# Stilbenes in grape berries and wine and their potential role as anti-obesity agents: A review

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## Abstract

### Background

Stilbenes are a group of naturally occurring phenolic compounds. These compounds are synthetized by plants in response of biotic or abiotic stress situations. The major dietary sources of stilbenes for humans are grape berries and wine. To accurately identify and quantify these compounds, the research community has undertaken considerable efforts to optimise samples preparations and analytical methods. In addition, stilbenes are well-known to possess a wide range of biological activities for human health. One of the most recent and promising properties demonstrated by stilbenes are their anti-obesity effects.

### Scope and Approach

The principal objectives of this review to address and discuss about: i) stilbenes in grape berries and wine, the factors that can modulate their concentrations and the most efficient sample preparation techniques and analytical methods used for their detection; ii) the most important investigations related to the *in vitro* and *in vivo* anti-obesity effects of grape and wine stilbenes and the associated molecular mechanisms.

### Key Findings and Conclusions

Stilbene concentration in grape and wines can vary substantially. The composition of stilbenes in red wine is much more complex than in white wine. Until today, more than 30 stilbenes have been identified in grapes and wines. The liquid chromatography coupled to mass spectrometry is the most efficient method to investigate stilbene content. Regarding anti-obesity properties of stilbenes, a great number of *in vitro* and *in vivo* studies have allowed to demonstrate not only the positive implications of these bioactives but also the underlying mechanisms of the observed effects.



**Keywords:** stilbenes; resveratrol; grape, wine; *Vitis vinifera*; obesity

**Abbreviation list**

**ACC:** acetylCoA carboxylase

**ACO:** acyl-coenzyme A oxidase

**aP2:** adipocyte protein 2

**ATAD3:** ATPase family AAA Domain-containing protein 3

**ATGL:** adipose triglyceride lipase

**BAT:** brown adipose tissue

**Bmp2:** bone morphogenetic protein 2

**CE:** capillary electrophoresis

**C/EBPs:** CCAAT/enhancer binding proteins

**CHS:** chalcone synthase

**CLA:** conjugated linoleic acid

**COX:** cyclooxygenase

**CPT-1:** carnitine palmitoyltranferase 1

**CRP:** C-reactive protein

**Cyc-D:** cyclin D

**DAD:** diode array detector

**Ddit3:** DNA-damage inducible transcript 3

**DLLME:** dispersive liquid-liquid microextraction

**ERK:** extracellular receptor kinase

**FABP4:** fatty acid binding protein 4

**FAS:** fatty acid synthase

**Fgf10:** fibroblast growth factor 10

**Fiaf:** fasting-induced adipose factor

**FLRD:** fluorescence detector

**FW:** fresh weight

**GC:** gas chromatography

**G6PDH:** glucose-6-phosphate dehydrogenase

**GLUT4:** glucose transporter 4

**HFCSD:** high fructose corn syrup diet

**HFD:** high fat diet

**HO-1:** heme-oxygenase 1

**HPD:** high protein diet

**HPLC:** high performance liquid chromatography
**HSL:** hormone-sensitive lipase
**IFN:** interferon
**IL:** interleukin
**IR:** insulin receptor
**KLF9:** Kruppel-like factor 9
**KR:** β-ketoacyl reductase
**LDL:** low density lipoprotein
**LPL:** lipoprotein lipase
**LXRα:** liver X Receptor alpha
**MS:** mass spectrometry
**MCP-1:** monocyte chemoattractant protein 1
**ME:** malic enzyme
**MEPS:** microextraction by packed sorbents
**Mfn2:** mitofusin 2
**miRNA:** microRNA
**MRM:** multiple reaction monitoring
**MS:** mass spectrometry
**mTOR:** mammalian target of rapamycin
**MTTP:** microsomal triglyceride transfer protein
**NF-ĸB:** nuclear Factor Kappa B
**Nrf1:** nuclear respiratory factor 1
**PDA:** photodiode array detector
**PDE3B:** phosphodiesterase 3B
**PKA:** protein kinase A
**PKCδ:** Protein Kinase C delta
**PPARγ:** peroxisome proliferator-activated receptor gamma
**PRDM16:** PR domain-containing 16
**PVPP:** polyvinylpolypyrrolidone
**QqQ:** triple quadrupole
**QTOF:** quadrupole time-of-flight
**Rip 140:** receptor interacting protein 140
**ROS:** reactive oxygen species

**SBSE:** stir-bar sorptive extraction

**SCD-1:** stearoyl-CoA desaturase-1

**SD:** standard diet

**SIRT1-AMPK-FOXO1:** sirtuin 1-AMP-activated protein kinase-Forkhead box protein O1

**SPE:** solid phase microextraction

**SPME:** solid phase microextraction

**SREBP1:** sterol regulatory element binding transcription factor 1

**STS:** stilbene synthase

**TG:** triglycerides

**TLR:** Toll-like receptor

**TNF-α:** tumor necrosis factor alpha

**UCP-1:** uncoupling protein 1

**UV:** ultraviolet

**WAT:** white adipose tissue

**WHO:** world health organization

## Highlights

- Grape berries and wines are among the major sources of stilbenes in human nutrition
- Red wines contain more complex stilbenes than white wines
- Stilbenes could reduce obesity by regulating different pathways
- Some stilbenes show better anti-obesity activities than resveratrol
- Combination of stilbenes with others polyphenols give promising results

## Introduction

Stilbenes (1,2-diphenylethylene) are phenolic compounds derived from the general phenylalanine pathway (**Figure 1**). Among the commonly identified stilbenes, resveratrol is the most popular compound (Gambini et al., 2015). The structural unit is constituted by two phenyl rings linked together by an ethylene bridge forming a C6-C2-C6 chain. This double bond allows stilbenes to exist in the *trans* (E) and in the *cis* form (Z) (Rivière et al., 2012). The aromatic rings could be substituted by different functional groups such as hydroxyl, methoxyl, prenyl or geranyl groups. Moreover, monomeric units can also be coupled, leading to the formation of oligomers. Over a thousand of natural stilbenes have been described in the literature. Despite this chemical diversity, only a limited number of plant families produce these secondary metabolites, such as Polygonaceae, Cyperaceae, Pinaceae or Vitaceae (Rivière et al., 2012). Furthermore, stilbenes are considered as phytoalexins since they are associated with the resistance of plants to diseases and their synthesis is often a response to an attack by phytopathogenic agents and other stress factors like UV irradiation, ozone, heavy metal ions, injury or frost (Błaszczyk et al., 2019).

Grapes and red wine are among the major dietary sources of stilbenes for human nutrition, especially in European countries (Guerrero et al., 2009; Weiskirchen and Weiskirchen, 2016). However, it should be noted that stilbenes are also present in minor quantities in other foodstuffs such as peanut, pistachio, almonds, berries, banana, pineapple, apple, peach, passion fruit or dark chocolate (Neveu et al., 2010; Weiskirchen and Weiskirchen, 2016). Focusing only on grapes berries and wines, it is noteworthy that stilbene amounts can be extremely variable (Guerrero et al., 2016; Hasan and Bae, 2017). Several factors could influence their quantities in grapes such as the stage of ripening, the grape varieties or various external stimuli. The duration of maceration, yeast activity, and other winemaking processes

148 are also important factors that contribute to the final stilbene amounts described in wines.

149 For a long time, stilbene analyses in grape berries and wines were limited to resveratrol and
150 piceid (Lamuela-Raventós et al., 1995; Mattivi et al., 1995). Today, thanks to the analytical
151 methods such as ultra-high performance liquid chromatography tandem mass spectrometry
152 (UHPLC–MS/MS), more than thirty-three stilbenes have been identified and quantified in
153 grape berries and wines (**Figure 2**). In addition, it must be emphasized that not only the
154 selection of the most adapted analytical method but also the sample preparation techniques
155 are crucial to have reliable and accurate results.

156 Stilbenes have demonstrated to possess a great range of biological activities potentially
157 beneficial for human health such as neuroprotective, antioxidant and antitumor effects
158 (Weiskirchen and Weiskirchen, 2016). Among the more recent research lines, stilbenes are
159 gaining considerable interest as potential anti-obesity agents. Obesity is the most common
160 nutritional disorder in the world. According to the World Health Organization (WHO),
161 obesity is defined as an abnormal or excessive fat accumulation that may impact health.
162 Prevalence data estimate that 650 millions of adults were obese in 2016, representing about
163 13% of the world adult population. Moreover, alarming figures are presented regarding young
164 population. In fact, more than 124 millions of children and adolescents were obese in 2016
165 (WHO, 2018, http://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight). It is
166 well known that the fundamental cause of obesity is an energy imbalance between calories
167 intake and loss, as a consequence globally, of a high intake of energy-fat foods and a
168 sedentary style of life. When a positive energy imbalance occurs, triglycerides (TG) are
169 accumulated in adipocytes producing an increase in the number of adipocyte (hyperplasia) or
170 an increase of its size (hypertrophy) (Hausman et al., 2001). Additionally, obesity can also
171 bring a potential risk to develop cardiovascular diseases, diabetes and some types of cancer,

endometrial, breast, ovarian, prostate, liver, gallbladder, kidney, and colon, among others (Gallagher and LeRoith, 2015). Due to the increase of the prevalence and the associated complications, several global government policies, laws and regulations have been developed to halt and reverse the obesity epidemic. The first solution to stem obesity is focused in a change of lifestyle by decreasing the energy/fat/sugar intake and increasing physical activity. However, the implementation and effectiveness of these recommendations are usually unsatisfactory. The research community tries then to find anti-obesity bioactive molecules such as stilbenes that can be combined with other recommendations and treatments in order to improve the results.

It has been shown that stilbenes may reduce obesity by regulating different pathways related to fat metabolism as adipogenesis, lipogenesis, lipolysis and thermogenesis (Chou et al., 2018; Fernández-Quintela et al., 2017). Resveratrol has been the most studied bioactive compound, but a considerable number of works are already indicating that other stilbenes are promising anti-obesity agents and may even be more potent than resveratrol.

For all above explained, the aim of this review is to address and discuss about: i) stilbene compounds in grape berries and wines, the principal factors that can modulate their concentrations and the most efficient sample preparation techniques and analytical methods used for their detection; ii) the most important investigations related to the *in vitro* and *in vivo* anti-obesity effects of grape and wine stilbenes and the associated molecular mechanisms.

## Stilbenes content in grape berries and wine

### *Grape berries stilbenes*

In grape berries, stilbenes as other polyphenols are mainly concentrated in skins (Babazadeh et al., 2017). They present a great variability in composition and content depending on

195 different biotic and abiotic factors including grape variety, stage of ripening, viticultural
196 factors and practices (Bavaresco et al., 2012; Błaszczyk et al., 2019).

197 The stilbene content offers sharp contrasts due to many potential external stimuli (Vincenzi et
198 al., 2013). Red varieties seem to present higher stilbene content than white ones (Guerrero et
199 al., 2010; Viñas et al., 2011). Concerning monomers, glucosides (piceid and astringin) are the
200 main compounds identified in grape berries (**Table 1**). The piceid (mean 1.36 mg/kg, *cis*- and
201 *trans*-isomers) is the main compound followed by astringin (mean 0.83 mg/kg), and
202 resveratrol (mean 0.68 mg/kg). Both isomeric forms, *trans*- and *cis*-isomers, were identified
203 in similar levels for piceid and mainly *trans* forms for astringin and resveratrol. These
204 compounds were observed in all berry growth stages in different concentrations (Jeandet et
205 al., 1991). They are subject to enzymatic transformations leading to the formation of a pool of
206 different compounds (Chong et al., 2009). The hydroxylation of resveratrol and piceid leads
207 to the formation of piceatannol and its glucoside, astringin (Bavaresco et al., 2002). In
208 addition to these three monomers some other minor monomers were identified such as
209 pterostilbene (Pezet et al., 1994), and isorhapontigenin (Fernández-Marín et al., 2012). The
210 oxidative coupling of resveratrol induces the formation of more complex oligomers including
211 dimers, trimers and tetramers (Takaya et al., 2005). Significant levels of oligomers were
212 reported (Rosso et al., 2016). In *Vitis vinifera* cultivars, dimers compounds were identified
213 such as pallidol (Vrhovsek et al., 2012), ε-viniferin and δ-viniferin (Flamini et al., 2013). In
214 addition to these dimers, trimers were identified, like miyabenol C and α-viniferin, and a pool
215 of tetramers including hopeaphenol and isohopeaphenol (Flamini et al., 2016; Rosso et al.,
216 2016). Unfortunetly, few studies were focused on the quantification of these complex
217 compounds in grape berries. In contrast, wild *Vitis* species appear to contain a greater number
218 and diversity of oligomeric stilbenes (He et al., 2009; Jiang et al., 2012).

Different biotic and abiotic factors affect the stilbene content in grape berries, including the grape varieties or species, stage of ripening, environmental conditions or postharvest treatments (Hasan and Bae, 2017; Błaszczyk et al., 2019). The main factors that can have an impact on stilbene quantities in grapes were described below.

***Stage of ripening***

The development of grape berries is a dynamic process that involves a complex series of changes divided into three major phases: before veraison, veraison and after veraison. Before veraison, the cell division is rapid and all cells are established within two weeks of flowering, followed by a subsequent sigmoidal increase in berry size (Deluc et al., 2007). At the end of this period, the STS is accumulated and reaches its maximum two weeks before veraison. The stage after veraison is characterized by the initiation of colour development (accumulation of anthocyanins in red grapes) until maturity and the accumulation of stilbenes (Wang et al., 2016). Even if the STS its maximum level two weeks before veraison, the accumulation of stilbenes only starts in the second week after veraison and then increases until maturity from 5 to 35 mg/kg (Wang et al., 2016).

***Grape varieties and species***

The accumulation of stilbenes seems to depend on the *Vitis vinifera* grape cultivar. In a comparative study between three different cultivars, Syrah, Tempranillo and Merlot, Guerrero et al. have shown that Syrah had the highest stilbene content 4.02 mg/kg followed by Merlot and Tempranillo with 3.59 and 0.45 mg/kg; respectively (Guerrero et al., 2010). This result was confirmed by Gatto et al. that compared 78 different cultivars during three years (Gatto et al., 2008). Firstly, they observed higher stilbene content in red varieties than in white or pink ones. Secondly, Pinots and related cultivars (Pinot Gris, Tête de Negre, and Noir) exhibited

242 the highest stilbene levels. Biochemical and transcriptomic analyses have shown the genotype
243 influence on stilbene accumulation in healthy grapevine berries. In the high yielding varieties,
244 glucosylated forms such as piceid were accumulated preferentially, resveratrol being mainly
245 produced after external stimuli such as fungal infection.

