CIÊNCIA E TÉCNICA VITIVINÍCOLA

Ciência Téc. Vitiv. 37(1) 13-28. 2022

Review

DIFFERENT APPROACHES TO ENHANCE RESVERATROL CONTENT IN WINE

DIFERENTES ABORDAGENS PARA AUMENTAR O TEOR DE RESVERATROL NO VINHO

Zeynep Şeyda Erdemir Tıraş[1,2,*], Hatice Hazal Okur[1], Zülal Günay[1], Hatice Kalkan Yıldırım[1]

[1]Ege University, Food Engineering Department, 35100, Izmir, Turkey.

[2]Olive Research Institute, 35100, İzmir, Turkey.

*Corresponding author: Tel.: + 90 5072905537; e-mail: zeynepseydaerdemir@windowslive.com.

(Received 22.11.2021. Accepted 28.02.2022)

SUMMARY

Resveratrol is a polyphenol with antioxidant properties and possible beneficial effects on human health. Grapes, peanuts, berries, cacao beans and red wine contain resveratrol. Resveratrol attracts attention due to its bioactive properties, however, the concentration of this compound is not high in grape and wine. Therefore, different studies have been carried out to increase resveratrol level in these products. Several factors such as the grapevine variety, the climatic conditions and the viticultural practices used to create stress on the vine affect the level of resveratrol. Winemaking technologies applied during pre-fermentation, fermentation and post–fermentation stages could also have an effect on the concentration of this stilbene. In addition, recent studies have evaluated biotechnological approaches through the use of different bacteria and yeast strains to produce wine with increased resveratrol content. In this review, the most important factors contributing to increase the resveratrol concentration in grapes and wines are examined. Besides, analytical methods to determine resveratrol content in wine are addressed.

RESUMO

O resveratrol é um composto fenólico com propriedades antioxidantes e possíveis efeitos benéficos na saúde humana. Uvas, amendoins, frutos vermelhos, grãos de cacau e vinho tinto contêm resveratrol. O resveratrol tem sido alvo de atenção devido às suas propriedades bioativas, apesar da concentração deste composto na uva e no vinho não ser elevada. Por conseguinte, diferentes estudos foram realizados para aumentar o nível de resveratrol nestes produtos. Diversos fatores, como as variedades de videira, as condições climáticas e as práticas vitícolas utilizadas para criar stress na videira afetam o teor de resveratrol. As tecnologias de vinificação aplicadas nas fases pré-fermentativa, fermentativa e pós-fermentativa também podem afetar a concentração deste estilbeno. Por outro lado, estudos recentes avaliaram abordagens biotecnológicas, recorrendo ao uso de diferentes estirpes de bactérias e de leveduras, para produzir vinho com maior teor de resveratrol. Nesta revisão são examinados os fatores que mais contribuem para o aumento da concentração de resveratrol em uvas e vinhos. Por outro lado, são abordados métodos analíticos para determinar o teor de resveratrol no vinho.

Keywords: resveratrol, viticultural practices, oenological technology, grape, wine.
Palavras-chave: resveratrol, práticas vitícolas, tecnologia enológica, uva, vinho.

INTRODUCTION

Resveratrol is a phenolic compound that belongs to the group of stilbenes (Vuong, 2017). In this class of polyphenols, resveratrol is the most abundant stilbene found in a small number of edible plants. Resveratrol (trans-3,4',5-trihydroxystilbene) is commonly found in grapes, and has been associated with several health benefits, chiefly driven via the anti-inflammatory metabolic regulation in human (Christenson *et al.*, 2016). It can be found in low amounts in the human diet due to its low concentrations in foods (Vuong, 2017). It is present in red wine, red grape juice and mulberries, being synthesized under stress conditions resulting from the attack of pathogens, such as *Botrytis cinerea*, UV (ultraviolet light), irradiation, ozone, heavy metal ions, injury and frost (Keskin *et al.*, 2009; Li *et al.*, 2013).

Resveratrol can be produced as dietary supplements and used to cope with high cholesterol, cancer, heart diseases and many other diseases (Keskin *et al.*, 2009).

Article available at https://www.ctv-jve-journal.org or https://doi.org/10.1051/ctv/ctv20223701013

This compound exists as two isomers: *cis* and *trans*-resveratrol; the latter is more abundant in nature. The glycosylated forms of *cis*- and *trans*- resveratrol are called piceid - Figure 1 (Kostadinović *et al.*, 2012). Resveratrol has also monomeric (e.g. piceatannol, pterostilbene), dimeric (e.g. viniferins, pallidol, caraphenols) and trimeric (e.g. miyabenol) derivatives - Figure 1 (Gutiérrez-Escobar *et al.*, 2021).

There is a growing global interest towards resveratrol. However, the natural synthesis and accumulation of resveratrol in grapes is quite low. For this reason, research aimed at promoting the increase of resveratrol in grapes and wines is of utmost importance (Hasan and Bae, 2017). There are several factors that affect the resveratrol concentration in wine. Grapevine variety, stress conditions, weather conditions, geographical area, techniques applied in winemaking, and fermentation conditions are quite important in terms of the resveratrol content in wine (Guerrero *et al.*, 2010a). In this review, viticultural practices, pre-fermentation, fermentation and post-fermentation stages as the main factors related to the regulation of resveratrol in wines are discussed.

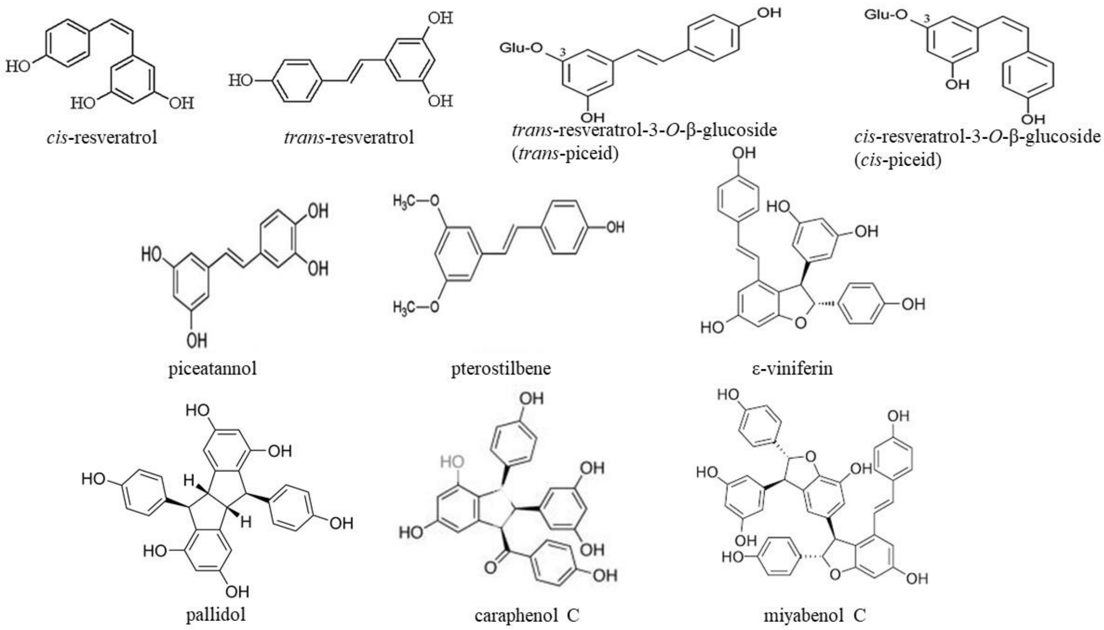

Figure 1. Chemical structure of *cis*-resveratrol, *trans*-resveratrol, *trans*-piceid, *cis*-piceid and some resveratrol derivatives

THE IMPORTANCE OF RESVERATROL FOR HUMAN HEALTH

Moderate and regular wine consumption could be associated with health benefits due to the presence of phenolic compounds, including stilbenes like resveratrol (Salehi *et al.*, 2018; Pappalardo *et al.*, 2019). This is particularly significant in terms of cardiovascular health, revealed by the 'French paradox'. According to this phenomenon, despite having a high fat diet, French people have less cardiovascular problems due to their high red wine consumption (Castaldo *et al.*, 2019). It has been demonstrated that *trans*-resveratrol and its glucoside can inhibit LDL oxidation in the initial stage of the pathogenesis of atherosclerosis, contributing to the cardioprotective properties of red wine (Burns *et al.*, 2002).

