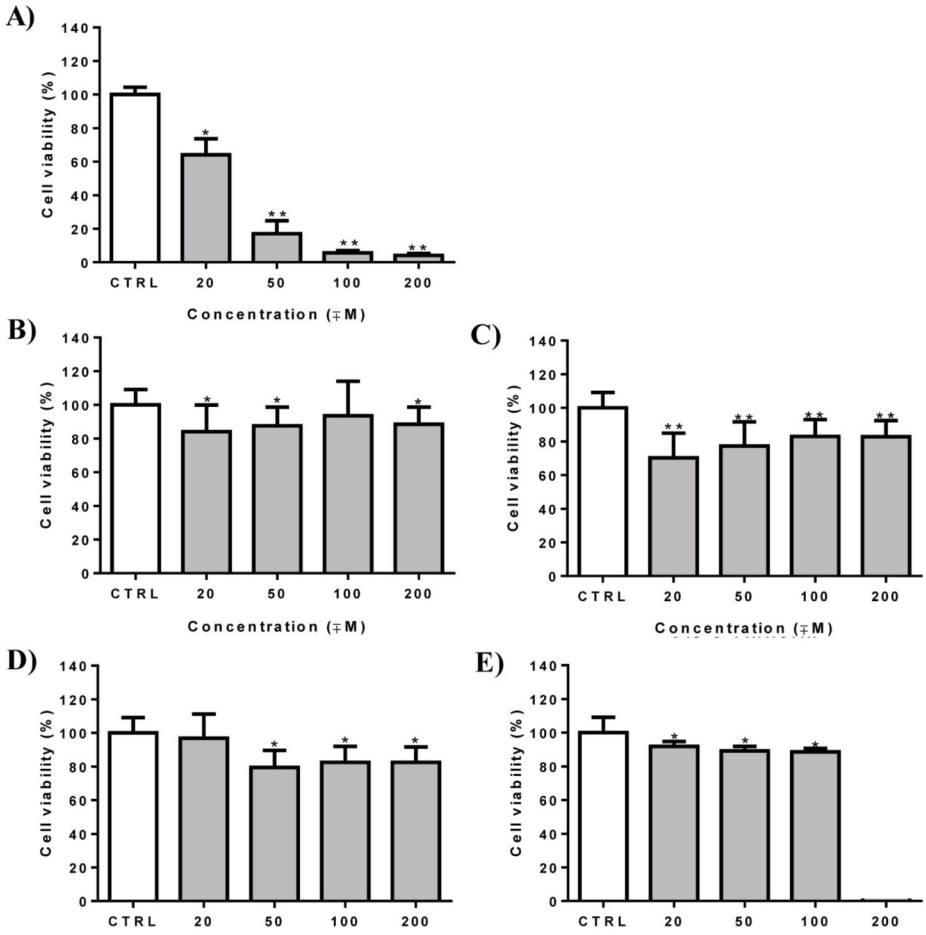


FIGURE 2. Effect of resveratrol (A), resveratroloside (B), resveratrol rutinoside (C), *trans*-ε-viniferin diglucoside (D) and *cis*-ε-viniferin diglucoside (E) on the viability of HepG2 cells.
CTRL, negative control (no added stilbenes). Compared with control group: *p < 0.05, **p < 0.005.

2. Cytotoxicity in human hepatoma HepG2 cells

The cytotoxic activity of resveratroloside, resveratrol rutinoside, and *trans*- and *cis*-ε-viniferin diglucosides in HepG2 cells was evaluated, using resveratrol as a positive control (Figure 2). The results for resveratrol showed this stilbene to be cytotoxic in a dose-dependent manner, with a half-maximal inhibitory concentration (mean ± SE) of 37.2 ± 9.9 µM at 72 h. It showed significant cytotoxicity at concentrations as low as 20 µM, well below previously reported cytotoxic concentrations (Su *et al.*, 2013). All the glucosylated stilbenes showed moderate but significant cytotoxicity against HepG2 cells. The most active compound was resveratrol rutinoside, which at the lowest concentration tested, 20 µM, decreased cell viability by 30%.

Although *trans*-ε-viniferin diglucoside was not active at 20 µM, it reduced viability significantly, by 20%, when assayed at higher concentrations (50–200 µM). The *cis*-ε-viniferin diglucoside isomer was less cytoxic, producing an 11% decrease in viability. These results highlight the importance of the *trans* stereoisomer in cytotoxicity. In the case of *trans* and *cis* isomers of resveratrol and piceid, the former are more thermodynamically stable and quantitatively more abundant in nature than the latter (Cicero *et al.*, 2019).

The finding that glucoside derivatives exert lower toxic effects than resveratrol could be due to the lower availability in the cell of the free active forms of these glucoside compounds, as has previously been suggested for piceid in comparison with resveratrol (Su *et al.*, 2013).

CONCLUSION

This is the first study to show the presence of glucosylated derivatives of resveratrol, other than piceid, in the woody parts of grapevine. In addition to piceid, four compounds were identified: resveratroloside, resveratrol rutinoside, and the *trans*- and *cis*-ε-viniferin diglucosides. All the compounds showed moderate cytotoxicity against the human hepatoma HepG2 cell line. However, they showed lower biological activity than resveratrol.

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