246 Nevertheless, these data have to be substantiated by consistent results because external
247 stimuli, such as light or pathogen infection could have higher effect than the intrinsic
248 differences between cultivars (Hasan and Bae, 2017). As for other secondary metabolites
249 (Hilbert et al., 2015), it is likely that wild species present higher content and diversity of
250 stilbene than the cultivated one (Jiang et al., 2012). In a recent article, Gabaston et al.
251 compared the stilbene content of nine wild *Vitis* species to *Vitis vinifera* showing that stilbene
252 content in wild *Vitis* was generally richest and more complex than the cultivated *Vitis*
253 (Gabaston et al., 2020). For example, *Vitis champinii*, an American species, may contain up to
254 ten times more stilbenes than *Vitis vinifera* (208.8 versus 20.5 mg/kg, respectively). These
255 results are in agreement with the data concerning other parts of the grapevine, such stem or
256 roots. Wild *Vitis* species, that have higher resistance to external stress, seem to contain more
257 stilbenes than cultivated vine (Pawlus et al., 2013b).

258 ***External stimuli***

259 Several external stimuli could modulate the stilbene content in grape berries including
260 pathogen infection, elicitor applications, or UVC treatments. The effects of stimuli could
261 increase the stilbene content more than ten times the normal. As stilbenes are well-known
262 phytoalexins (Langcake and Pryce, 1977), the effect of different pathogens on stilbenes
263 accumulation in grape was widely investigated. Infection by *Botrytis cinerea* induce the
264 accumulation of resveratrol mainly in its glucosidic form from 2.06 mg/kg before infection to
265 63.60 mg/kg after induction (Roldán et al., 2003). Similar results were observed for

*Plasmopara viticola*, *Uncinula necator* and *Rhizopus stolonifera* (Hasan and Bae, 2017), with accumulation rate ranging between three and twelve times than control. Remarkably, the increase of the resveratrol level in berries due to pathogen infection does not lead to a significant modification of the stilbene content in wines (Jeandet et al., 1995; Roldán et al., 2003). Authors suppose that grape berries with a high *Botrytis* infestation presented lower resveratrol contents due to the oxidation of resveratrol by the laccase enzymes secreted by fungi. In the same manner, chemical compounds such as elicitors are able to induce the production of stilbenes (Krisa et al., 1999). This effect was mainly demonstrated in grape cell cultures using different chemicals such as methyl jasmonate, salicylic acid, glucan, or chitosan (Vuong et al., 2014). The induction could increase stilbene production ten times compared to the control. This observation was confirmed in grape berries, where methyl jasmonate induced a significant increase of resveratrol (from 0.78 to 1.40 mg/kg), piceatannol (from 0 to 0.20 mg/kg), isorhapontigenin (from 0.15 to 0.21 mg/kg) and ε-viniferin (from 0.14 to 0.29 mg/kg) content up to two times in comparison to the control (Fernández-Marín et al., 2014). Physical processes could also stimulate the production of stilbenes. Pre- and post-harvest treatments by UVC induce an increase of the stilbene content in grape berries (Adrian et al., 2000; Guerrero et al., 2010). The values were ranged between one and twenty times the normal resveratrol concentration (Błaszczyk et al., 2019). In addition to the increase in the amount of resveratrol, levels of other stilbenes rise in the same proportion. This effect was observed on different stilbenes including piceid, piceatannol, ε-viniferin, δ-viniferin and hopeaphenol (Guerrero et al., 2016).

To conclude, several biotic and abiotic factors can strongly influence the stilbenes content in grape berries including species and various external stimuli. It is difficult to draw conclusions on the relative impact of each of these factors. But some of these external stimuli such

290 elicitors and UVC treatments could be combined to increase artificially the stilbene content in
291 grape berries before and/or after harvest.

292 ***Wine stilbenes***

293 Wine is an important dietary source of resveratrol (Kasiotis et al., 2013), in which it can be
294 found at concentrations up to 20 mg/L (Ribeiro De Lima et al., 1999). As for grape berries,
295 the monomeric forms are the most abundant stilbenes in wine, while oligomeric forms were
296 mainly identified in red wines (Guerrero et al., 2020). The main compounds identified in
297 wines were piceid (*cis*- and *trans*-isomers), resveratrol (*cis*- and *trans*-isomers), astringin (*cis*-
298 and *trans*-isomers) and piceatannol (**Table 1**). In addition to these compounds several other
299 stilbenes were identified including dimers such as pallidol (Landrault et al., 2002), ε-viniferin
300 (Amira-Guebailia et al., 2009; Landrault et al., 2002), δ-viniferin (Moss et al., 2013), ω-
301 viniferin (Guerrero et al., 2020), parthenocissin A (Vitrac et al., 2001), quadrangularin A
302 (Pawlus et al., 2013a); trimers such as miyabenol C (Guerrero et al., 2020), and α-viniferin
303 (Arraki et al., 2017); and tetramers such as hopeaphenol (Guebailia et al., 2006),
304 isohopeaphenol, and r2-viniferin (Guerrero et al., 2020). Glucosidic and diglucosidic forms of
305 these compounds were also identified including ε-viniferin diglucosides, pallidol 3-O-
306 glucoside, and pallidol diglucosides (Baderschneider and Winterhalter, 2000). In addition,
307 analyses by mass spectrometry indicated the presence of several other oligomers in wines
308 (Moss et al., 2013).

309 Red wines have a higher content in stilbenes than white wines (**Table 1**). Piceid is the main
310 stilbene in wines (means 8.26 and 0.88 mg/L in red and white wines, respectively).
311 Surprisingly, the *cis*-isomer levels are higher in both cases (means 6.20 and 0.68 mg/L in red
312 and white wines, respectively). In red wines, the piceid is followed by resveratrol (mean
313 2.29 mg/L). The derivatives of piceatannol are present at a concentration of about 1.73 mg/L.

Oligomers are minor compounds except isohopeaphenol with a mean value of 1.39 mg/L in red wines (**Table 1**). No oligomers were reported in white wines. Several parameters are able to modulate the stilbene content in wine including mainly the extraction from grape, but also yeast strains, and enological practices.

***Duration of maceration***

Red wines contain higher stilbene levels than white wines that are obtained from a limited maceration with the pomaces (**Tables 1**). In fact, the stilbene content in wines is strongly modulated by the duration of the maceration and the solubility of these compounds in alcohol (Mattivi et al., 1995; Kostadinović et al., 2012). Due to their polarity, monomeric glucosides are extracted before their aglycone forms (Mattivi et al., 1995). While oligomers such as δ-viniferin are observed in wines after few days of maceration (Poussier et al., 2003). After a long time of maceration the concentration of stilbenes decrease mainly that of glucosides such as *cis*- and *trans*-piceid (Poussier et al., 2003). The decrease of piceid could be attributed to the β-glucosidase activity of the different yeasts (Jeandet et al., 1994). In addition to this phenomenon, the *cis/trans* isomerization of stilbenes could explain the formation of some of these compounds such as *cis*-resveratrol. The levels of this compound are similar to those of *trans*-resveratrol in red wines and significantly lower in grapes (**Table 1**). Finally, even if few studies about resveratrol degradation during maceration were conducted, yeasts seem to be able to induce a degradation of resveratrol during wine fermentation (Vacca et al., 1997).

***Yeast activities***

As previously mentioned, yeast activities influence the stilbene content in wines. A comparison between French and Macedonian yeasts demonstrated a variation of resveratrol content up to four times depending on the yeast and maceration times (Kostadinović et al.,

2012). The β-glucosidase activities of yeasts induce the hydrolyze of glucosides which leads to the formation of non glucosylated stilbenes (Mattivi et al., 1995). Thus, the selection of exogenous yeasts could significantly affect the stilbene content in wines. The use of specific yeasts enriched in β-glucosidase could positively increase the level of resveratrol in wines (González-Candelas et al., 2000). Nevertheless more studies are needed to better understand the impact of yeast activities on stilbene content in wines.

***Winemaking processes and wine ageing***

Few studies were focused on the impact of winemaking processes on the stilbene content in wines. Grapes exposure to UVC radiations before winemaking induces an increase of stilbene production in wines (Threlfall et al., 1999; Cantos et al., 2003). This positive effect is observed on monomeric stilbenes such as resveratrol and piceatannol whereas other stilbenes such as ε-viniferin are not affected (Fernández-Marín et al., 2014). On the contrary, the use of some fining agents, such as polyvinylpolypyrrolidone (PVPP), could reduce the stilbene content in wines (Threlfall et al., 1999; Vrhovsek et al., 1997).

As for winemaking processes few studies were focusing on the stilbene stability during wine ageing. Stilbenes are known to be relatively stable compounds (Bavaresco et al., 2012; Gaudette and Pickering, 2011). Nevertheless, even if the total stilbene content is not affected, the ratio between resveratrol and piceid isomers could be impacted during wine ageing (Sun et al., 2006; Favre et al., 2020). In addition some specific ageing processes such as those used in Sherry wines could reduce the resveratrol content (Roldán et al., 2010). Finally, heat could induce oxidative coupling between monomeric stilbenes inducing the formation of oligomers in wines (El Khawand et al., 2020).

## Analytical methods for stilbenes analysis in grapes and wines

The relatively low concentration of stilbenes, their structural diversity, and the complexity of grape and wine matrices restrain their identification and quantification. Today, the studies are mainly focused on the monomeric stilbenes. Several analytical procedures were developed in order to determine the stilbene content in grapevines and wines from monomers to complex oligomers. These strategies often require multi-steps sample preparation (Baderschneider and Winterhalter, 2000; Romero-Pérez et al., 2001; Liu et al., 2013).

Concerning grapevines, the first step consists of the extraction of stilbenes from the raw material. Several extraction procedures were applied including classical solvent extraction from fresh, frozen, dried or lyophilized berries (Romero-Pérez et al., 2001), or more recently ultrasonication-assisted extraction (Cho et al., 2006). The classical solvent extraction remains the most applied technique the main used methodology using acetone, chloroform, ethanol, ethyl acetate, methanol, and some mixed solvents. Methanol, pure or mixed, is the most widely used solvent for stilbene extraction from grapevine berries. Several studies were focused on optimizing the extraction conditions form grapevine berries (Liu et al., 2013; Romero-Pérez et al., 2001; Sun et al., 2006). The main parameters analyzed were the solvent, the extraction time, the temperature, and the ratio solid to solvent. Based on Liu et al. (2013) studies (Liu et al., 2013), the best extraction solutions were: methanol or methanol/ethyl acetate (1:1 (v/v)) with a ratio solid to solvent of 1 g/10 mL at 25°C for 24 h. In addition, in order to avoid *cis*/*trans* isomerization, extraction should be carried out in the dark (Careri et al., 2003). Interestingly, innovative extraction techniques such as ultrasonication-assisted extraction seem to be able to increase the stilbene extraction rate while reducing time and solvent consumption (Cho et al., 2006).

As for grape berries, several methods were proposed to extract stilbenes in wines, from direct

383 analyses (Lamuela-Raventós et al., 1995) to more complex procedures using solid phase
384 extraction (Mattivi et al., 1995), stir-bar sorptive extraction (Viñas et al., 2008),
385 microextraction by packed sorbents (Gonçalves and Câmara, 2011), liquid–liquid extraction
386 (Rabesiaka et al., 2011), dispersive liquid–liquid microextraction (Rodríguez-Cabo et al.,
387 2012), semi preparative liquid chromatography (Amira-Guebailia et al., 2009), or counter
388 current chromatography (Fernandez-Marin et al., 2012). The main drawback of these methods
389 is that they are mainly focused on resveratrol and piceid. In the research conducted by
390 Baderschneider and Winterhalter a combination of solid phase extraction and counter current
391 chromatography were used to identify new stilbene skeletons in wines (Baderschneider and
392 Winterhalter, 2000).

393 Several methods were used for stilbene analysis in grape berries and wines including capillary
394 electrophoresis (CE), gas chromatography (GC), high performance liquid chromatography
395 (HPLC) and ultra-high performance liquid chromatography (UHPLC).

396 The capillary electrophoresis is appropriate for the separation of small molecules and could
397 separate some optical isomeric forms. This method allows separating positional isomers as
398 well as optical isomers. This method has different advantages such as fast and accurate
399 analysis, low amount and consumption (Coelho et al., 2016).

400 Gas chromatography (GC) was successfully used for resveratrol quantification in wines
401 (Barbanti et al., 1996), and grapes (Viñas et al., 2009). Today, GC analyses were coupled with
402 mass spectrometry detector (GC–MS) in order to increase the accuracy and sensibility of the
403 detection (Rodríguez-Cabo et al., 2016). These methods provide limits of detection close to
404 ng/L in wines. However, GC analyses have different drawbacks such as isomerization,
405 degradation of analytes.

High-performance liquid chromatography (HPLC) is considered among the most commonly applied method for stilbenes analysis in grapes (Błaszczyk et al., 2019) and wines (Fabjanowicz et al., 2018), using different detection systems such as UV-visible or diode array detectors (Mattivi et al., 1995; Sun et al., 2006), or fluorescence detectors in order to increase sensitivity and specificity (Vitrac et al., 2002). Nowadays, HPLC combined with mass spectrometry (HPLC-MS) has become the most used technique for the determination of phenolic compounds in general and stilbenes in particular (Pugajeva et al., 2018). This method allows the identification of all stilbenes (free and conjugated) without any derivatization or hydrolysis of samples. Different mass detectors were used including triple quadrupole (QqQ) and quadrupole time-of-flight (QTOF). Information on liquid chromatography methods developed for stilbenes identification and quantification in grape berries and wines are summarized in **Table 2**.