Along with cardiovascular benefits, resveratrol also exerts anticancer, anti-oxidative, anti-inflammatory, and neuroprotective effects (Salehi *et al.*, 2018). This compound demonstrates antitumor activity by interfering with the stages of carcinogenesis and modulating transcription factors (Jang *et al.*, 2009; Elshaer *et al.*, 2018). Some studies showed that resveratrol could be used as a therapeutic agent in various cancer treatments, such as those used in breast (Sinha *et al.*, 2016), pancreas (Cheng *et al.*, 2018), skin and colorectal cancers (Elshaer *et al.*, 2018). Its positive health impact on certain metabolic diseases, like obesity and diabetes, through the ability to alter gene expression favorably and modulate insulin levels, respectively, has also been reported (Szkudelska and Szkudelski, 2010). However, further research is needed to find out whether these effects observed in animal studies could be achieved in human cells as well. In addition, some doubts exist on the therapeutic activity of resveratrol because the research in older people showed no relationship between the urinary resveratrol metabolite concentration and inflammatory markers, cardiovascular disease, cancer, or mortality (Weiskirchen and Weiskirchen, 2016).

Resveratrol could regulate the immune system by interacting with multiple molecular targets (Fu *et al.*, 2018). It performs this function by interfering with immune cell regulation, pro-inflammatory cytokines' synthesis, and gene expression. The toll-like receptor (TLR) and pro-inflammatory genes' expression could be suppressed by resveratrol activity. Innate and adaptive immunity could be promoted by consumption of this compound. However, immunosuppression can be observed at high doses in opposition to the beneficial effects resulting from low doses (Malaguarnera, 2019).

There are studies demonstrating antiviral activity of resveratrol against several viruses, including coronavirus (Ramdani and Bachari, 2020). Indeed, severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) were found susceptible to resveratrol in *in vitro* research (Filardo *et al.*, 2020). Lin *et al.* (2017) reported that resveratrol can reduce cell death caused by MERS-CoV, decrease RNA expression and viral yield of MERS-CoV as well as inhibit Caspase 3 cleavage induced by this infection. This function of resveratrol stems from stimulation of the immune system, downregulation of pro-inflammatory cytokines release, promotion of SIRT1 and p53 signaling pathways and enhancing natural killer immune cells (Ramdani and Bachari, 2020). Resveratrol treatment used in chronic obstructive pulmonary disease (COPD), which could increase the severity of COVID-19, showed that some inflammatory cytokines like nuclear factor kappa B, tumor necrosis factor, and matrix metalloprotease-9 protein expression in lymphocytes were reduced in patients (Hoang, 2021). Although there is no clinical evidence to suggest that resveratrol may be effective in treating or attenuating the severity of SARS-CoV-2 infection, its potential as an adjunct antiviral agent can be explored taking into account previous studies (Marinella, 2020).

When administered orally, resveratrol is rapidly metabolized and its bioavailability is quite low (Pannu and Bhatnagar, 2019). For this reason, it is not possible to reach the required doses to produce a therapeutic effect by drinking wine or consuming other foods (Weiskirchen and Weiskirchen, 2016). Therefore, a resveratrol-enriched wine may be more effective in terms of this compound intake. Studies have indicated that these 'functional wines' may also be preferred over conventional wine by consumers, which can create a market opportunity (Vries *et al.*, 2018; Kontaxakis *et al.*, 2020). Some attempts exist to increase bioavailability of resveratrol, such as enhancing its solubility, using other phytochemicals as adjuncts, changing the route of administration and creating new formulations with the use of nanotechnology (Pannu and Bhatnagar, 2019; Vries *et al.*, 2018). However, many countries have legislations that restrict the term 'functional' because wine is an alcoholic beverage (Kontaxakis *et al.*, 2020).

MAIN SOURCES OF RESVERATROL

Resveratrol is known as a phytoalexin produced by plants as a response to damage. It possesses *cis* and *trans* configurations, which can transform into each other under certain conditions and due to the existence of a C-C double bond (Burns *et al.*, 2002; Tian and Liu, 2020).

Resveratrol is found in more than 70 different fruits/plants, including grapes, berries, pines, plums, legumes, and some herbs - Table I (Bay Karabulut, 2008). Resveratrol has also been identified in pistachio and edible peanut varieties grown in Turkey. It was found that peanuts contain 0.03-1.92 µg/g of *trans*-resveratrol, while pistachio contains 0.09-1.67 µg/g (Tokusoglu *et al.*, 2005).

According to Guerrero *et al.* (2010a), the grape skin contains 50 to 100 µg/g of resveratrol. Resveratrol is

Table I

Sources of resveratrol and *trans* isomer concentration

Sources	*Trans*-resveratrol content	Reference
Red wines	0.352-1.99 mg/L	Gerogiannaki-Christopoulou *et al.* (2006)
White wines	0.005-0.57 mg/L	Gerogiannaki-Christopoulou *et al.* (2006)
Grape skin	50-100 µg/g	Aggarwal and Shishodia (2005); Guerrero *et al.* (2010a)
Peanut	0.03-1.92 µg/g	Tokusoglu *et al.* (2005)
Pistachios	0.09–1.67 µg/g	Tokusoglu *et al.* (2005)
Cocoa liquor	at least 0.5 mg/L *trans*-resveratrol, 1.2 mg/L *trans*-piceid	Counet *et al.* (2006)
Dark chocolate	at least 0.4 µg/g *trans*-resveratrol, 1 µg/g *trans*-piceid	Counet *et al.* (2006)
Grape cane waste	3.45 mg/g	Rayne *et al.* (2008)
Cacao powder	1.85 µg/g	Hurst *et al.* (2008)
Milk chocolates	0.10 µg/g	Hurst *et al.* (2008)
Chocolate syrups	0.09 µg/g	Hurst *et al.* (2008)
Mulberry fruit	50.61 µg/g	Shrikanta *et al.* (2015)

naturally found in wine because it is extracted from crushed grape berries during the must preparation and fermentation (Kontaxakis *et al.*, 2020). Red wine contains 0.352-1.99 mg/L of resveratrol, while in white wine this level varies between 0.005 and 0.57 mg/L (Gerogiannaki-Christopoulou *et al.*, 2006). Generally, red wine has higher resveratrol content than white wine because the grape pomace is removed after pressing during the production of the latter (Kontaxakis *et al.*, 2020). 'Muscadine' (*Vitis rotundifolia*) wines have comparable amounts of resveratrol to *Vitis vinifera* wines. Dark skinned 'Muscadine' derived products (wine, unfiltered juice, whole berries, purees) have higher amount resveratrol than the bronze-skinned counterparts (Ector *et al.*, 1996).

A higher concentration of resveratrol has been observed in 'Itadori' tea as compared to peanuts and grapes. Therefore, it can be suggested as a suitable substitute for red wine for people who do not prefer consuming alcohol. Nevertheless, more research is needed on the potential biological effects of other endogenous compounds in 'Itadori' tea, and more information is required on the absorption of free and conjugated resveratrol and its biomedical effects in vivo (Burns *et al.*, 2002).

Trans-resveratrol and *trans*-piceid were also found in dark chocolate and cocoa liquor extracts. Chocolate products show higher antioxidant activity than commercial stilbene extracts due to high procyanidin content (Counet *et al.*, 2006). Tempeh, a traditional fermented food of Indonesia, and soybeans are also alternative sources of *trans*-resveratrol, which have been reported to prevent cell death through apoptosis (Irnidayanti and Sutiono, 2019).

ENRICHMENT OF RESVERATROL IN WINE

Viticultural practices

Different strategies can be used in order to increase the resveratrol content in grapes, such as different grapevine varieties, production under different climatic conditions and injuring the plant to create stress.