In recent years, UHPLC coupled with mass spectrometry (UHPLC-MS) has been widely used as an alternative for other methods due to its higher sensitivity, accuracy, rapidity, and low solvent consumption for grape berry (Flamini et al., 2013), and wine analyses (Moss et al., 2013; Guerrero et al., 2020). For example, based on a targeted metabolomics approach using UHPLC-QTOF mass spectrometer, Flamini et al. have identified and quantified eighteen stilbenes in grape berries including oligomers. In wines, an UHPLC-QqQ-MS method was designed to identify and quantify fifteen stilbenes in white and red wines with limit of detection ranging between 4 and 28 µg/L (Guerrero et al., 2020). Similarly, using a UHPLC-QTOF mass spectrometer, forty-one stilbenes were identified in red wines, including six monomers, twenty-three dimers, eight trimers and four tetramers (**Table 3**).

Due to the complexity and the diversity of stilbene structures, pure compounds are needed as standard to obtain accurate results. Unfortunately, since pure samples of complex stilbene

oligomers are often unavailable, results are expressed in resveratrol or piceid equivalent (Flamini et al., 2013). This approach could lead to severe underestimation of the oligomeric stilbene content (Biais et al., 2017). For example, the quantification of ε-viniferin using resveratrol by a HPLC-DAD method underestimated the concentration ε-viniferin, R-viniferin and isohopeaphenol by a factors upper than two, five and ten, respectively.

## Stilbenes, *in vitro* and *in vivo* anti-obesity effects and molecular mechanisms

### *Anti-obesity in vitro effects of stilbenes*

As was noted in the Introduction section, stilbenes might act as anti-obesity agents by regulating different fat metabolism pathways such as adipogenesis, lipogenesis, lipolysis and thermogenesis (Chou et al., 2018; Fernández-Quintela et al., 2017).

Adipogenesis is defined as the differentiation process of preadipocytes to fully mature to adipocytes. This process can be divided in different stages: growth phase and growth arrest, clonal expansion, gene expression of lipogenic proteins inducing triglyceride (TG) accumulation and differentiation and cell death (apoptosis) (Esteve Ràfols, 2014). Some transcription factors like the peroxisome proliferator-activated receptor gamma (PPARγ), the sterol regulatory element binding protein 1c (SREBP-1c) and CCAAT-enhancer binding proteins (C/EBPs) are key elements in production of the fully mature adipocytes (Rosen et al., 2002). Moreover, others proteins such as glucose transporter 4 (GLUT4), adipocyte protein 2 (aP2) or lipoprotein lipase (LPL) are also involved in this process (MacDougald and Mandrup, 2002).

Concerning the anti-adipogenic effects of stilbenes, the most investigated molecule was resveratrol. Several papers demonstrated that resveratrol is able to inhibit preadipocyte and adipocyte differentiation through the decrease of gene and protein expressions of PPARγ,

C/EBPα and C/EBPβ at concentrations ranging between 0.03-400 μM in mouse, bovine and human cells (**Table 4**). In addition to suppressing the expression of several key lipogenic genes, resveratrol can interfere by diminishing preadipocyte proliferation and inhibiting the clonal expansion stage or the cell cycle entry to G2/M phase. Actually, a decrease of the expression of cell cycle genes, such as cyclin D1 and A2, cyclin-dependent kinase 2 and 4, and DNA-damage inducible transcript 3 (Ddit3, also known as Chop-10), was observed (Kwon et al., 2012b; Mitterberger and Zwerschke, 2013; Santos et al., 2014). Furthermore, resveratrol interacted with the insulin receptor (IR) in 3T3-L1 preadipocyte cells and inhibited the insulin signaling pathway in the early phase of adipogenesis (Kwon et al., 2012b).

More recently, a very interesting work of Eseberri et al. showed that some resveratrol metabolites, and specifically resveratrol 3'- and 4'-glucuronide (at 25 μM concentration), were able to regulate and inhibit the expression of C/EBPβ and Krüppel-like factor (KLF9) that mediates both the early and late stages of the differentiation program (Eseberri et al., 2017).

Some of these studies, also showed that resveratrol decrease or attenuates the production of other key adipogenic proteins such as fatty acid binding protein 4 (FABP4) that regulates adipogenesis by downregulating PPARγ (Garin-Shkolnik et al., 2014). Santos et al. also reported an important modulation role of resveratrol on the gene expression of Adipogenic, Bone morphogenetic protein 2 (Bmp2), fatty acid synthase (FAS), fibroblast growth factor 10 (Fgf10) and leptin (Santos et al., 2014). Likewise, this lipid-lowering effect has been associated and depends on the sirtuin 1-AMP-activated protein kinase-Forkhead box protein O1 (SIRT1-AMPK-FOXO1) pathway (Liu et al., 2018). It is well know that SIRT 1 is responsible of fat mobilization in mature adipocytes and its activation give rise to the inhibition of PPARγ expression (Picard et al., 2004). Additionally, AMPK pathway plays an important role on the control of body fat stress. In fact, some studies have demonstrated that

hormones, such as leptin and adiponectin, adrenergic agonists, and metformin, activate AMPK in adipocytes (Rossmeisl et al., 2004). AMPK negatively regulates white adipogenesis, specifically blocking the clonal expansion of preadipocytes by attenuating adipocyte differentiation (Kang et al., 2005). In addition, AMPK activation in the early phase of differentiation inhibits PPARγ and C/EBPα expression as well as late adipogenic markers such as FAS and acetylCoA carboxylase (ACC). For these reasons, it is well accepted that AMPK activity is inversely related to white adipogenesis.

Moreover, resveratrol can induce the cell death in both mice 3T3-L1 cells (Rayalam et al., 2008), and human pre-adipocytes (Liu et al., 2018). In fact, a modulation of the expression of caspase-3, and the pro-apoptotic protein Bax was demonstrated after resveratrol treatment that also implicated the SIRT1-AMPK-FOXO1 pathway (Liu et al., 2018).

Concerning other stilbenes, r- and r2-viniferin (tetrameric stilbenes) that were recently identified in wine (Guerrero et al., 2020), are also thought to be able to inhibit adipocytes differentiation and reduce lipid accumulation in 3T3-L1 cells by decreasing the expression of PPARγ, C/EBPα and FABP4 genes (Tie et al., 2018). In accordance with these results, r2-viniferin suppressed the adipogenic process by blocking the cell cycle at the G1-S phase through p21- (CDK inhibitor) and Rb-dependent suppression of transcription in 3T3-L1 cells (Kim et al., 2008). Long-term treatment at low concentrations (5-10 μM) by pterostilbene, a methylated derivative of resveratrol, inhibited adipocyte differentiation in 3T3-L1 preadipocytes and 3T3-F442A cells (Gomez-Zorita et al., 2017; Hsu et al., 2012). This compound induced heme-oxygenase 1 (HO-1) expression which acts as a regulator of Chop10, suppressing in consequence the initiation of mitotic clonal expansion (Seo et al., 2017). Piceatannol acts in the early phase of adipogenesis delaying the cell cycle entry into G2/M phase at 24 h after initiation of adipogenesis and suppressing the mitotic clonal and the

activation of the insulin-signaling pathways (Kwon et al., 2012a). Furthermore, ε-viniferin, a resveratrol dimer, showed anti-adipogenic effects by downregulating PPARγ mRNA levels at 50 μM concentration (Ohara et al., 2015).

Additionally, the combination of stilbenes with other polyphenols may present synergistic or additional effects. Some studies proved that the combination of resveratrol with genistein, quercetin or epigallocatechin gallate enhanced the resveratrol efficiency by inhibiting adipogenesis and decreasing the lipid accumulation and TG content in 3T3-L1 and human primary adipocytes cells (**Table 4**). More specifically, the treatment with these compounds (30 μM) decreased the protein expression of PPARγ, C/EBPα, FABP4 and perilipin (Ahmed et al., 2017). Additionally, an increase of the apoptotic process has also been observed in early- and mid-phase maturing and lipid-filled mature human primary adypocites after resveratrol, genistein and quercetin treatment (Park et al., 2008).

Lipogenesis process involves *de novo* fatty acid and TG synthesis from glucose metabolism products (Wang et al., 2004). In human body this pathway is active in liver and adipose tissue. Once glucose is incorporated into the cells, it undergoes a series of biochemical transformations (glycolysis) to produce acetyl-CoA. This last compound is transformed in malonyl CoA by acetyl-CoA carboxylase (ACC) which is a substrate for fatty acid synthase (FAS) to synthetize fatty acids. Two other enzymes, malic enzyme (ME) and glucose-6-phosphate dehydrogenase (G6PDH) supply NADPH to fatty acid synthesis reactions. SREBP-1c has also an important role as a transcription factor by regulating the expression of ACC and FAS (Vázquez-Vela et al., 2008).

In addition, at adipose tissue level, the fatty acids involved in triacylglycerol synthesis can be transported via triacylglycerol-rich lipoproteins (chylomicrons and low density lipoproteins (LDL)). The enzyme lipoprotein lipase (LPL), which is located in the luminal surface of

endothelial cells, hydrolyses lipoprotein triacylglycerols into two free fatty acids and one monoacylglycerol. In this case, PPARγ is the transcriptional factor that controls the expression of this enzyme. AMPK plays again an important role because its phosphorylation is related with the decrease of fatty acid synthesis and the activation of ACC and also with the downregulation of SREBP-1c through the mammalian target of rapamycin (mTOR) and Liver X Receptor alfa (LXRα) (Zhang et al., 2009).

Resveratrol showed anti-lipogenic effects at both hepatic and adipose levels (**Table 4**). Treatment with this bioactive compound at low doses down regulates, PPARγ, SREBP-1c, ACC, FAS gene expression in adipocyte cells (Chen et al., 2011; Liang et al., 2013). A similar effect has also been described for pterostilbene (5-10 μM) that is able to reduce the G6PDH activity in 3T3-L1 cells (Hsu et al., 2012). The ability of stilbenes to increase the phosphorylation of APMK and their capacity to bond to the ketoacyl reductase (KR) domain of FAS are two mechanisms implicated in the anti-lipogenic effects of these bioactives (Chen et al., 2011; Li et al., 2016; Liang et al., 2013).

Alternatively, by using different hepatocytes cell lines, resveratrol and oxyresveratrol are able to decrease the hepatic lipogenesis by suppression of SREBP-1, FAS, ACC and stearoyl- CoA desaturase-1 (SCD-1) (Gnoni and Paglialonga, 2009; Jin et al., 2013; Choi et al., 2014; Lee et al., 2018). This last protein is a rate-limiting enzyme that catalyzes the synthesis of monounsaturated fatty acids and it is essential for the assembly of VLDL particles, which transport triacylglycerol (TG) from liver to adipose tissue and other sites (Li et al., 2009). AMPK activation and the inhibition of LRXα which activate the SREBP-1 have been the molecular pathways related (Jin et al., 2013; Choi et al., 2014; Lee et al., 2018).

Lipolysis and β-oxidation occur when the body requires energy. In adipocytes the TG are metabolized giving rise to glycerol and fatty acids by the catabolic action of adipose

549 triglyceride lipase (ATGL) and hormone-sensitive lipase (HSL). HSL activation depends on
550 protein kinase A (PKA) phosphorylation, which is mediated via the accumulation of cAMP
551 (Duncan et al., 2007). With regard to the lipolytic effects of stilbenes, resveratrol was the
552 main compound studied. Some published articles proved that resveratrol, at different doses
553 (0.03-400 μM), is able to enhance the free fatty acid and the glycerol release by increasing
554 HSL and ATGL expression in some cellular models (bovine intramuscular adipocytes, 3T3-
555 L1 and SGBS adipocytes) (Rayalam et al., 2007; Chang et al., 2016; Lee et al., 2018).
556 Interestingly, resveratrol had also synergistic action with genistein, CLA and epinephrine
557 enhancing its lipolytic capacity (Rayalam et al., 2007; Szkudelska et al., 2009; Lasa et al.,
558 2011).

559 An increment of β-oxidation capacity in adipocyte cells was demonstrated by resveratrol and
560 oxyresveratrol. In fact, the upregulation of carnitine palmitoyltransferase 1 (CPT-1) which is
561 necessary for mitochondrial import of fatty acids and the repression of receptor interacting
562 protein 140 (rip 140), a suppressor of oxidative metabolism, was involved (Mercader et al.,
563 2011; Lee et al., 2018).

564 Finally, another important pathway related to fat metabolism is thermogenesis that is literally
565 defined as heat production. The white adipose tissue (WAT) and the brown adipose tissue
566 (BAT) are the main types of adipose tissues with antagonistic functions. WAT stores the
567 excess of energy in the form of TG and BAT is specialized in heat production. BAT is
568 specialized in dissipate energy thanks to the high number of mitochondria. Mitochondria
569 membranes contain high amounts of Uncoupling protein 1 (UCP-1), an inner membrane
570 protein that uncouples the electron transport chain from ATP synthesis resulting in energy
571 dissipation rather than ATP synthesis (Madden, 2017). Under certain conditions (e.g. extreme
572 low temperature or β-3 adrenergic agonist) the number of mitochondria increased drastically;

this process is named “browning” and the type of WAT is called “beige” (Bartelt and Heeren, 2014). Thus, an increase of BAT thermogenesis is considered nowadays as a potential strategy to reduce obesity.

Several recent *in vitro* studies have revealed that resveratrol (10 μM) can activate the “browning” process. In particular, an increase of UCP-1 expression in stromal vascular cells from interscapular WAT and BAT has been observed (Wang et al., 2015; Wang et al., 2017). Beyond this, these studies have also demonstrated an increase of expression of others transcriptional factors of brown adipogenic program as PR domain-containing 16 (PRDM16) that leads to the activation of mitochondrial biogenesis. This effect was related with AMPK signaling pathway activation. Other papers showed that resveratrol at 100 μM concentration up-regulated the gene expression of some mitochondrial activity regulators such as SIRT3 that influences the mitochondrial function by reducing membrane potential, mitofusin 2 (Mfn2) that participates in mitochondrial fusion in mammalian cells, and ATPase family AAA Domain-containing protein 3 (ATAD3), a protein that regulates mitochondrial biogenesis (Rayalam et al., 2008; Li et al., 2016).

To conclude, resveratrol but also others stilbenes and the combinations or these with other bioactive compounds have proved be able to counteract the adipogenic and the lipogenic (adipose and hepatic level) processes by reducing the gen and protein expression of several transcription factors, avoiding the adypocites differentiation/proliferation or promoting the apoptosis program with a direct implication of SIRT, AMPK and FOXO pathway. Additionally, these compounds can enhance not only the lipolysis and β-oxidation but also the thermogenesis and mitochondrial biogenesis although more studies are necessary to be able to claim the mechanism of action.

***Anti-obesity in vivo effects of stilbenes***

Regarding the *in vivo* effects and similarly with the *in vitro* studies the most examined stilbene molecule was resveratrol.

Several animal models were used to investigate the anti-obesity effects of stilbenes, mices (Swiss, C57BL/6J, FVB/N, CD1, kunming) and rats (Sprague-Dawley, Wistar, Zucker (*fa/fa*)) being the most commonly used. In addition, other animal models such as *Megalobrama amblycephala* (fish) or *Caenorhabditis elegans* were used. Experimentally, these species were treated with standard (SD), high fat (HFD), high protein (HPD), high fructose corn syrup (HFCSD) diets supplemented with stilbenes (between 1 to 300 mg/kg/day) during different periods of time varying from some hours to 20 weeks (**Table 5**). This large numbers of conditions (animal model, dose, diet and period of treatment) makes sometimes difficult the understanding of results found by these studies. Nevertheless, several studies showed that resveratrol is able to mitigate the body weight gain in different animal models. In some instances, even a 50% reduction was described (Choi et al., 2014; Jeon et al., 2014; Majumdar et al., 2014; Qiao et al., 2014; Mendes et al., 2016).

In addition to weight reduction, an attenuation of lipid deposition on internal adipose tissues such as epididymal and intraperitoneal tissues was observed after resveratrol treatment (Gómez-Zorita et al., 2013; Jeon et al., 2014; De Almeida Pinheiro et al., 2017; Zhang et al., 2018). This fact was related to the capacity of resveratrol to control and reduce the adipogenesis process. Particularly, resveratrol (0.4%) reversed the HFD-induced up-regulation of key adipogenic genes such as PPARγ, C/EBPα, SREBP-1c, FAS, LPL, aP2, and leptin in mice adipose tissues (Kim et al., 2011). The results reported by Kim et al. highlighted that galanin-mediated signaling molecules are also implicated on the anti-adipogenesis effects of resveratrol. Galanin is a neuropeptide that plays a role in food intake

620 and its circulating serum levels are elevated in obese individuals (Kim and Park, 2010).
621 Resveratrol has demonstrated its capacity to significantly reverse the HFD-induced up-
622 regulation of galanin and its receptors along with increased expression and/or activation of
623 downstream molecules related to adipogenesis, such as Protein Kinase C Delta (PKCd),
624 cyclin D (Cyc-D), transcriptional factor E2F1, and Extracellular Receptor Kinase (ERK)
625 (Kim et al., 2011).

626 There is evidence that microbiota has an important role in obesity. In fact, the presence of
627 certain bacteria and overall, the relative proportions and composition of microbial
628 communities is key for energy homeostasis (Tennyson and Friedman, 2008). Although this
629 research line is recent and remains not fully explored, some studies were published indicating
630 that in obese people exposed to low calorie diet, *Bacteriodetes* level increased while
631 *Firmicutes* levels decreased (Ley et al., 2006). In addition, it seems that gut microbiota can
632 abolish the expression of fasting-induced adipose factor (Fiaf) that belongs to the family of
633 fibrinogen/angiopoietin-like proteins. When Fiaf was suppressed an increase of LPL and a
634 higher deposition of TG in adipose tissues have been observed (Bäckhed et al., 2004). For this
635 reason, the study of gut microbiota in obesity research is gaining more and more relevance.

636 HFD was related with microbiota dysbiosis (promoting the growth of endotoxin producers)
637 producing a decrease of *Lactobacillus* and an increase of *Enterococcus faecalis*. In this
638 context it is worth mentioning that resveratrol long term (12 weeks) treatment in Kunming
639 mice's demonstrated that this stilbene increased the *Bacteriodetes* to *Firmicutes* ratio and
640 diminished the growth of *Enterococcus feacalis* (Qiao et al., 2014). Similarly, the numbers of
641 *Lactobacillus* and *Bifidobacterium* were significantly increased. At intestinal level, this work
642 showed that resveratrol increases the Fiaf expression which can be linked to the suppression
643 of LPL and SCD-1 expressions in the liver, and with the expression of adipogenesis/

644 lipogenesis genes (PPARγ, ACC1, and FAS) in adipose tissues (Qiao et al., 2014).

645 Likewise, some of the above-mentioned papers proved that resveratrol can also be able to
646 reduce lipogenesis process. A reduction of expression levels of FAS, ACC, SCD-1, and
647 G6PDH, and therefore, a suppression of fatty acid uptake and TG synthesis at adipose and
648 hepatic level has been observed (**Table 5**). Furthermore, resveratrol causes the increase of
649 GLUT2 mRNA expression allowing to restore the normal glucose fluxes induced by HFD
650 (Zhang et al., 2018). Another recent work showed for the first time that resveratrol modifies
651 the microRNA (miRNA) profile in WAT. Actually, the reduction of protein levels of FAS,
652 SREBP-1 and SP-1 (acts together with SREBP1 to synergistically activate the promoter of
653 FAS) has been linked to the up-regulation of miR-539-5p (Gracia et al., 2016).

654 An inhibition of adipogenesis by resveratrol at hepatic level has also been evidenced. Some
655 works have mentioned a decrease of mRNA expression of PPARγ, SREBP-1c and FAS after
656 resveratrol supplementation with HFD, HFSCD or atherogenic diets (Ahn et al., 2008; Shang
657 et al., 2008; Alberdi et al., 2013; Andrade et al., 2014; Sadi et al., 2015). Furthermore, this
658 action is mediated by the activation of AMPK/SIRT1 axis (Shang et al., 2008; Alberdi et al.,
659 2013). Indeed, Shang et al. showed an increase of 164% of AMPK phosphorylation level in
660 liver after the oral administration of resveratrol (100 mg/Kg/day) during 10 weeks (Shang et
661 al., 2008). Furthermore, higher gene and protein expressions levels of a great number of
662 insulin-signaling molecules including IR, IRS-1/2, eNOS as well as SIRT1 have been outlined
663 after resveratrol supplementation (Sadi et al., 2015).

664 One of the key developments in obesity research is the recognition that this disorder is also
665 characterized by chronic mild inflammation. Indeed, an increase of circulating levels of
666 inflammatory markers in obese people such as CRP (C-reactive protein), tumor necrosis
667 factor alpha (TNF-α), interleukin (IL)-6 and IL-18, was described (Festa et al., 2001;

668 Monteiro and Azevedo, 2010). In this context, some papers indicated that a reduction of
669 inflammatory markers (TNF-α, interferon IFNα, IFNβ, IL-6, monocyte chemoattractant
670 protein 1 (MCP-1), and CRP) was observed in the adipose tissues of mice and rat after
671 resveratrol oral treatment, relating that with the repression of Toll-like receptor (TLR)2- and
672 TLR4-mediated pro-inflammatory signaling cascades (as Nuclear Factor Kappa B (NF-KB)
673 pathway) in the adipose tissues of mice and rat after resveratrol oral treatment (Kim et al.,
674 2011; Gómez-Zorita et al., 2013). This action was also observed at hepatic level and
675 evidenced by the reduction of TNF-α, IL-1β, IL-6 and NF-κB expression in liver in
676 association with the up-regulation of SIRT1 in mice treated with an HFD and resveratrol
677 (Andrade et al., 2014).

678 Additionally, resveratrol is able to improve fatty acid oxidation in liver and WAT.
679 Particularly, Enzyme activities involved in fatty acid oxidation as CPT-Ia, a marker of
680 mitochondrial oxidation, and acyl-coenzyme A oxidase (ACO), a marker of peroxisome
681 oxidation, were significantly increased by resveratrol in liver (Gómez-Zorita et al., 2012;
682 Alberdi et al., 2013). It was furthermore demonstrated by other authors that the increase of
683 expression levels of both CPT-1 and UCP-2 may exert a protective effect of resveratrol on
684 mitochondrial dysfunction not only by inhibition of fatty acid oxidation but also in association
685 with reactive oxygen species (ROS) generation (Khaleel et al., 2018). By using a fish animal
686 model (*M. amblycephala*), the supplementation with different doses of resveratrol (0.04, 0.36
687 and 1.08%) resulted in a significant reduction of ATGL, CPT-1 and the microsomal
688 triglyceride transfer protein (MTTP) implying up-regulation of lipolysis and β-oxidation
689 (Zhang et al., 2018). Finally, an augmentation of HSL, without affecting the ATGL levels,
690 was observed in Zucker (*fa/fa*) rats after oral supplementation of 15 mg/Kg/day of resveratrol
691 during 6 weeks (Gómez-Zorita et al., 2013).

Finally, a strengthening of "browning" and mitochondrial biogenesis has been observed by increasing protein contents of UCP1, PRDM16, and Cytochrome C along with an increase of AMPK in CD1 mice treated with 0.1% of resveratrol (Wang et al., 2015).

As for *in vitro* tests, the combination of resveratrol with other polyphenols, bioactives and drugs has been object of certain studies (**Table 5**). Two works published by the same research group have proved that the mixture of resveratrol (15 mg/Kg/day) and quercetin (30 mg/Kg/day) for a 6 weeks period of time decreases the weight of liver and all the fats depots. This effect has been related with the reduction of LPL activity and ACC and the increase of ATGL and CPT-1 (Arias et al., 2015; Arias et al., 2016). However, non-synergistic effects have been found when resveratrol is combined with conjugated linoleic acid (CLA) (Arias et al., 2014). Melatonin is a neurohormone related with the circadian rhythms but also a bioactive found ubiquously in several foods and also in wine (Hornedo-Ortega et al., 2016). The supplementation of melatonin (3 mg/kg/day) with resveratrol in ovariectomized rats reduced the body weight by 16% and body mass index (BMI) by 19%. Moreover, this combination is able to reduce the insulin resistance and macrophage infiltration in liver (Majumdar et al., 2014).

With regard to other stilbenes, some *in vivo* studies pointed out that piceatannol, pterostilbene and oxyresveratrol are interesting molecules to combat obesity (**Table 5**). Starting with the first one and by utilizing *C. elegans* as *in vivo* model, authors demonstrated that this compound reduced the fat accumulation induced by high glucose conditions; an attenuation of SBP-1 (encode SREBP-1c) and FAS and a reduction on HOSL-1 expression (encodes HSL) prove that piceatannol can prevent the lipid synthesis and stimulate the lipolysis (Shen et al., 2017). Furthermore, Tung et al. showed that piceatannol (0.1 and 0.25%; 18 weeks) can decrease the C/EBPα, PPARγ, FAS and CPT-1 and consequently promote the mitochondrial

716 FA, oxidation and lipid accumulation in adipocytes and liver. As was displayed for
717 resveratrol, this compound can also alter the composition of gut microbiota specifically by
718 increasing of *Firmicutes*/*Lactobacillus* and decreasing *Bacteroidetes* (Tung et al., 2016).

719 Pterostilbene at low doses (15 and 30 mg/Kg/day) can interfere in *de nov*o lipogenesis at
720 adipose and hepatic level by reducing the activity of: ME, FAS, ACC, G6PDH, CPT-1, which
721 is in part explained by the increase of *p*-AMPK levels (Gómez-Zorita et al., 2014). This paper
722 highlighted that pterostilbene was more efficient than resveratrol at a dose of 15 mg/kg/day
723 while at 30 mg/kg/day both stilbenes had similar responses. This fact can be explained, by the
724 higher bioavailability of pterostilbene (Gómez-Zorita et al., 2014). Using the same doses of
725 pterostilbene, a thermogenic and oxidative capacity by increasing of brown adipose tissue
726 markers (UCP-1, CPT-1b, nuclear respiratory factor 1 (Nrf1), cyclooxygenase 2 (COX2)) was
727 observed (Aguirre et al., 2016).

728 Finally, an improvement of insulin resistance and hyperglycemia accompanied by the
729 reduction in body weight (up to 26%), liver weight (up to 28%), and visceral fat (up to 51%)
730 was observed for oxyresveratrol in C57BL/6 mouse experiments. The down regulation of
731 G6PDH expression was interpreted as the repression of free glucose production in liver. They
732 also observed an increase of GLUT4 and IRS1 that also plays a vital role in intracellular
733 glucose uptake (Tan et al., 2017).

734 In summary, there is seemingly compelling *in vivo* evidence that demonstrate that overall
735 resveratrol but also other stilbenes possess anti-adipogenic and anti-lipogenic effects with
736 SIRT and AMPK as implicated molecular pathways. In addition, a significant reduction on
737 body and adipose tissue weight, accompanied with a reduction of cholesterol, TG and glucose
738 blood levels has been confirmed. The enhancement of the browning process or mitochondrial
739 biogenesis and the possible control of the microbiota dysbiosis displayed by resveratrol is

740 gaining attention as promising molecular approaches to combat obesity even though more
741 studies are still necessary.

742 An important concern that should be taken in account after examined the *in vivo* animal anti-
743 obesity effects of resveratrol and other stilbenes is the quantity that should be consumed to
744 reach the bioactivity. In fact and although wine and grapes are the richest sources of stilbenes
745 in diet, the required quantities cannot be reached with a normal diet. If we take into account
746 only the consumption of red grapes and wine (resveratrol mean of 0.67 mg/kg and 1.41 mg/L,
747 respectively) more than one hundred kg of red grapes or more than fifty liters of wine per day
748 should be consumed. It should not be forgotten that the high consumption of grapes and wine
749 can be exacerbates the obesity and the related disorders due to the high content of sugar or
750 ethanol. Consequently, it is therefore essential to turn to food supplements in order to achieve
751 these concentrations. One of the objectives of this review has been to examine the literature
752 about the anti-obesity effects of resveratrol in combination with other polyphenols, nutrients
753 or other bioactives. Several of these such as quercetin, CLA or melatonin are ubiquitously
754 present in food and consequently, the potential effects of resveratrol and other stilbenes can
755 be improved. Moreover, this experimental approach represents undoubtedly a more realistic
756 situation.