The grapevine varieties may contain different amounts of *trans*-resveratrol. Goldberg *et al.* (1995) found that wines from 'Pinot noir' had considerably higher amount of resveratrol regardless of the geographical origin. Geana *et al.* (2015) studied the effect of different red grapevine varieties ('Mamaia', 'Feteasca Neagra', 'Cabernet Sauvignon', 'Merlot' and 'Pinot Noir') grown in wine producing area, Dobrogea, during two harvest years under the same agronomic conditions, and one harvest year with specific microclimatic conditions. *Trans*-resveratrol content found in the skins of these five varieties was significantly different. Regardless of the variety and harvest year, the highest *trans*-resveratrol concentration in grapes was found on the last sampling day. The authors explained this situation as ripening highly affects the resveratrol content in red grapes. The amount of *trans*-resveratrol was higher in 2012 harvest than 2013. The authors stated that more favorable climatic conditions, like warmer and drier weather and greater number of sunny days in 2012 played an important role in the accumulation of *trans*-resveratrol in grapes. *Trans*-resveratrol contents in grape skins and in the corresponding wines also showed significant positive correlations. Burns *et al.* (2002) studied the influence of different grapevine varieties and stress conditions created by a disease on the amount of resveratrol. They found that grapes contained mainly *trans*-resveratrol glucoside in concentrations between 1.5 and 7.3 µg/g. The aglycone *trans*-resveratrol was also found to be at 0.5 µg/g concentrations in two of the four samples. However, *cis*-resveratrol could not be detected in any analyzed samples. The stilbene content of grapes was influenced by the variety, time and disease stress. *Trans*-resveratrol content of Californian table grapes from different clones exhibited an approximate 20-fold variation. The level of *trans*-resveratrol was reported to be around 3.0 µg/g for 'Fantasia' seedless grapes. However, for 'Crimson' seedless grapes, resveratrol level was noted to be around 0.16 µg/g (Burns *et al.*, 2002). The levels of stilbenes in red wines were found in different ranges due to different vinification approaches, grapevine varieties and climate conditions. In red wines, stilbenes present as aglycones were much more abundant than glucosides (Burns *et al.*, 2002). Liu *et al.* (2010) also studied the effect of grapevine variety and ultraviolet-C light (UV-C) irradiation on stilbene content. The relationship between stilbene production and four different grape genotypes, leaf, berry exocarp and seed tissues and UV-C irradiation were studied by using grape calli systems. Results showed that non-embryogenic callus accumulated more resveratrol and piceids than embryogenic and pro-embryogenic calli. Application of UV-C irradiation for 20 min was the most effective treatment to increase the callus growth index and the resveratrol and piceids contents. Results of this study demonstrated that resveratrol and piceid production in UV-C irradiated leaf derived calli over 72 hours was dynamic; the optimum harvesting time for the most stilbene presence was 48 hours. Accumulation of stilbenes in UV-C irradiated calli highly depended on tissue type and genetic background, with higher stilbene contents in two interspecific root stocks and exocarp explants or leaves. In another study, UV-C of 254 nm was expressed as the most effective wavelength applicable for resveratrol stimulation in vines (Barlass *et al.*, 1987).

In a different study, Fernández-Marin *et al.* (2013) applied methyl jasmonate (MJ), which is a biostimulant and the most active derivative of jasmonic acid, as a pre-harvest treatment by spraying the vines 20, 16 and 13 days before harvesting. The UV-C treatment was applied after harvest. Results demonstrated that the combined treatment provided the highest trans-resveratrol content and the stilbene concentration reached its maximum level three days earlier in comparison to the UV-C treatment alone. The authors concluded that this result is important in terms of accelerated stilbene biosynthesis and preservation of grape quality. Therefore, this technique was found to be applicable to obtain stilbene-enriched grape products (Fernández-Marin *et al.*, 2013).

The effect of some nitrogen sources (proline, phenylalanine, urea and commercial fertilizers) on the stilbene concentrations of 'Tempranillo' wines was evaluated (Garde-Cerdán *et al.*, 2015). Aqueous solutions of the nitrogen sources were applied to the grapevines at *veraison* and a week later. These grapes were used for winemaking and stilbene concentrations were determined. Results showed that the urea promoted greater increase of resveratrol synthesis and total stilbenes content in must and wine than the other treatments. Phenylalanine increased *trans*-piceid concentration in wine but not as high as urea did. Other nitrogen sources (proline and commercial fertilizers) were not effective in increasing the stilbene concentration in wine (Garde-Cerdán *et al.*, 2015).

When a plant is microbially infected, resveratrol synthesis could be induced as a response from the plants' defense systems because increased resveratrol content could provide enhanced fungal resistance (Hasan and Bae, 2017; Rathburn *et al.*, 2020). High concentrations of resveratrol in grapes can be obtained by a moderate *Botrytis cinerea* pressure (Adrian *et al.*, 2000). Flamini *et al.* (2016) investigated the effect of a stress factor caused by an infection on the resveratrol content in grape. For this purpose, grapes of 'Negro Amaro' variety were inoculated with *Aspergillus carbonarius*, which is an ochratoxin producing fungus. They reported that infected samples had significantly higher amounts of *trans*-resveratrol and some resveratrol dimers, especially E-ε-viniferin, ω-viniferin, caraphenol and δ-viniferin, as well as some resveratrol trimers like α-viniferin and E-miyabenol C. Since resveratrol oligomers were found in both infected and non-infected berries, it could be assumed that the pathogen could not metabolize these compounds. They were produced by the plant as a defense mechanism against the stress conditions. Similarly, Mattivi *et al.* (2011) used disease infection and wounding methods to create stress conditions for vine. Viniferins are relatively restricted group of *trans*-resveratrol oligomers in *Vitaceae* and they have antifungal properties. Therefore, they could provide plants to cope with pathogen attack. Mattivi *et al*. (2011) infected leaves of hybrid *Vitis vinifera* ('Merzling Teroldego') genotypes with *Plasmopara viticola* for six days in order to isolate and characterize the whole class of viniferins that accumulate in the plant. It was demonstrated that infected plants involved different dimers, with some new ones in grapevine, such as ampelopsin D, quadrangularin A, E-ω-viniferin, and Z-ω-viniferin. Additionally, some new trimer (Z-miyabenol C and E-*cis*-miyabenol C) and tetramer (isohopeaphenol, ampelopsin H, and a vaticanol C-like isomer) stilbenoids were observed. In tissues infected by *Plasmopara viticola*, isolation of a dimer that derives from the condensation of (+)-catechin with *trans*-caffeic acid was also noted (Mattivi *et al.*, 2011). Some cultivars could be more sensitive to fungal attacks. For example, 'Pinot Noir' was shown to produce higher levels of resveratrol under fungal infection than other grapevine varieties (Pastor *et al.*, 2019).

The cultivation, production and quality of grapes and eventually wines are greatly influenced by climatic factors such as temperature, humidity and solar radiation (Figueiredo *et al.*, 2017). Burgundy, Bordeaux, 'Pinot Noir' and 'Merlot' wines have higher levels of free resveratrol, while the wines from warm and dry regions, such as Spain, Italy, Portugal and South America, have low concentration of free isomers (Moreno-Labanda *et al.*, 2004). Similarly, *trans*-resveratrol levels in 'Cabernet Sauvignon' wines were found to be relatively higher than those from cool-climate countries like Ontario and the Bordeaux region of France. On the contrary, *trans*-resveratrol contents of wines from warmer climate countries, such as South America and Australia were much lower (Goldberg *et al.*, 1995). Adrian *et al.* (2000) stated that wines from Burgundy and Switzerland had higher resveratrol content because northern vineyards are more vulnerable to *Botrytis cinerea* infection, which could increase accumulation of resveratrol in fruits. Moreno-Labanda *et al.* (2004) showed the stilbene profile of 'Monastrell' wines from two Spanish regions. The results showed that *trans*-piceid levels were higher than *trans*-resveratrol levels in the vast majority of wines produced by different winemaking methods. Comparing with similar red wines, such as 'Pinot Noir' or 'Merlot' (which had around 4 mg/L *trans*-piceid) or red wines from France, Canada, Spain (which had around 3–7 mg/L *trans*-piceid), 'Monastrell' wines showed quite high level of *trans*-piceid (ranging from 15 to 17 mg/L). In most cases, the levels of *cis* isomers were lower than the corresponding *trans* isomers. These authors concluded that low aglycone content and high resveratrol glucoside concentration could be evaluated as characteristics of 'Monastrell' variety. This fact could also be valid for other red wines derived from grapes grown in warm regions, such as Portuguese and French varieties (Moreno-Labanda *et al.*, 2004).