757 Even if it is not one of the goals of this work it can be mentioned that until recently there was
758 a considerable controversy about the effects of resveratrol as anti-obesity agent proved by
759 human intervention studies because the majority of these studies had not noted any effect of
760 resveratrol concerning body weight or body composition. Multiple reasons might explain the
761 lack of link between animal and human studies. For example, in human studies participants
762 consume generally their usual diet and not a high-fat or high-calorie diet in contrast to the
763 animal studies. Concerning doses, in human trials a relatively low dose of resveratrol (75-

764 3000 mg/day) have been used, however at these doses in animals no effect is observed.
765 Another fact that should not be overlooked is that the digestion, metabolism or absorption
766 differs between humans and animals. Furthermore, the duration of the resveratrol
767 supplementation could also have been too short in the human intervention studies in
768 comparison with animal studies. However, two recent systematic reviews and meta-analysis
769 has concluded by using random-effects model that resveratrol supplementation significantly
770 decrease body weight, body mass index, fat mass and waist circumference in trials using
771 resveratrol at the dosage under 500 mg/day, those with long-term interventions (≥ 3 month),
772 and performed on people with obesity (Akbari et al., 2020; Mousavi et al., 2019).

773 **Challenges and future trends**

774 Both, the analytical determination of grapes and wine monomeric/oligomeric stilbenes and,
775 the study on their biological activities represent nowadays a major challenge for the research
776 community. Consideration must be given concerning the deep matrix complexity of grapes
777 and wine, which makes the stilbene analysis more exigent. Thanks to the widespread
778 development on sample preparation, extraction techniques and detection instrumentation such
779 as mass spectrometry, more accurate stilbene identification is possible nowadays. However, it
780 should be kept in mind that a generalized problem is the lacks of commercial standards
781 (overall of oligomers) that force to express the results in terms of monomers (resveratrol or
782 piceid equivalent). This lack of precision could severally underestimate the oligomeric
783 stilbene content.

784 Regarding anti-obesity properties of grapes and wine stilbenes, a great number of *in vitro* and
785 *in vivo* studies have allowed to demonstrate the positive implications of these bioactives and
786 the underlying mechanisms of the observed effects. The understanding of these mechanisms is
787 an essential task since the scientists seeks the development of more specific dietary

recommendations to prevent or combat obesity. Apart from resveratrol, other stilbenes (pterostilbene, oxyresveratrol, viniferins and vitisins) and the combination of these bioactives with others polyphenols or drugs, are showing promising results. However, more studies are necessary to allow reliable conclusions. To finish, it is important to emphasize that a great number of published papers use in general high doses, and without reflecting important processes such as absorption and metabolism or even the role of gut microbiota. Furthermore, intervention studies are still necessary in order to prove these beneficial effects in humans.

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1346 **Figure legends**

1347 **Figure 1.** Biosynthesis of trans-resveratrol and its chemical diversification pathways.(Chong
1348 et al., 2009)

1349 **Figure 2.** Main stilbenes identified in grape berries and wines.

1350

**Table 1.** Stilbenes content in berries (in mg/kg fw) and wines (in mg/L) (mean, standard deviation, minimum and maximum, number of studies, and number of measures).

| Compounds | Content | SD | Min. | Max. | n | N | Ref. |
|---|---|---|---|---|---|---|---|
| **Berries** | | | | | | | |
| ***Monomers*** | | | | | | | |
| *trans*-resveratrol | 0.67 | 0.97 | 0.00 | 3.56 | 12 | 84 | (Brillante et al., 2018; Rosso et al., 2016; Flamini et al., 2016; Fernández-Marín et al., 2013; Flamini et al., 2013; Vincenzi et al., 2013; Vrhovsek et al., 2012 ; Viñas et al., 2011; Guerrero et al., 2010; Viñas et al., 2009; Kolouchová-Hanzlíková et al., 2004; Bavaresco et al., 2002) |
| *cis*-resveratrol | 0.01 | 0.07 | 0.00 | 0.40 | 5 | 38 | |
| *Total resveratrol* | 0.68 | | | | | | |
| piceatannol | 0.12 | 0.22 | 0.00 | 1.35 | 11 | 76 | |
| *trans*-piceid | 0.65 | 1.30 | 0.00 | 6.87 | 7 | 32 | |
| *cis*-piceid | 0.71 | 1.61 | 0.00 | 6.77 | 7 | 32 | |
| *Total piceid* | *1.36* | | | | | | |
| *trans*-astringin | 0.71 | 0.58 | 0.12 | 1.73 | 5 | 7 | |
| *cis*-astringin | 0.12 | 0.09 | 0.04 | 0.29 | 4 | 6 | |
| *Total astringin* | *0.83* | | | | | | |
| **Red wines** | | | | | | | |
| ***Monomers*** | | | | | | | |
| *trans*-resveratrol | 1.41 | 1,17 | 0.00 | 3.75 | 8 | 103 | (Guerrero et al., 2020; Arraki et al., 2017; Lukić et al., 2019; Viñas et al., 2009; Buiarelli et al., 2007; Rennaker, 2007; Careri et al., 2004; Kolouchová-Hanzlíková et al., 2004; Lee and Sato et al., 1997) |
| *cis*-resveratrol | 0.88 | 1.07 | 0.00 | 6.08 | 7 | 96 | |
| *Total resveratrol* | *2.29* | | | | | | |
| piceatannol | 0.68 | 0.94 | 0.00 | 5.22 | 3 | 35 | |
| *trans*-piceid | 2.06 | 2.19 | 0.00 | 9.31 | 6 | 82 | |
| *cis*-piceid | 6.20 | 8.09 | 0.00 | 38.47 | 6 | 75 | |
| *Total piceid* | *8.26* | | | | | | |
| *trans*-astringin | 0.52 | 0.61 | 0.00 | 3.00 | 3 | 32 | |
| *cis*-astringin | 0.13 | 0.32 | 0.00 | 1.59 | 2 | 28 | |
| *Total astringin* | *0.65* | | | | | | |
| ***Dimers*** | | | | | | | |
| *trans*-ε-viniferin | 0.06 | 0.21 | 0.00 | 0.81 | 2 | 15 | |
| *trans*-ω-viniferin | 0.03 | 0.10 | 0.00 | 0.30 | 1 | 10 | |
| ***Others*** | | | | | | | |
| miyabenol C | 0.14 | 0.45 | 0.00 | 1.41 | 1 | 10 | |
| hopeaphenol | 0.08 | 0.15 | 0.00 | 0.49 | 2 | 15 | |
| Isohopeaphenol | 1.39 | 1.80 | 0.00 | 7.47 | 3 | 19 | |
| R2-viniferin | 0.42 | 1.05 | 0.00 | 3.28 | 1 | 10 | |
| **White wines** | | | | | | | |
| ***Monomers*** | | | | | | | |
| *trans*-resveratrol | 0.08 | 0.20 | 0.00 | 1.16 | 6 | 55 | (Guerrero et al., 2020; Lukić et al., 2019; Arraki et al., 2017; Viñas et al., 2009; Buiarelli et al., 2007; Lee and Rennaker, 2007; Sato et al., 1997) |
| *cis*-resveratrol | 0.04 | 0.13 | 0.00 | 0.76 | 5 | 55 | |
| ***Total resveratrol*** | *0.12* | | | | | | |
| piceatannol | 0.04 | 0.16 | 0.00 | 0.59 | 3 | 14 | |
| *trans*-piceid | 0.20 | 0.39 | 0.00 | 1.91 | 6 | 61 | |
| *cis*-piceid | 0.68 | 2.23 | 0.00 | 16.26 | 6 | 61 | |
| ***Total piceid*** | *0.88* | | | | | | |
| *trans*-astringin | 0.05 | 0.16 | 0.00 | 0.72 | 3 | 20 | |
| *cis*-astringin | 0.11 | 0.35 | 0.00 | 1.32 | 2 | 14 | |
| ***Total astringin*** | *0.16* | | | | | | |

**Table 2.** Fragmentation patterns and tentative assignments of stilbenes in red wines (Moss et al., 2013).

| Compounds | RT (Min) | Formula | Calculated | Experimental | Mass error (ppm) | CE (eV) | MS/MS product ions |
|---|---|---|---|---|---|---|---|
| *trans*-resveratrol | 20.005 | $C_{14}H_{11}O_3$ | 227.0714 | 227.0725 | 4.84 | 22.5 | 185; 143 |
| *cis*-resveratrol | 21.96 | $C_{14}H_{11}O_3$ | 227.0714 | 227.0717 | 1.32 | 22.5 | 185; 143 |
| piceatannol | 14.242 | $C_{14}H_{11}O_4$ | 243.0663 | 243.0659 | -1.65 | 25 | 201; 159 |
| *trans*-piceid | 11.185 | $C_{20}H_{21}O_8$ | 389.1242 | 389.1235 | -1.8 | 20 | 227 |
| *cis*-piceid | 13.561 | $C_{20}H_{21}O_8$ | 389.1242 | 389.1263 | 5.4 | 20 | 227 |
| astringin | 8.209 | $C_{20}H_{21}O_9$ | 405.1191 | 405.1206 | 3.7 | 15 | 243; 201; 159 |
| pallidol | 21.459 | $C_{28}H_{21}O_6$ | 453.1344 | 453.1347 | 0.66 | 20 | 359; 265 |
| parthenocissin A | 23.959 | $C_8H_{21}O_6$ | 453.1344 | 453.1344 | -4.19 | 20 | 359; 289 |
| ampelopsin D | 26.765 | $C_{28}H_{21}O_6$ | 453.1344 | 453.1363 | 4.19 | 20 | 359; 289 |
| *cis*-ε-viniferin | 31.448 | $C_{28}H_{21}O_6$ | 453.1344 | 453.1345 | 0.22 | 20 | 435; 411; 369; 359; 347; 333; 225 |
| *trans*-ε-viniferin | 33.833 | $C_{28}H_{21}O_6$ | 453.1344 | 453.1376 | 7.06 | 20 | 435; 411; 369; 359; 347; 333; 225 |
| *cis*-ω-viniferin | 32.202 | $C_{28}H_{21}O_6$ | 453.1332 | 453.1344 | -2.65 | 20 | 435; 411; 369; 359; 347; 333; 225 |
| *trans*-ω-viniferin | 34.34 | $C_{28}H_{21}O_6$ | 453.1344 | 453.1357 | 2.87 | 20 | 435; 411; 369; 359; 347; 333; 225 |
| *cis*-δ-viniferin | 39.705 | $C_{28}H_{21}O_6$ | 453.1344 | 453.1329 | -3.31 | 25 | 453; 411; 369; 359; 333 |
| *trans*-δ-viniferin | 38.789 | $C_{28}H_{21}O_6$ | 453.1344 | 453.1356 | 1.77 | 25 | 435; 411; 369; 359; 333 |
| *trans*-scirpusin A | 27.93 | $C_{28}H_{21}O_7$ | 469.1293 | 469.1307 | 2.98 | 25 | 451; 427; 385; 375; 359; 347; 333; 241 |
| restrisol A | 11.303 | $C_{28}H_{23}O_7$ | 471.1449 | 471.1447 | -0.42 | | 377; 349; 255; 121 |
| parthenostilbenin A | 19.64 | $C_{29}H_{25}O_7$ | 485.1606 | 485.1635 | 5.98 | 15 | 453; 391; 359; 289; 255; 187 |
| parthonostilbenin B | 21.088 | $C_{29}H_{25}O_7$ | 485.1606 | 485.1594 | -2.47 | 15 | 453; 391; 359; 289; 255; 187 |
| ε-viniferin glucoside | 25.202 | $C_{34}H_{31}O_{11}$ | 615.1872 | 615.1878 | 0.98 | 20 | 453; 411; 359; 347 |
| ampelopsin C | 30.044 | $C_{42}H_{32}O_9$ | 679.1974 | 679.1981 | 1.03 | 30 | 585; 573; 491; 479; 385 |
| *trans*-miyabenol C | 35.372 | $C_{42}H_{32}O_9$ | 679.1974 | 679.1978 | 0.59 | 30 | 661; 637; 585; 573; 555; 451; 479; 357; 345 |
| *cis*-miyabenol C | 36.322 | $C_{42}H_{32}O_9$ | 679.1974 | 679.1984 | 1.47 | 30 | 661; 637; 585; 573; 555; 479; 451; 357; 345 |
| hopeaphenol | 31.695 | $C_{56}H_{41}O_{12}$ | 905.2604 | 905.2573 | -3.42 | 35 | 811; 717; 611; 451; 359; 265 |

**Table 3.** Information on liquid chromatography methods for the identification and quantification of stilbenes in grape berries and wines.

| Compounds | Sample preparation | Analytical methods | LOD | LOQ | References |
|---|---|---|---|---|---|
| **1,2** | **Wine:** direct injection<br>**Grape skin:** extraction ethanol (80%)<br>**Standard used:** *trans*- and *cis*- resveratrol | HPLC- UV | 3-15 µg/L | - | (Kolouchová-Hanzlíková et al., 2004) |
| **1, 7, 9, 15, 24** | **Wine:** extraction ethyl acetate<br>**Grape berries:** water/acetonitrile (1:1, v/v)<br>**Standard used:** pure compounds | HPLC-UV | wine: 5-8 ng | - | (Landrault et al., 2002) |
| **1, 7, 8** | **Grape skin:** extraction with various solvent<br>**Standard used:** pure compounds | UPLC-MS/MS (identification)<br>HPLC-DAD (quantification) | - | - | (Sun et al., 2006) |
| **1** | **Wine:** direct injection<br>**Grape skin and pomace:** extraction methanol/ethanol (4:1, v/v)<br>**Standard used:** *trans*-resveratrol | HPLC-UV<br>HPLC-ESI-MS/MS | 10 µg/L | 16 µg/L | (Careri et al., 2004) |
| **1, 3, 15, 20** | **Grape skin:** extraction methanol<br>**Standard used:** *trans*-resveratrol | UPLC-MS/MS (identification)<br>HPLC-DAD (quantification) | 0.01 mg/kg | 0.04 mg/kg | (Guerrero et al., 2010) |
| **1, 2, 9, 14, 15, 16, 17, 24, 27, 28, 29, 31** | **Wine:** direct injection<br>**Grape berries:** extraction water/methanol/chloroform (1:2:2, v/v/v)<br>**Standard used:** pure compounds | UPLC-QqQ-MS/MS | - | 8-400 pg | (Vrhovsek et al., 2012) |
| **1, 2, 3, 7, 8, 9, 10, 12, 15, 17, 28, 30, 31, 32, 33** | **Wine:** direct injection<br>**Standard used:** pure compounds | UPLC-QqQ-MS/MS | 5-28 µg/L | 12-84 µg/L | (Guerrero et al., 2020) |
| **1, 3, 7, 9** | **Wine:** solid-phase extraction (SPE) protocol<br>**Standard used:** *trans*-resveratrol, *trans*-piceid, *trans*-piceatannol | UPLC-QTOF-MS/MS (identification)<br>UPLC-QqQ-MS/MS (quantification) | 48-50 µg/L | 160-167 µg/L | (Buiarelli et al., 2007) |
| **1, 3, 7, 8, 9, 10, 11, 14, 15, 17, 19, 24, 27, 28, 29, 30, 31** | **Grape berries:** extraction methanol<br>**Standard used:** *trans*-resveratrol, *trans*-piceid. ε-viniferin | UPLC-QTOF-MS/MS | - | - | (Flamini et al., 2016; Rosso et al., 2016; Flamini et al., 2013) |
| **1, 2, 3, 7, 8, 9, 11, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 28, 29, 30, 31** | **Wine:** extraction diethyl ether | UPLC-QTOF-MS/MS | - | - | (Moss et al., 2013) |