Pre-Fermentation treatments

Pre-fermentation treatments can increase the resveratrol level in wine. Some post-harvest treatments, such as UV-C radiation, ozone application, ultrasonication and the use of certain chemicals, have been reported to have a positive effect on resveratrol content (Hasan and Bae, 2017).

Post-harvest UV-C treatment can be effective in promoting the concentration of phenolic compounds and some secondary metabolites in grape berries by activating the key genes in certain biosynthesis pathways and stimulating the defense system of plants (Zhang *et al.*, 2021). Suzuki *et al.* (2015) found that UV-C irradiation enabled the grapes to accumulate 3.492 µg/g *trans*-resveratrol, which was 355 times higher than that of non-irradiated samples. Cantos *et al.* (2001) stated that UV treatment (irradiation power: 510 W, irradiation time: 30 s, irradiation distance: 40 cm, number of elapsed days to achieve the highest resveratrol accumulation: 3 days) to red 'Napoleon' grapes resulted in the maximum resveratrol content (11 times higher than the control group). Same research group studied the effects of a similar UV-C treatment (510 W, 40 cm, 60 s) on some red and white table grape varieties. Results demonstrated that 'Red Globe' variety had the highest level of resveratrol (2.3 mg/100 g) (Cantos *et al.*, 2002).

The increase in the level of resveratrol in grape skin could also significantly enhance resveratrol content in the final product (Cantos *et al.*, 2003). The use of UV-C irradiated 'Monastrell' grapes during winemaking resulted in an approximately two-fold increase in resveratrol compared to control wine without any change in oenological parameters (pH, density, acidity, hue and alcoholic strength) (Cantos *et al.*, 2003). Another work showed that UV-C treated grapes and two hours of pre-fermentative maceration significantly increased the concentration of resveratrol in wine (González-Barrio *et al.*, 2009). In a similar study, Guerrero *et al.* (2010a) produced white wines by using grapes treated with UV-C in order to rise the resveratrol content. Indeed, this treatment increased *trans*-resveratrol and total stilbenes contents in the grapes approximately 2.5 and 3.7 times, respectively, compared to untreated ones. The wine obtained from UV-C treated grapes had significantly higher resveratrol content than the control group. This could be assigned to the changes in the must during alcoholic fermentation due to the presence of UV-C treated grapes, which provide an increase in stilbene concentration in wine. Moreover, this process enabled wine to show high color intensity and astringency due to higher extraction of phenolic compounds, including resveratrol. This research group also produced red wine using the same technique. *Trans*-resveratrol content of the UV-C treated grapes and of the resulting wines increased 9.6 and 3.2 times compared to that quantified in the control grapes and wines, respectively (Guerrero *et al.*, 2010b).

Ozone treatment can stimulate the synthesis of resveratrol during storage. During this stage, ozone used for preventing fungal growth could increase the resveratrol concentration in grape berries, at an even higher level than UV-C treatment (Hasan and Bae, 2017). Segade *et al.* (2019) studied the effect of ozone treatments (different doses and durations) on stilbene concentration in fresh and dried 'Moscato bianco' grapes after harvest. They reported that the loss of stilbenes due to the dehydration process was prevented and their accumulation was stimulated with short term (24 h) and high doses (60 µl/L) and long term (48 h) exposures. This elicitor effect was considerable for *trans*-resveratrol (+ 37.3%). In another study, ozone treatment (3.88 g/h, 5 hours) promoted resveratrol levels similar to those of UV-C treated grapes (1 min, 510 W, 40 cm) after two days storage (González-Barrio *et al.*, 2006). In terms of the total stilbene accumulation, ozone was more efficient than UV-C. However, UV-C light can be seen as less harmful to grape berries than ozone. In the ozone treatment, the sensory quality of grapes can be harmed due to the browning of the skin upon extended storage time, therefore, it would be better to apply this treatment to obtain resveratrol-enriched must and grape extracts and not for marketing fresh grapes (González-Barrio *et al.*, 2006).

Ultrasound as a post-harvest treatment of grapes could be effective in increasing resveratrol content in the fruit skin. It was found that resveratrol content in grape fruits and leaves increased in reaction to ultrasonication, which was synergistically correlated with the up-regulation of RS mRNA, indicating a regulatory procedure of the gene expression by this treatment. This procedure did not cause any negative effect on the amount of total soluble solids in grapes (Hasan and Baek, 2013). Therefore, it could have a practical significance in enology in terms of producing resveratrol-rich wine (Hasan and Baek, 2013). Another investigation on the resveratrol accumulation in grape juice prepared from 'Campbell Early', 'Muscat Bailey A' (MBA), and 'Kyoho' varieties of grapes was performed, showing that post-harvest ultrasonication cleaning significantly increased resveratrol level (Hasan *et al.*, 2014).

Methyl jasmonate (MJ) enantiomers were used in combination with ethanol as a post-harvest treatment in order to obtain polyphenol-enriched grapes (Flores and del Castillo, 2016). For this purpose, red grapes were exposed to vapor of MJ enantiomers in ethanol. After storage at 4 ºC for 5 days, the concentration of resveratrol and quercetin glycosides were determined. A significant increase in resveratrol concentration (from 27 to 39 µg/g) was observed in comparison to control. Authors stated that this could possibly stem from the induction of enzymes taking part in the bioformation pathways (Flores and del Castillo, 2016). In addition, Fernández-Marin *et al.* (2014) reported that MJ-UVC treated grapes used for winemaking gave rise to a *trans*-resveratrol concentration approximately 2-fold higher than the control.

In a different study, Averilla *et al.* (2019) attempted to increase the resveratrol content in grape skin through the combined usage of heat and enzyme treatment as resveratrol is mainly found in the form of glycoside in the skin. Results showed that heating the skin at 95 ºC for 10 min and a subsequent enzyme treatment containing glucanase and pectinases at 50 ºC for 60 minutes enhanced the conversion of piceid into resveratrol dramatically. On the other hand, higher extraction of resveratrol was observed. Authors reported that this process could be an alternative to prepare resveratrol-enriched food products, like wine.

Thermovinification is applied as a pre-fermentative technology. It includes the heating of crushed grapes over 70 ºC for 30-40 min and cooling before alcoholic fermentation. In this way, water soluble phenolic compounds can be transferred from the cells of the fruit to the wine (Gutiérrez-Escobar *et al.*, 2021). Atanacković *et al.* (2012) showed that two different thermovinification applications (60 ºC for one hour or 80 ºC for 3 min) resulted in the production of wines with higher concentrations of phenolic compounds and enhanced antioxidant potential. However, it was stated that resveratrol content was mainly affected by the grapevine variety.

Fermentation stage

Besides the grapevine variety, stress conditions, climate conditions, geographical area and pre-fermentative treatments, the effect of alcoholic fermentation conditions is also quite important for the resveratrol concentration of wine (Guerrero *et al.*, 2010a).

Selection of a suitable yeast strain is crucial for winemaking in order to obtain a high-quality final product. Yeasts affect the level of resveratrol in wine with their β-glucosidase activity. They can hydrolyze glucosidal forms of resveratrol to release *cis*- and *trans*-resveratrol (Kammerer and Carle, 2009; Caridi *et al.*, 2017). It is a desirable feature because resveratrol is more bioactive than its glucosidal forms (Basholli-Salihu *et al.*, 2016). In addition, yeasts can adsorb polyphenols on cell walls or absorb and metabolize them. All these characteristics are strain-dependent (Kammerer and Carle, 2009; Caridi *et al.*, 2017; Claus and Mojsov, 2018).

Sorrentino *et al.* (2012) isolated *Saccharomyces* / non-*Saccharomyces* yeasts (*S. cerevisiae* AGYP37 and *Metchnikowia fructicola* AGYP28) from 'Aglianico' grapes/musts and made culture combinations to produce 'Aglianico' wine. At fermentation step, commercial yeast was also involved in combinations. The outcomes revealed that when commercial strain, AGYP37 and AGYP28 were combined all together, resveratrol reached the maximum level (8.4 mg/L) in wine. The resveratrol content was quite close to this level (8.1 mg/L) when the mixture of two autochthonous strains was used. The wine with the lowest amount of resveratrol (4.3 mg/L) resulted from the use of the commercial strain/AGYP28 combination. Similarly, Grieco *et al.* (2019) used two autochthonous yeasts (*S. cerevisiae* ITEM14093 and ITEM 14077) to produce 'Primitivo' and 'Negroamaro' wines. Focusing on comparing the effects of commercial and autochthonous yeasts, they determined the polyphenol content and resveratrol levels in the wines. The results showed that autochthonous strains had a highly positive effect in increasing *trans*-resveratrol concentrations in both wines. The use of these indigenous starters provided an increase in total stilbenes concentration up to 5.5 and 3.63 times for 'Primitivo' and 'Negroamaro' wines, respectively.