**Table 4.** *In vitro* effects of resveratrol, other stilbenes and combination of stilbenes and other bioactives on adipogenesis, apoptosis, lipogenesis, lipolysis and thermogesis.;

| ADIPOGENESIS & APOPTOSIS | | | |
|---|---|---|---|
| **Effect/mechanism of action** | **Cell model** | **Doses** | **Reference** |
| **Resveratrol and metabolites** | | | |
| ↓ PPARγ,C/EBPα, CEBPβ, FAS, FGF10, leptin, LPL, BMP2, HSL | Bovine intramuscular adipocytes | 1-400 μM | (Liu et al., 2018; Eseberri et al., 2017; Chang et al., 2016; Hu et al., 2015; Zhang et al., 2012; Rayalam et al., 2008; Costa et al., 2011) |
| ↑ adiponectin | | | (Costa et al., 2011) |
| ↓Preadipocyte proliferation and adipogenic differentiation<br>↓Cell cycle entry (↓AKT, MAPK, cyclin D1)<br>↓Clonal expansion (cyclin A2) | Human SGBS cells | | (Santos et al., 2014; Mitterberger and Zwerschke, 2013; Kwon et al., 2012b; Fischer-Posovszky et al., 2010) |
| ↑SIRT1, SIRT 2, AMPKα, FOXO1 | Human visceral adipocytes | | (Liu et al., 2018; Santos et al., 2014; Costa et al., 2011; Fischer-Posovszky et al., 2010) |
| ↑ apoptosis (↑ Caspase-3, Bax) | 3T3-L1 cells | | (Liu et al., 2018; Rayalam et al., 2008) |
| ↓IR activity | | | (Kwon et al., 2012b) |
| ↓IL-6, IL-8 | | | (Fischer-Posovszky et al., 2010) |
| **Other stilbenes: Pterostilbene, R-viniferin, R2-viniferin, ε-viniferin** | | | |
| ↓PPARγ, C/EBPα, FABP4, aP2, CHOP10, leptin, resistin, FAS | 3T3-L1 cells | 6-50 μM | (Tie et al., 2018; Seo et al., 2017; Ohara et al., 2015; Hsu et al., 2012; Kim et al., 2008) |
| ↑ adiponectin | | | (Hsu et al., 2012) |
| ↓Preadipocyte proliferation and adipogenic differentiation<br>↓Cell cycle entry at the G1-S and G2/M phase | | | (Tie et al., 2018; Hsu et al., 2012; Kim et al., 2008) |
| ↑ HO-1 | | | (Seo et al., 2017) |
| **Combination resveratrol with other polyphenols and bioactives ( quercetin, genistein, CLA, EGCG)** | | | |
| ↓ PPARγ, C/EBPα, FABP4, perilipin | Primary human adipocytes (HAs)<br>3T3-L1 cells | 10-50 μM | (Yang et al., 2008; Rayalam et al., 2007) |
| ↑ apoptosis | | | (Park et al., 2008) |
| ↓Preadipocyte proliferation and adipogenic differentiation | | | (Ahmed et al., 2017; Lasa et al., 2011) |
| ↓ERK ½, ↑JNK phosphorylation | | | (Yang et al., 2008; Rayalam et al., 2007) |

| LIPOGENESIS (adipose and hepatic) | | | |
|---|---|---|---|
| **Effect/mechanism of action** | **Cell model** | **Doses** | **Reference** |
| **Resveratrol** | | | |
| ↓Lipogenesis (adipose and hepatic) | Human SGBS cells | 1-100 μM | (Li et al., 2016; Choi et al., 2014; Liang et al., 2013; Chen et al., 2011; Mercader et al., 2011; Szkudelska et al., 2009; Jin et al., 2013; Gnoni and Paglialonga, 2009) |
| ↓ACC ↓ FAS | 3T3-L1 cells | | (Li et al., 2016; Choi et al., 2014; Liang et al., 2013; Gnoni and Paglialonga, 2009) |
| ↓SREBP-1c, PPARγ, SCD-1 | H4IIEC3 cells | | (Choi et al., 2014; Chen et al., 2011; Mercader et al., 2011; Jin et al., 2013) |
| ↓ LXR-α | HepG2 cells | | (Jin et al., 2013) |
| ↓AMPK | | | (Chen et al., 2011) |
| **Pterostilbene** | | | |
| ↓Lipogenesis (adipose) | | | |
| ↓ PPARγ, FAS | 3T3-L1 cells | 5-10 μM | (Hsu et al., 2012) |
| ↓GPDH | | | |
| **Oxyresveratrol** | | | |
| ↓Lipogenesis (hepatic) | HepG2 cells | 30 μM | (Lee et al., 2018) |
| ↓SREBP-1c, PPARγ, SCD-1 | | | |
| ↓ LXR-α | | | |

| LIPOLYSIS | | | |
|---|---|---|---|
| **Effect/mechanism of action** | **Cell model** | **Doses** | **Reference** |
| **Resveratrol** | | | |
| ↓ PPARγ | Bovine intramuscular adipocytes | 0.03-400 μM | (Liu et al., 2018; Chang et al., 2016) |
| ↑HSL, ATGL | | | (Liu et al., 2018; Lasa et al., 2012) |
| ↓TG content | 3T3-L1 cells | | (Rosenow et al., 2012) |
| ↑Glycerol release | Rat adipocytes (epididymal tissue) | | ( Gomez-Zorita et al., 2017; Chang et al., 2016; Rosenow et al., 2012; Szkudelska et al., 2009) |
| ↑ β-oxidation | | | (Mercader et al., 2011) |
| ↑ CPT-1 | 3T3-F442A cells | | |
| ↓TNFα-induced lipolysis | Human SGBS cells<br>3T3-F442A cells | | (Chang et al., 2016) |
| **Resveratrol + CLA or + genistein** | | | |
| ↓ PPARγ<br>↑HSL, ATGL<br>↓TG content<br>↑Glycerol release | 3T3-L1 cells | 10-25 μM | (Lasa et al., 2011; Rayalam et al., 2007) |
| **Pterostilbene** | | | |
| ↑Glycerol release | 3T3-F442A cells | 100 nM-10 μM | (Gomez-Zorita et al., 2017) |
| **Oxyresveratrol** | | | |
| ↑ β-oxidation<br>↑ CPT-1 | HepG2 cells | 30 μM | (Lee et al., 2018) |
| **THERMOGENESIS/MITOCONDRIAL BIOGENESIS** | | | |
| **Effect/mechanism of action** | **Cell model** | **Doses** | **Reference** |
| **Resveratrol** | | | |
| ↑ PRDM16 | 3T3-L1 cells | 10-200 μM | (Wang et al., 2017; Wang et al., 2015) |
| ↑ UCP-1 | Adipocytes derived from primary mouse embryonic fibroblasts (MEF) | | (Wang et al., 2017; Wang et al., 2015; Santos et al., 2014; Mercader et al., 2011; Rayalam et al., 2008) |
| ↑ ATAD3 | | | (Li et al., 2016) |
| ↑ SIRT3 | | | (Rayalam et al., 2008) |
| ↑ Mfn2 | Human SGBS cells | | (Rayalam et al., 2008) |
| ↑AMPKα | Vascular cells isolated from iBAT | | (Wang et al., 2017; Wang et al., 2015) |

**Table 5.** *In vivo* effects of resveratrol, other stilbenes and combination of stilbenes and other bioactives on adipogenesis, apoptosis, lipogenesis, lipolysis and thermogesis.

| Stilbene and dose | Diet/Model | Doses/Duration | Reference |
|---|---|---|---|
| **Resveratrol** | | | |
| ↓Adipogenesis<br>↓PPARγ, C/EBPα, SREBP-1c, ACC, FAS, leptin<br>↑ SIRT1<br>↓ Galanin-mediated signaling molecules: GalR1/2, PKCd, Cyc-D, E2F1, p-ERK | HFD, HPD<br>FVB/N mice<br>Kunming mice<br>C57BL/6J mice<br>Wistar rats | 30-300 mg/Kg/day<br>6-12 weeks | (Mendes et al., 2016; Qiao et al., 2014; Andrade et al., 2014; Alberdi et al., 2013; Kim et al., 2011) |
| ↓Lipogenesis (adipose or hepatic)<br>↓ACC, FAS, ME, G6PDH<br>↓PPARγ, SREBP-1c<br>↑ SIRT1, eNOS<br>↑ AMPK | SD, HFD, HFCSD, atherogenic diet<br>Blunt snout bream (*Megalobrama amblycephala*)<br>Swiss mice<br>FVB/N mice<br>Kunming mice<br>C57BL/6J mice<br>ICR mice<br>Apo-E deficient mice<br>SAMP10 mice<br>Wistar rats<br>Sprague-Dawley rats | 15-300 mg/Kg/day<br>2 days-20 weeks | (Zhang et al., 2018; Khaleel et al., 2018; De Almeida Pinheiro et al., 2017; Mendes et al., 2016; Gracia et al., 2016; Sun et al., 2015; Sadi et al., 2015; Choi et al., 2014; Andrade et al., 2014; Qiao et al., 2014; Jeon et al., 2014; Alberdi et al., 2013; Gómez-Zorita et al., 2013; Kim et al., 2011; Ahn et al., 2008; Shang et al., 2008; Shiozaki et al., 2011) |
| ↓ Body weight, BMI<br>↓ Body adiposity and weight adipose tissue<br>↓ Iwat index (iwat mass/body weight)<br>↓ Adipocyte diameter | SD, HFD, HFCSD<br>Blunt snout bream (*Megalobrama amblycephala*)<br>Swiss mice<br>FVB/N mice<br>C57BL/6J mice<br>Kunming mice<br>CD1 mice<br>Apo-E deficient mice<br>Wistar rats<br>Zucker (*falfa*) rat | 0.0125-0.4%<br>1-300 mg/Kg/day<br>4-12 weeks | (Zhang et al., 2018; De Almeida Pinheiro et al., 2017; Mendes et al., 2016; Chang et al., 2016; Sun et al., 2015; Sadi et al., 2015; Wang et al., 2015; Andrade et al., 2014; Majumdar et al., 2014; Jeon et al., 2014; Qiao et al., 2014; Kim et al., 2011; Ahn et al., 2008)<br>(Gómez-Zorita et al., 2013) |
| ↓Total cholesterol<br>↓TG, LDL<br>↑HDL-cholesterol<br>↓TG | HFD, HPD, HFCSD, atherogenic diet<br>Blunt snout bream (*Megalobrama amblycephala*)<br>FVB/N mice<br>Apo-E deficient mice<br>C57BL/6J mice<br>ICR mice<br>CD1 mice | 0.0125-1.08 %<br>15-300 mg/Kg/day<br>2 days-12 weeks | (Zhang et al., 2018; Mendes et al., 2016; Wang et al., 2015; Andrade et al., 2014; Majumdar et al., 2014; Qiao et al., 2014; Jeon et al., 2014; Choi et al., 2014; Kim et al., 2011; Ahn et al., 2008) |

| | | | |
|---|---|---|---|
| | Sprague-Dawley rats | | |
| ↑Insulin sensitivity<br>↓Insulin plasma level<br>↓Blood glucose<br>↑Glucose transporter 2 | SD, HFD<br>Blunt snout bream (*Megalobrama amblycephala*)<br>Swiss mice<br>Kunming mice<br>Wistar rats | 0.04-1.08 %<br>20-200 mg/Kg/day<br>1-12 weeks | (Khaleel et al., 2018; Zhang et al., 2018; De Almeida Pinheiro et al., 2017; Andrade et al., 2014; Qiao et al., 2014; Shang et al., 2008) |
| ↓ Lipolysis<br>↑ HSL, ATGL<br>↑ Beta-oxidation<br>↑ CPT-1, MTTP, UCP-1, UCP-2, ACO | SD, HFD<br>Blunt snout bream (*Megalobrama amblycephala*)<br>CD1 mice<br>SAMP10 mice<br>Wistar rats<br>Sprague-Dawley rats | 0.04-1.08 %<br>20-30 mg/Kg/day<br>4-10 weeks | (Zhang et al., 2018; Khaleel et al., 2018; Wang et al., 2015; Alberdi et al., 2013; Shiozaki et al., 2011) |
| ↑Browning<br>↑Mitochondrial biogenesis<br>↑UCP-1, PRDM16, Cytochorme C<br>↑AMPKα | HFD<br>CD1 mice | 0.01 %<br>4 weeks | (Wang et al., 2015) |
| ↓ Inflammation<br>↓TNF-α, IL-6, IFNα, IFNβ, NF-kB, MCP-1, CRP<br>↓ Macrophage infiltration | SD, HFD<br>FVB/N mice<br>C57BL/6J mice<br>Zucker (*fa/fa*) rat<br>Sprague-Dawley rats | 0.04-1.08 %<br>20-30 mg/Kg/day<br>6-20 weeks | (Andrade et al., 2014; Majumdar et al., 2014; Gómez-Zorita et al., 2013; Kim et al., 2011) |
| Gut microbiota<br>↑Fiaf<br>↑*Bacteroidetes* to *Firmicutes* ratios<br>↓*Enterococcus faecalis*<br>↑*Bifidobacterium* , *Lactobacillus* | HFD<br>Kunming mice | 200 mg/Kg/day<br>12 weeks | (Qiao et al., 2014) |