In another study on wines produced from 'Shiraz' grapes, four industrial yeast cultures (*S. cerevisiae* Fermivin PDM, *S. cerevisiae* Fermirouge, *S. cerevisiae* Fermicru VR5, and *S. cerevisiae* Oenoprox L 68-72) were selected relying on their capacity to degrade phenolic substances. The effects of the cultures on resveratrol content in wines were compared. Fermentation lasted for six days, and at the end of the process a significantly higher level of *trans*-resveratrol in the wine produced with *S. cerevisiae* Fermirouge than the control wine was observed. The increment associated with the use of L 68-72 and VR5 strains was not significant. In terms of total resveratrol content, the highest level was obtained with VR5 strain. This study highlighted the importance of yeast selection as a determining factor of resveratrol content in wine (Clare *et al.*, 2005).

The appropriate yeast strains should be selected according to their ethanol producing capacity and β-glucosidase activity in order to increase resveratrol level in wines (Gaensly *et al.*, 2015). Gaensly *et al.* (2015) selected and identified yeast strains with β-glucosidase activity and the potential to increase resveratrol level in the fermentation of *Vitis labrusca* 'Bordo' grapes. Among β-glucosidase active strains, those capable of hydrolyzing piceid were used in winemaking at the ratio of 10^7 cells/mL. Fourteen yeast strains, the majority of them belonging to *Hanseniaspora* genus, increased free resveratrol level by 102 %. Moreover, among them, eight *H. uvarum* strains produced higher amount of ethanol than expected. A positive correlation was found between ethanol and resveratrol level. Authors indicated that ethanol could enhance the solubility of resveratrol (Gaensly *et al.*, 2015). This approach was previously proposed by Kostadinović *et al.* (2012). They produced wines by using two different yeasts (*S. cerevisiae* marketed in Macedonia and France).

Resveratrol content was higher when French yeast was used, which was ascribed to the different fermentation kinetics of yeasts and the ethanol formation level. French yeast possibly performed fermentation faster, producing higher amounts of alcohol, which may have promoted greater extraction of polyphenols from the grapes. The authors also reported that the different adsorption capacity of phenolic compounds by yeasts may have contributed to the observed effect (Kostadinović *et al.*, 2012).

The use of pectolytic enzymes along with yeasts could also affect resveratrol content in wines (Tomić *et al.*, 2018). The effect of two yeast strains (Uvaferm BDX *S. cerevisiae* and Lalvin 71B *S. cerevisiae*) and different pectolytic enzymes (Lalzyme OE and Lalzyme EX-V) in the chemical composition of blackberry "wines" produced by using 'Thornfree' cultivar was evaluated. Enzymes were added (1 g/100 L) when the maceration started and alcoholic fermentation was carried out with yeast inoculation. A control wine was produced by spontaneous fermentation and without enzymes. Control wine had the lowest *trans*-resveratrol concentration while the combined use of Lalvin 71B *S. cerevisiae* and Lalzyme OE resulted in wines with significantly higher levels of *trans*-resveratrol. It was thought that yeast with higher enzyme activity could be more successful in increasing *cis*- and *trans*-resveratrol levels while decreasing *trans*-resveratrol glucosidase. The authors concluded that blackberry "wine" could be a promising source of *trans*-resveratrol (Tomić *et al.*, 2018).

The extraction of resveratrol from some plant tissues that synthesize it could be possible. However, this is not an effective method due to the high cost because the required number of plants and solvents are quite high. Further, there could be some problems regarding purity. Therefore, biotechnological methods could be a more feasible way for this purpose (Sun *et al.*, 2015). Yeasts do not have the genes encoding enzymes involved in resveratrol biosynthesis. By transferring these genes to them, large amount of resveratrol could be produced. Also, yeasts can be tailored to produce some other specific enzymes, like β-glucosidase and when they are used in winemaking, resveratrol content could be increased (Jeandet *et al.*, 2012).

Tyrosine ammonia lyase (TAL) enzyme takes part in the biosynthesis of resveratrol by directly catalysing *p*-coumaric acid formation from tyrosine; *p*-coumaroyl-CoA is produced by 4-coumarate-CoA ligase (4CL). At the last step, resveratrol is formed as a result of resveratrol synthase (RS) activity (Hasan and Baek, 2013). Sun *et al.* (2015) transferred 4CL and RS genes into *S. cerevisiae* EC118, which is used in winemaking industry. They produced wines from 'Kyoho' grapes by inoculating transgenic yeast at the fermentation step. The results showed that twice as much resveratrol was obtained with the use of engineered yeast compared to control. Authors concluded that resveratrol level in wine fermentation could be enhanced with this strain. In a similar study, Wang *et al.* (2011) engineered a *S. cerevisiae* strain in order to increase *p*-coumaric acid formation and ultimately resveratrol content. For this purpose, a mutation was created for TAL via codon changing for enhanced translation. Also, as arabinose transporter (araE) gene is thought to provide increased resveratrol accumulation in the cells, yeast was provided to express this gene. It was found that yeast with araE had the ability to produce 2.44 times more resveratrol than the control yeast (that did not carry this transporter). They produced white wine with this recombinant strain and observed that the level of resveratrol was close to the values found in most of the red wines. The authors emphasized that increasing the resveratrol level in white wine by metabolic engineering may add value to this kind of wine. Another experiment was conducted in Malaysia in white wine production by using two different recombinant strains of *S. cerevisiae* T73, namely YCA1 and YCB35. These transgenic strains were engineered to express a gene from *Aspergillus niger* or *Candida molischiana*, which encodes important enzymes in winemaking, α-L-arabinofuranosidase and β-glucosidase, respectively. In wines fermented with YCB35 strain, *cis*- and *trans*-resveratrol levels were ten and four times higher, respectively, than in the control wines. The authors explain these results based on the ability of the β-glucosidase enzyme encoded by *C. molischiana* BgiN gene to hydrolyze derivatives linked by glycosidic bonds. This gene could cause release of resveratrol from cellular structures by providing more substrate for this purpose. Another reason could be the presence of unknown conjugated resveratrol forms. This study put forward the technological feasibility of β-glucosidase from *C. molischiana* in vinification to increase the resveratrol content in white wines (González-Candelas *et al.*, 2000).

The length of maceration and the presence of skins, seeds and stems could influence the resveratrol content in wine as well. Generally, it is stated that extended maceration could have a positive effect on resveratrol level due to the increased solubility (Fabjanowicz *et al.*, 2018). Kostadinović *et al.* (2012) used three different maceration time (3, 6 and 10 days) in 'Vranec' and 'Merlot' wine production. They found that resveratrol and piceid concentration of wines were higher when maceration lasted ten days. Also, the antioxidant activity of these wines was enhanced. Poklar Ulrih *et al.* (2020) stated that extended the maceration up to 13 days and ageing of 250 days increased the level of *cis*- and *trans*-resveratrol in red wine produced from 'Blaufränkisch' grapevine variety.

During white wine production, skins and seeds are separated, and so resveratrol content is quite low because these parts of the grape are the main source of this stilbene. At the fermentation/maceration step of red wine, skins and seeds are present and so resveratrol could be released from the pomace into the wine (Bavaresco *et al.*, 2016). Surguladze and Bezhuashvili (2017) applied different techniques and assessed the resveratrol levels in dry bulk red and pink wines from 'Saperavi' grapevine variety. They produced two types (European and Kakhetian) of wines. In European type, they produced pink wines with fermentation by natural microflora (1) and by a dry yeast, B2000 (2). Another red wine was produced with fermentation by natural microflora and with no stem pomace (3). In Kakhetian type, red wines were produced with fermentation by natural microflora and with stem pomace (4), and with an initial fermentation of cluster stem before alcoholic fermentation by natural microflora (5). Authors reported that wine-4 produced with Kakhetian style had higher concentration of resveratrol due to the use of stems and skins, which enriched the wine in terms of stilbenoids. However, wine-5 had less total resveratrol content than wine-4. This could stem from oxidation during preliminary fermentation. Also, the use of yeast in European type wine resulted in a decrease in total piceids level due to the hydrolysis of glucosidal bonds. Hence, an increase in total resveratrol was observed.

A technique, which is similar to a Spanish method called 'double pasta', was used in order to determine the changes of resveratrol level in wines made from four different cultivar grapes, 'Merlot', 'Cabernet Sauvignon', 'Pinot Noir' and 'Propukac' (Atanacković *et al.*, 2012). In this technique, the proportion of the solid parts (skins or seeds) in the crushing grapes is increased by separating 30 % and 50% of the must. A pure yeast strain was inoculated to start alcoholic fermentation. Maceration and fermentation lasted for 14 days at 25 ºC. For 'Cabernet Sauvignon' and 'Propukac' cultivars, wines produced by separation of 50 % of must yielded the highest level of total resveratrol, however, they were not statistically different from the control samples. It was indicated that grapevine variety affect the resveratrol content rather than the technique applied (Atanacković *et al.*, 2012). In another study, no significant difference between wines made by stem contact and non-stem contact in terms of resveratrol concentration was found. Wines subjected to carbonic maceration had significantly lower resveratrol concentration than wines produced with traditional winemaking technologies irrespective of the use of stems (Sun *et al.*, 2003).

Pérez-Navarro *et al.* (2018) studied the effects of different maceration/fermentation temperatures (17 ºC, 21 ºC and 25 ºC) on the phenolic profile of red wines produced from 'Petit Verdot' grapes. Commercial *S. cerevisiae* yeast was used during alcoholic fermentation. Results demonstrated that free resveratrol concentration of wines could not be detected. However, the concentration of piceid was significantly higher when maceration/fermentation steps was performed at 21°C and 25°C. Fermentation time could also have an effect on wine quality (Sener and Yildirim, 2013). Franco *et al.* (2002) examined the effect of different fermentation time (3, 10, 60 days) on the resveratrol content by inoculating 'Cannanou' must with autochthonous yeast strains. Fermentation was carried out at 25°C, and for the third sampling, wine was kept at 10°C for 60 days. After the tenth day, free forms of resveratrol increased while the glucosidase forms decreased. During the second month of fermentation, the level of all resveratrol types decreased, especially the free forms. The authors emphasized that the stage between the third and tenth days of the fermentation was crucial for the formation of free resveratrol.

Malolactic fermentation is the process by which lactic acid bacteria convert malic acid into lactic acid. It usually occurs after alcoholic fermentation. Due to metabolic activities of lactic acid bacteria, primarily *Oenococcus oeni*, wine acidity decreases and wine gains some extra flavors. Malolactic fermentation could affect the resveratrol content depending on the strain used. Due to the β-glucosidase activity of bacteria, piceid levels could decrease while *trans*-resveratrol increases in wine (Kammerer and Carle, 2009). Pezet and Cuenat (1996) reported that in the wine from 'Gamay' grapes, the concentration of resveratrol was almost twice after malolactic fermentation (46 days) than that observed at the end of alcoholic fermentation.

Hernandez *et al.* (2007) studied the effects of malolactic fermentation carried out by *Oenococcus oeni* (Oe-18 and Oe-159) and *Lactobacillus plantarum* (Lp-39 and Lp-51) strains on non-flavonoid composition of 'Tempranillo' red wines. The wines that underwent malolactic fermentation had higher levels of *trans*-resveratrol and *trans*-resveratrol glucosidase than those obtained after alcoholic fermentation. This increase was more evident during spontaneous fermentation and when Oe-18was used. The authors proposed that lactic acid bacteria can influence the resveratrol level and ultimately the antioxidant activity of wine. In a similar study, Yunoki *et al.* (2001), using red grapevine varieties grown in Japan, observed that the levels of *trans*-resveratrol were higher (1.1 to 1.9-fold) after malolactic fermentation than that after alcoholic fermentation. After this step, it was also observed that the level of piceid decreased. The authors assigned this effect to the β-glucosidase activity of the bacteria involved in malolactic fermentation; with their enzyme activity, they hydrolyzed piceid to free resveratrol. Poussier *et al.* (2003) also demonstrated the positive effects of lactic acid bacteria (*Oenococcus oeni*) on stilbene content in 'Merlot' wine.

Post-Fermentation operations

After fermentation is completed, wine is subjected to clarification to remove unstable components (Vernhet, 2019).

The wine composition is complex and changes during the ageing process. Phenolic compounds contribute to the sensory properties of wine, such as odor and mouthfeel sensations, and the phenolic content is an important criterion for determining the quality of wine. Ageing in oak barrels allows the wine to be enriched with aromatic compounds (Tao *et al.*, 2014). Sartor *et al.* (2019) studied the effect of mannoproteins on the evolution of rosé sparkling wines during over-lees aging by analyzing polyphenols, organic acids, macro and microelements. The most abundant polyphenolic compounds found in rose wines through ageing were caffeic acid, catechin, gallic acid, and malvidin-3-O-glucosides. The addition of mannoproteins positively affected the concentration of phenolic compounds and organic acids in wines over time. These positive effects were observed at the end of extended ageing, particularly for tyrosol, *trans*-resveratrol, gallic acid, catechin, and hydroxycinnamic acids.

Similarly, Guld *et al.* (2019) investigated *trans*-resveratrol and anthocyanin content of Hungarian red wines (‘Kadarka’, ‘Kékfrankos’ and ‘Cabernet Franc’) under different production conditions using oak barrels over two-years. ‘Kékfrankos’ wine presented the highest initial concentration of anthocyanin and *trans*-resveratrol. *Trans*-resveratrol concentration increased by a small extent due to sulphuring during aging and ‘Kékfrankos’ wine had higher concentration of resveratrol than others. The initial concentration of resveratrol also increased with ageing in wooden barrel, but the wooden barrel reuse had negligible effect. In another study, Roldán *et al.* (2010) investigated the effect of sherry preparation on resveratrol and piceid levels. Resveratrol isomers and piceid content were determined from maturation of wine to the bottling during two vintages. Clarification, cold stabilization, and filtration processes strongly influenced resveratrol and piceid content. Nevertheless, biological ageing had the most significant effect, decreasing resveratrol content by 80%. Approximately 15 % loss of resveratrol was observed during cold treatment (-6 ºC for one week) and filtration. Sun *et al.* (2006) observed a decrease in the concentration of *trans*-resveratrol in ‘Castelão’ red wines during aging; in ‘Syrah’ red wines, *trans*-resveratrol increased in the first two months but then began to decrease; a marked decrease was found in *trans*-resveratrol level through six months of aging for ‘Tinta Roriz’ red wines. The authors concluded that although grape skin and stem contain high levels of stilbenes, a low amount of them was released into the wine. Similarly, Naiker *et al.* (2020) determined about 76% decrease in *trans*-resveratrol concentration in Australian red wines stored for 16 months in brown glass bottles in the dark at ambient temperature.

METHODOLOGIES FOR IDENTIFYING AND QUANTIFYING RESVERATROL IN WINE

There are different analytical ways to determine phenolic compounds in wine, including spectrophotometric and chromatographic methods. Spectrophotometric methods are generally preferred to quantify total phenolic compounds. Folin-Ciocalteu method is generally used for this purpose. Capillary electrophoresis (CE) and instrumental chromatographic techniques, high performance liquid chromatography (HPLC), ultra-high performance liquid chromatography (UHPLC) and gas chromatography (GC) can be used to determine individual phenolic compounds such as resveratrol (Prazeres *et al.*, 2021)

Extraction from the food or beverage sample is the first step to determine resveratrol. Solid phase extraction (SPE), solid phase micro-extraction (SPME), liquid-liquid extraction (LLE), micro-extraction by packed sorbent, stir bar sorptive extraction (SBSE) and dispersive liquid-liquid micro-extraction (DLLME) are the main techniques used for resveratrol. Wine is a complex matrix and therefore in some cases needs to be prepared properly before analysis. This step is called as derivatization. In this way, the sample could have increased volatility, improved sensitivity and separation properties (Fabjanowicz *et al.*, 2018). Acetic anhydride, dansyl chloride, ethylchloroformate, hexamethyldisilazane (HMDS) and bis(trimethylsilyl)- trifluoroacetamide (BSTFA) are most widely used derivatization agents for resveratrol determination (Cacho *et al.*, 2013; Preti *et al.*, 2016; Rodríguez-Cabo *et al.*, 2016; di Fabio *et al.*, 2020; Prazeres *et al.*, 2021).