*Continuation*

| Stilbene and dose | Diet/Model | Doses/Duration | Reference |
|---|---|---|---|
| **Combination resveratrol with other polyphenols and bioactives (quercetin, CLA, melatonin)** | | | |
| ↓ Body weight, BMI<br>↓ Weight adipose tissue<br>↓ Blood glucose<br>↓Adipogenesis (↓FAS, ACC)<br>↓Lipogenesis (↓FAS, ACC)<br>↓ Lipolysis (↑ HSL, ATGL)<br>↓Total cholesterol, TG | HFD, HFCSD<br>ICR mice<br>Wistar rats<br>Sprague-Dawley rats | Resveratrol: 15-50 mg/Kg/day<br>Others: 3-30 mg/Kg/day<br>10 days-12 weeks | (Arias et al., 2016; Zhao et al., 2016; Arias et al., 2014; Majumdar et al., 2014) |
| **Piceatannol** | | | |
| ↓ Body weight<br>↓Total cholesterol, LDL and HDL cholesterol<br>↓ Blood glucose<br>↑ AMPK<br>↑*Firmicutes*, *Lactobacillus*<br>↓*Bacteroidetes* | S, HG, HFD<br>*Caenorhabditis elegans*<br>C57BL/6 mice | 0.1 and 0.25%<br>50 and 100 μM<br>48 hours-18 weeks | (Shen et al., 2017; Tung et al., 2016) |
| **Pterostilbene** | | | |
| ↓ Lipolysis<br>↑ Beta-oxidation<br>↑ UCP-1<br>↓ Lipogenesis (hepatic)<br>↓ACC, FAS, ME, G6PDH<br>↑ AMPK | SD, HFD<br>Zucker (*falfa*) rats<br>OLETF rats<br>Wistar rats | 15 and 300 mg/kg/day<br>4-6 weeks | (Nagao et al., 2017; Aguirre et al., 2016; Gómez-Zorita et al., 2014) |
| **Oxyresveratrol** | | | |
| ↓ Body weight, BMI<br>↓ Insulin resistance<br>↓ C/EBPα, SREBP-1c,<br>↓ Fasting glucose<br>↓Total cholesterol, LDL cholesterol<br>↑ SIRT1<br>↑ AMPK | SD HFD<br>C57BL/6 mice | 0.25 and 0.5 %<br>10-30 mg/kg/day<br>4-8 weeks | (Lee et al., 2018; Tan et al., 2017) |

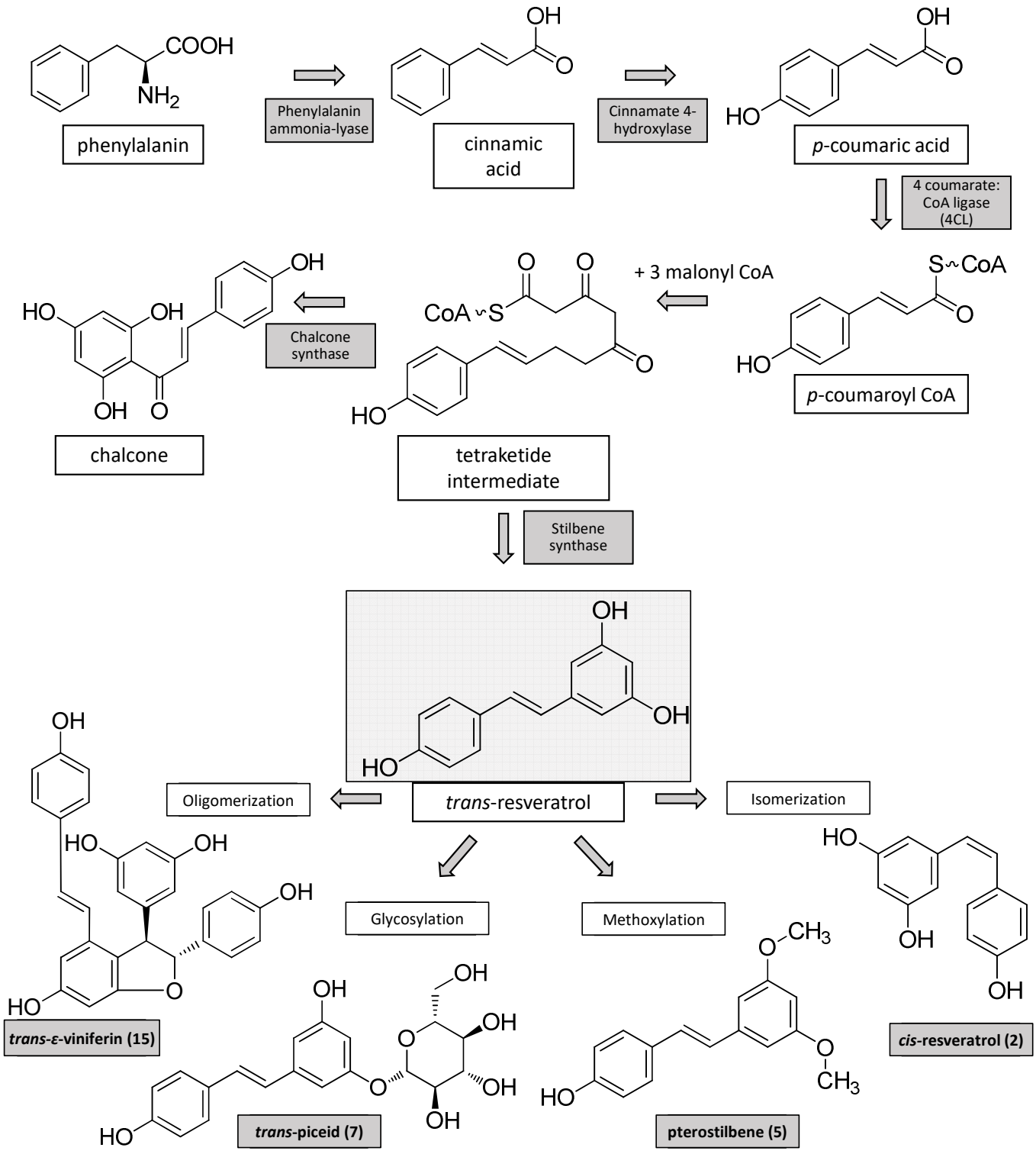
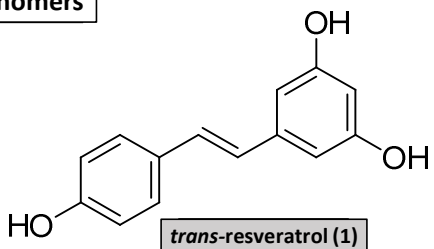
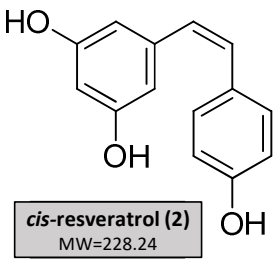

phenylalanin
Phenylalanin ammonia-lyase
cinnamic acid
Cinnamate 4-hydroxylase
p-coumaric acid
4 coumarate: CoA ligase (4CL)
p-coumaroyl CoA
+ 3 malonyl CoA
Chalcone synthase
chalcone
tetraketide intermediate
Stilbene synthase
trans-resveratrol
Oligomerization
Isomerization
Glycosylation
Methoxylation
trans-ε-viniferin (15)
trans-piceid (7)
pterostilbene (5)
cis-resveratrol (2)