High performance liquid chromatography has some advantages in terms of reliability, high sensitivity and robustness. Reverse phase columns composed of a C18 stationary phase are commonly used. The solvent system includes an aqueous and an organic phase (generally methanol or acetonitrile). HPLC methods combined with electrochemical, UV and fluorescence detectors are generally regarded as highly effective analytical tools and widely used in resveratrol research. For quantification, diode array detector (DAD) is commonly preferred. Recently, there has been an increasing usage of mass spectrometry (MS) for structural elucidation and quantification (Valls *et al.*, 2009; de Villiers *et al.*, 2012; Gutiérrez-Escobar *et al.*, 2021). Determination of resveratrol can be easily achieved by direct injection into the HPLC system but sometimes extraction/derivatization procedures needs to be used. SPE or LLE as extraction methods and dansyl chloride as derivatization agent are generally used in that cases (Fabjanowicz *et al.*, 2018).

UHPLC is a technique where separation is carried out in columns packed with particles of 2.5 µm or less and at elevated (>400 bar) pressures. The use of relatively short columns with small particles provide high speed and efficient separation compared to conventional HPLC system (Wu and Clausen, 2007; Kalili and de Villiers, 2011). This technique has been also used to determine phenolics and resveratrol in wine (Boutegrabet *et al.*, 2011; Lambert *et al.*, 2015).

The use of liquid chromatography is advantageous in terms of simplicity and good precision of the results. However, there is a need to use high-purity and high-cost organic solvents which usually end up as waste products at the end of the analysis. GC use could reduce the amount of organic waste. Also, GC is a good and sensitive technique to separate phenolic compounds (Prazeres *et al.*, 2021). When GC is used to determine resveratrol, a chemical derivatization step is necessary to obtain volatile and thermostable derivatives before analysis because resveratrol is a non-volatile compound. With the use of chemicals, like ethyl and methyl chloroformate, diazomethane and dimethyl sulfoxide in combination with methyl iodate, methyl or ethyl esters of phenolics can be obtained. Trimethylsilyl family compounds like BSTFA, can also be used for this purpose. The most common used columns in GC to quantify phenolics are fused silica capillaries (30 m length, 25–32 µm internal diameters) and stationary phase particle size of 0.25 µm. Flame ionization detector (FID) and MS are generally coupled with GC, and these methods are widespread for the detection of phenolics. The sensitivity and selectivity of GC can be increased when used in combination with MS. When GC-MS is used, the limits of detection and quantification are lower than of HPLC-MS (Fan *et al.*, 2011; Khoddami *et al.*, 2013; Prazeres *et al.*, 2021).

CE is a technique performed with a solution of ions in a narrow capillary column (Khoddami *et al.*, 2013). It can be used as an alternative to HPLC methods. High efficiency, speed, versatility and less solvent use are the main advantages of CE. Capillaries used in this method are easy to wash (Valls *et al.*, 2009). Also, in contrast to GC, it can be applied for thermally unstable compounds. However, lower sensitivity and robustness than HPLC are the drawbacks of CE. LLE and SPE could be used to concentrate the samples and to increase the sensitivity. Some other strategies, such as sample online pre-concentration (LVSS, large-volume sample stacking) are also significant in terms of enhancing sensitivity without loss of the separation efficiency (de Villiers *et al.*, 2012; Fabjanowicz *et al.*, 2018). In addition, CE coupled with MS could increase the sensitivity (Valls *et al.*, 2009). Capillary zone electrophoresis (CZE) and micellar electrokinetic chromatography (MEKC) have different separation modes and have been reported to use for resveratrol analysis. In CZE, generally, phosphate or borate-based electrolytes are preferred. DAD, UV and electrochemical detection (ED) are used in conjunction with CE for the determination of resveratrol (Fan *et al.*, 2011).

Table 2 shows resveratrol levels in different wines and the methods applied for its determination.

CONCLUDING REMARKS

Resveratrol is a phenolic compound with significant bioactive properties and therefore research has been focused on enhancing its concentration in foods. Grape berries contain resveratrol naturally and during winemaking it is also formed and extracted into the wine. There are several factors that affect the presence and quantity of resveratrol in wine. These factors can be divided into some groups, such as viticultural practices, pre-fermentation treatments, fermentation stage and post-fermentation operations.

Research has demonstrated that the levels of stilbenes depend on the climate conditions, grapevine varieties, vinification approaches and stress factors. In general, warmer and dry climates were found to be more favorable in terms of resveratrol accumulation. As resveratrol is a phytoalexin, its induction could be positively affected by stress factors, such as UV-C treatment and pathogen infection, like *Botrytis cinerea*. Some biostimulants, like methyl jasmonate have been used as a pre-harvest strategy; the combined use with UV-C promoted an increase in resveratrol concentration. However, the grapevine variety plays an important role in terms of getting a desirable change in resveratrol content for all applications.

Post-harvest UV-C, ozone and ultrasound treatments, some nitrogen sources or biostimulants have been used as different strategies to enhance resveratrol concentration in wine. These applications could have an effect in triggering some enzymes that are responsible for biosynthesis pathways. Among them, UV-C treatment has become more prominent. The resveratrol content can potentially increase with the use of UV-C-treated grapes in winemaking. Ultrasound and ozone applications could demonstrate the same effect. However, it should be noted that ozone usage could harm the quality of grapes. Thermovinification before alcoholic fermentation could also enhance the level of resveratrol by increasing the solubility of phenolic compounds.

Alcoholic fermentation is one of the most significant steps in winemaking. Besides having suitable oenological characteristics, the selected yeast strain should have appropriate phenolic adsorption capacity, β-glucosidase enzyme activity and ethanol-producing activity in order to increase resveratrol content in wine. The use of yeasts with higher ethanol producing capacity could be advantageous as ethanol increases the solubility of resveratrol.

Autochthonous yeast strains and their combinations have been found to be more effective than the commercial starters. Adding a pectolytic enzyme during maceration could promote the activity of yeast, as well. Some biotechnological approaches, like transferring the genes involved in resveratrol biosynthesis in the yeasts or tailoring the yeast strains to produce specific enzymes such as β-glucosidase, are innovative strategies in this field. However, one should bear in mind that the use of transgenic microorganisms is subjected to legal regulations. In addition, extended maceration, increasing the quantity of solid parts (skins and stems) in the must, and malolactic fermentation could also contribute to increased resveratrol levels in wine.

After fermentation, the concentration of phenolic compounds tends to decrease due to precipitation with proteins. Cold stabilization and filtration can cause a loss in resveratrol content. During aging, the resveratrol content mainly depends on grapevine variety. However, extended aging could cause a decrease in resveratrol level.