**Figure 1.**

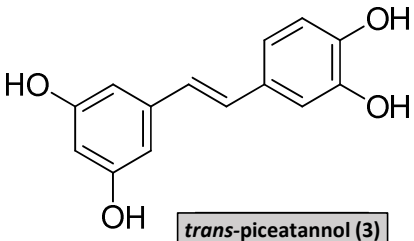
## Monomers



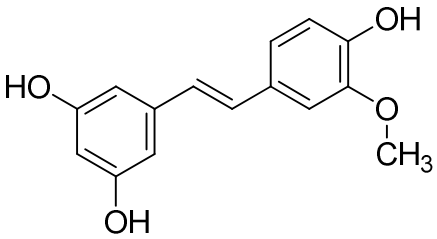
***trans*-resveratrol (1)**
MW=228.24



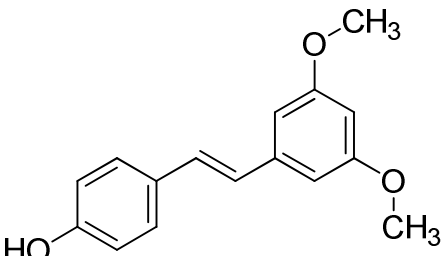
***cis*-resveratrol (2)**
MW=228.24



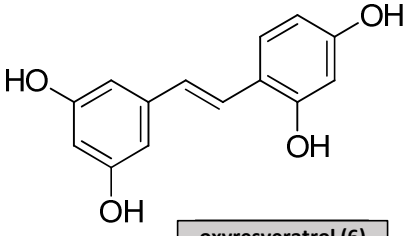
***trans*-piceatannol (3)**
MW=244.24



**isorhapontigenin (4)**
MW=258.27

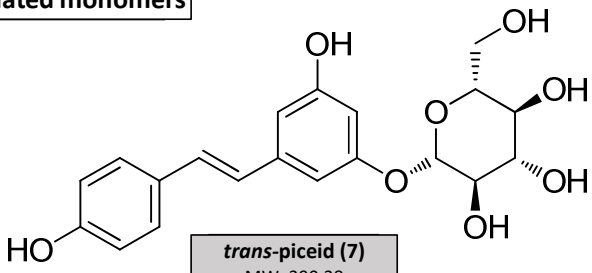


**pterostilbene (5)**
MW=256.30

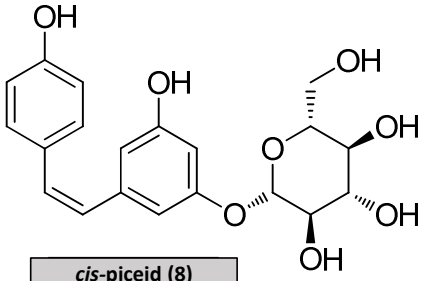


**oxyresveratrol (6)**
MW=256.30

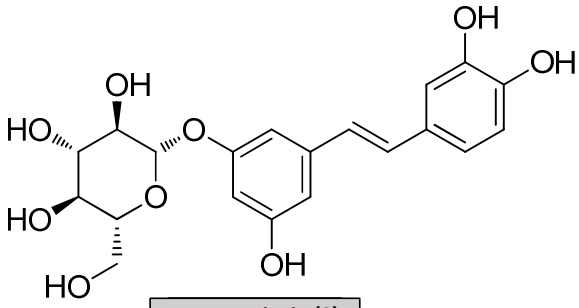
## Glycosylated monomers



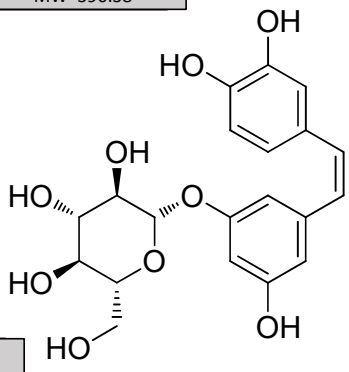
***trans*-piceid (7)**
MW=390.38



***cis*-piceid (8)**
MW=390.38

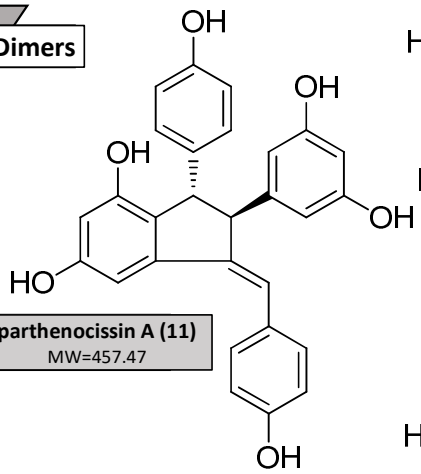


***trans*-astringin (9)**
MW=406.38

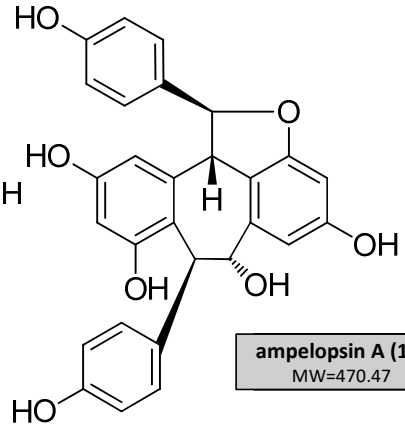


***cis*-astringin (10)**
MW=406.38

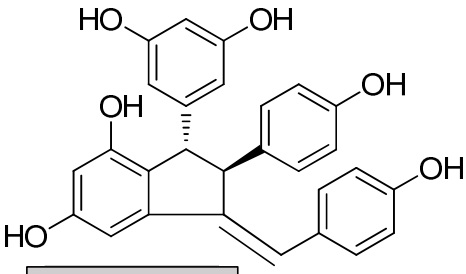
## Dimers



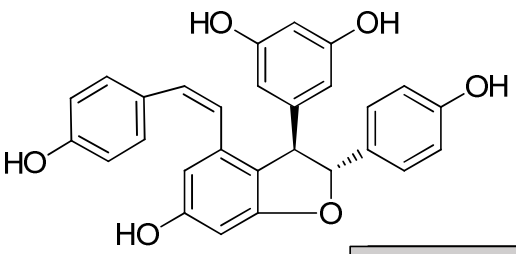
**parthenocissin A (11)**
MW=457.47



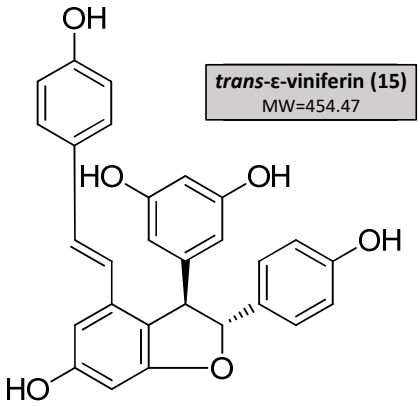
**ampelopsin A (12)**
MW=470.47



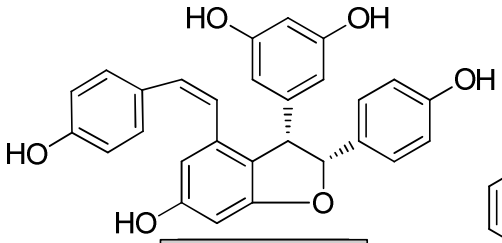
**ampelopsin D (13)**
MW=454.47



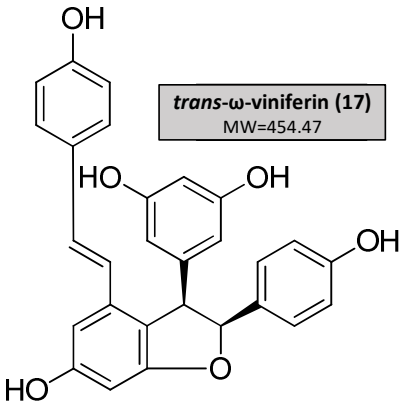
***cis*-ε-viniferin (14)**
MW=454.47



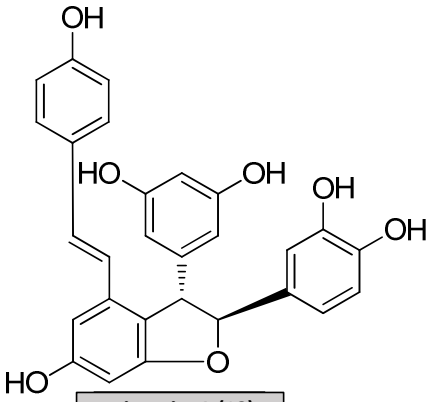
***trans*-ε-viniferin (15)**
MW=454.47



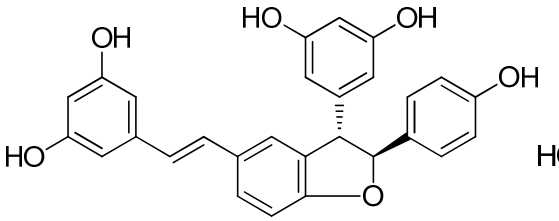
***cis*-ω-viniferin (16)**
MW=454.47



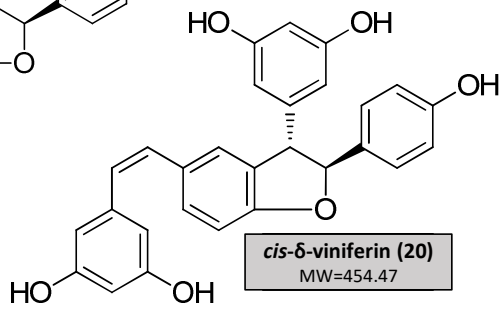
***trans*-ω-viniferin (17)**
MW=454.47



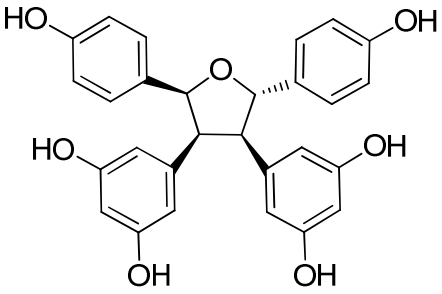
**scirpusin A (18)**
MW=470.47



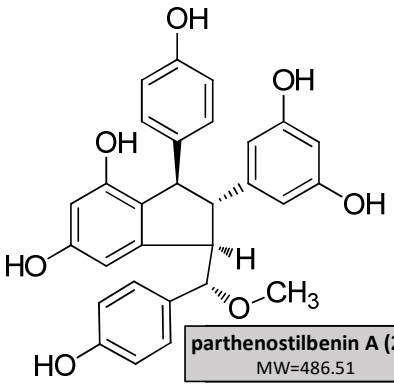
***trans*-δ-viniferin (19)**
MW=454.47



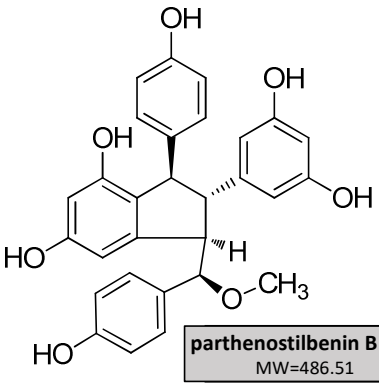
***cis*-δ-viniferin (20)**
MW=454.47



**retrytisol A (21)**
MW=472.48

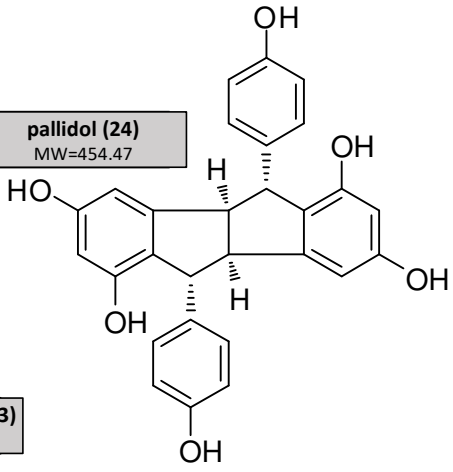


**parthenostilbenin A (22)**
MW=486.51

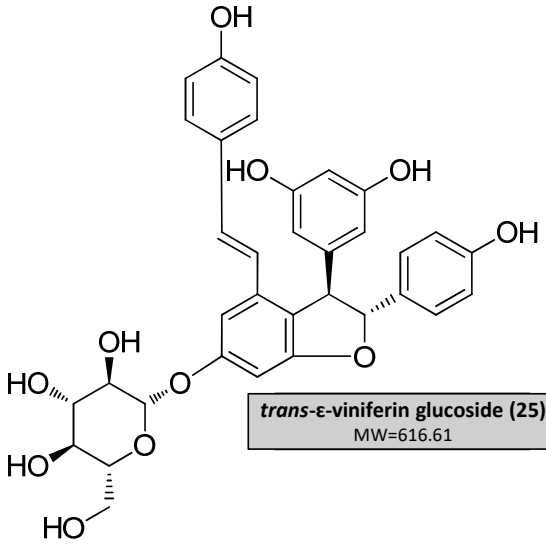


**parthenostilbenin B (23)**
MW=486.51

**pallidol (24)**
MW=454.47

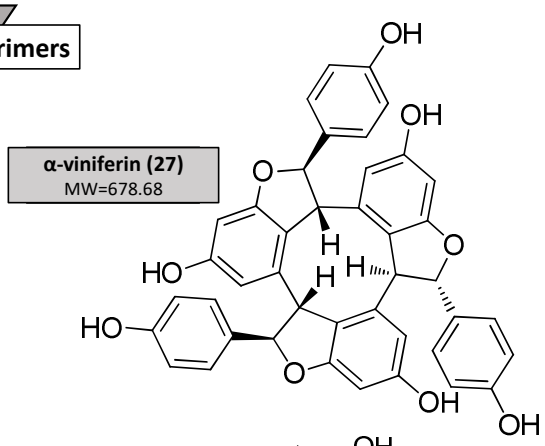


## Glycosylated dimer

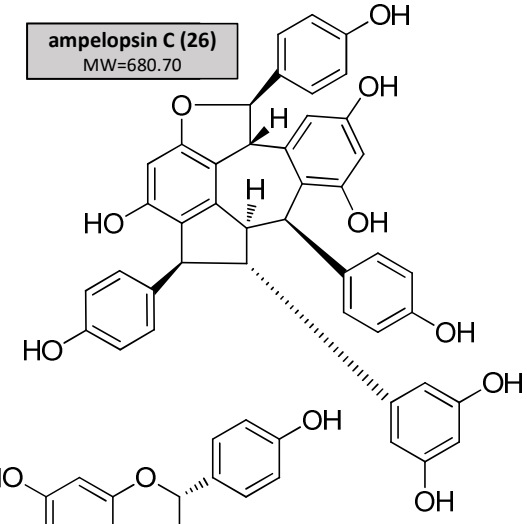


***trans*-ε-viniferin glucoside (25)**
MW=616.61

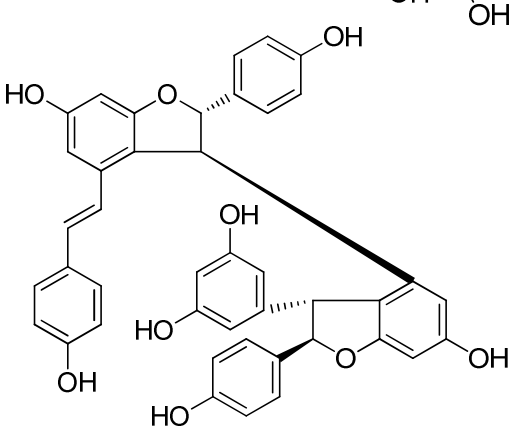
## Trimers



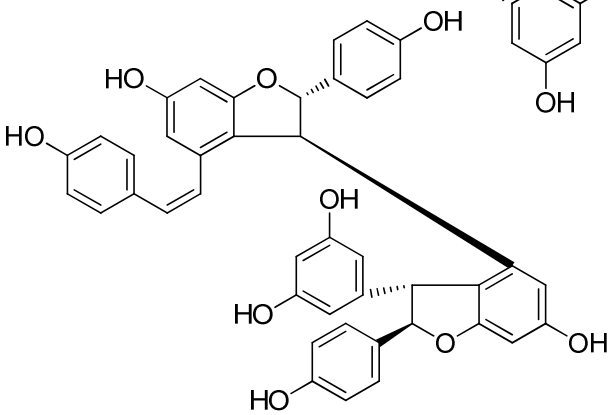
**α-viniferin (27)**
MW=678.68



**ampelopsin C (26)**
MW=680.70



***trans*-miyabenol C (28)**
MW=680.70



***cis*-miyabenol C (29)**
MW=680.70

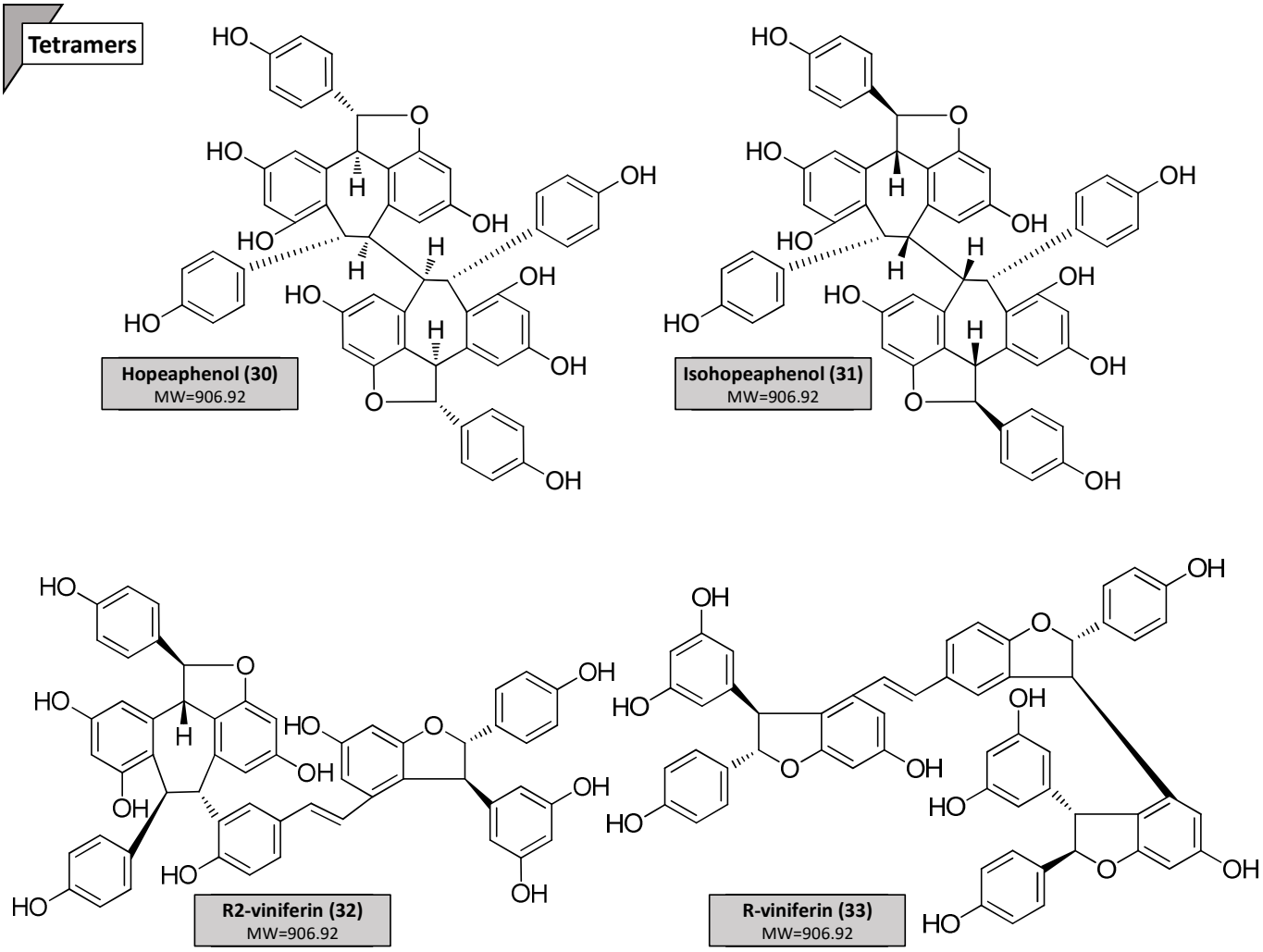

Tetramers
Hopeaphenol (30)
MW=906.92
Isohopeaphenol (31)
MW=906.92
R2-viniferin (32)
MW=906.92
R-viniferin (33)
MW=906.92

**Figure 2.**