Table II

Resveratrol levels found in different wines and the determination methods

Grapevine varieties	**Region**	**Method for identifying/quantifying resveratrol**	**Level of resveratrol**	**References**
'Montepulciano D'Abruzzo', 'Dolcetto D'Alba', 'Primitivo di Manduria', 'Syrah'	Italy	HPLC (LLE, fluorimetric detection)	0.72-5.36 mg/L	Preti *et al*. (2016)
'Cencibel', 'Garnacha', 'Merlot', 'Monastrell', 'Syrah', 'Tempranillo', 'Tintilla de Rota'	Spain	UHPLC-MS/MS (photodiode array (PDA) detector)	1.38-1.81 mg/L	Guerrero *et al. (*2020)
'Barbera' and 'Croatina' (blend)	Italy	HPLC-DAD	0.89 mg/L	Rocchetti *et al*. (2021)
Regent wines	Poland	HPLC (UV spectrometric detector)	0.82-11.13 mg/L	Bednarska *et al*. (2019)
Red ('Pinot Noir', 'Merlot', 'Cabernet Sauvignon', 'Fetească Neagră'), white ('Sauvignon Blanc', 'Grasă de cotnari') and rose ('Merlot Rose') wines	Romania	RP-HPLC-DAD	0.03-6.17 mg/L	Craciun and Gutt (2020)
'Pinot noir'	France	UHPLC (PDA detector)	0.53-5.08 mg/L	Boutegrabet *et al*. (2011)
Red, rose and white wines	Poland	GC-MS (ultrasound-assisted solvent extraction)	2.28-5.09 µg/mL (red wines) 2.21-2.32 µg/mL (rose wines) 2.20-2.51 µg/mL (white wines)	Robles *et al*. (2019)
Red ('Tempranillo') and white (mixture of 'Treixadura' and 'Torrontés') wines	Spain	GC-MS (dispersive liquid-liquid microextraction)	<100 ng/mL (white wines), 160-2620 ng/mL (red wines)	Rodríguez-Cabo *et al*. (2016)
Red wines ('Foch', 'St. Croix', 'Frontenac', 'Vincent', 'Marechal Foch'),	USA	GC-MS (solid-phase microextraction)	12.72-851.9 µg/L	Cai *et al*. (2009)
Dry red (Huaxia Great Wall, 'Merlot' France, Zhangyu, Dynasty) and medium dry white (Dynasty) wines	China	CE-ED	1.084-3.1561 mg/L	Gao *et al*. (2002)
Red and white wines	Australia	CZE (UV detection)	2.11-4.46 mg/L (red wines) 1.07-1.98 mg/L (white wines)	Spanila *et al*. (2005)

Resveratrol in wine can be determined with different analytical tools. The most commonly used are chromatographic techniques. Research in this field is mainly focused on the use of HPLC and GC with different detectors in order to determine resveratrol content in wine.

CONFLICTS OF INTEREST: The authors declare no conflict of interest.

REFERENCES

Adrian M., Jeandet P., Breuil A.C., Levite D., Debord S., Bessis R., 2000. Assay of resveratrol and derivative stilbenes in wines by direct injection high performance liquid chromatography. *Am. J. Enol. Vitic.*, **51**, 37-41.

Aggarwal B.B., Shishodia S., 2005. Resveratrol in health and disease. 712 p. CRC Press Taylor & Francis Group.

Atanacković M., Petrović A., Jović S., Bukarica L.G., Bursać M., Cvejić J., 2012. Influence of winemaking techniques on the resveratrol content, total phenolic content and antioxidant potential of red wines. *Food Chem.,* **131**, 513–518.

Averilla J.N., Oh J., Wu Z., Liu K.H., Jang C.H., Kim H.J., Kim J.S., Kim, J.S., 2019. Improved extraction of resveratrol and antioxidants from grape peel using heat and enzymatic treatments. *J. Sci. Food Agric.*, **99**, 4043-4053.

Barlass M., MillerR.M., DouglasT.J., 1987. Development of methods for screening grapevines forresistance to infection by downy mildewIIResveratrol production. *Am. J. Enol. Vitic.*, **38**, 65-68.

Basholli-Salihu M., Schuster R., Mulla D., Praznik W., Viernstein H., Mueller M., 2016. Bioconversion of piceid to resveratrol by selected probiotic cell extracts. *Bioprocess Biosyst. Eng.*, **39**, 1879-1885.

Bavaresco L., Lucini L., Busconi M., Flamini R., de Rosso M., 2016. Wine resveratrol: From the ground up. *Nutrients,* **8**, 222.

Bay Karabulut A., 2008. Resveratrol and its effects. *Turkey Clin. J. Med. Sci.*, **28**, 166-169.

Bednarska S., Dabrowa A., Kisala J., Kasprzyk I., 2019. Antioxidant properties and resveratrol content of Polish Regent wines from Podkarpacie region. *Czech J. Food Sci.*, **37**, 252-259.

Boutegrabet L., Fekete A., Hertkorn N., Papastamoulis Y., Waffo-Téguo P., Mérillon J.M., Jeandet P., Gougeon R.D., Schmitt-Kopplin P., 2011. Determination of stilbene derivatives in Burgundy red wines by ultra-high-pressure liquid chromatography. *Anal. Bioanal. Chem.*, **401**, 1513-1521.

Burns J., Yokota T., Ashihara H., Lean M.E.J., Crozie A., 2002. Plant foods and herbal sources of resveratrol. *J. Agric. Food Chem*., **50**, 3337–3340.

Cacho J.I., Campillo N., Viñas P., Hernández-Córdoba M., 2013. Stir bar sorptive extraction with gas chromatography–mass spectrometry for the determination of resveratrol, piceatannol and oxyresveratrol isomers in wines. *J. Chromatogr. A*, **1315**, 21-27.

Cai L., Koziel J.A., Dharmadhikari M., van Leeuwen J.H., 2009. Rapid determination of trans-resveratrol in red wine by solid-phase microextraction with on-fiber derivatization and multidimensional gas chromatography–mass spectrometry. *J. of Chromatogr. A*, **1216**, 281-287.

Cantos E., Espín J.C., Tomás-Barberán F.A., 2001. Postharvest induction modeling method using UV irradiation pulses for obtaining resveratrol-enriched table grapes: a new "functional" fruit? *J. Agric. Food Chem.*, **49**, 5052-5058.

Cantos E., Espín J.C., Tomás-Barberán F.A, 2002. Postharvest stilbene-enrichment of red and white table grape varieties using UV-C irradiation pulses. *J. Agric. Food Chem.*, **50**, 6322-6329.

Cantos E., Espín J.C., Fernández M.J., Oliva J., Tomás-Barberán F.A., 2003. Postharvest UV-C-irradiated grapes as a potential source for producing stilbene-enriched red wines. *J. Agric. Food Chem.*, **51**, 1208-1214.

Caridi A., Sidari R., Maria A., Teresa G., Pellicanò M., Sicari V., Zappia C., Poiana M., 2017. Test of four generations of *Saccharomyces cerevisiae* concerning their effect on antioxidant phenolic compounds in wine. *Eur. Food Res. Technol.*, **243**, 1287–1294.

Castaldo L., Narváez A., Izzo L., Graziani G., Gaspari A., Di Minno G., Ritieni A., 2019. Red wine consumption and cardiovascular health. *Molecules,* **24**, 3626.

Cheng L., Yan B., Chen K., Jiang Z., Zhou C., Cao J., Qian W., Li J., Sun L., Ma J., Ma Q., Sha H., 2018. Resveratrol-induced downregulation of NAF-1 enhances the sensitivity of pancreatic cancer cells to gemcitabine via the ROS/Nrf2 signaling pathways. *Oxid. Med. Cell. Longev.*, **2018**, 9482018.

Christenson J., Whitby S.J., Mellor D., Thomas J., McKune A., Roach P.D., Naumovski N., 2016. The effects of resveratrol supplementation in overweight and obese humans: A systematic review of randomized trials. *Metab. Syndr. Relat. Disord.*, **14**, 323–333.

Clare S.S., Skurray G.R., Shalliker R.A., 2005. Effect of yeast strain selection on the concentration of *cis*- and *trans*-resveratrol and resveratrol glucoside isomers in wine. *Aust. J. Grape Wine Res*., **11**, 9–14.

Claus H., Mojsov K., 2018. Enzymes for wine fermentation: Current and perspective applications. *Fermentation,* **4**, 1–19.

Counet C., Callemien D., Collin S., 2006. Chocolate and cocoa: New sources of *trans*-resveratrol and *trans*-piceid. *Food Chem.*, **98**, 649–657.

Craciun A.L., Gutt G., 2020. Determination of trans-resveratrol in romanian commercial wines by reversed-phase HPLC. *Food and Environment Safety*, **19**, 323 – 331.

De Villiers A., Albert P., Tredoux A.G., Nieuwoudt H.H., 2012. Analytical techniques for wine analysis: An African perspective; a review. *Anal. Chim. Acta*, **730**, 2-23.

Di Fabio E., Incocciati A., Palombarini F., Boffi A., Bonamore A., Macone A., 2020. Ethylchloroformate derivatization for GC–MS Analysis of resveratrol isomers in red Wwine. *Molecules*, **25**, 4603.

Ector B.J., Magee J.B., Hegwood C.P., Coign M.J., 1996. Resveratrol concentration in muscadine berries, juice, pomace, purees, seeds, and wines. *Am. J. Enol. Vitic.*, **47**, 57-62.

Elshaer M., Chen Y., Wang X.J., Tang X., 2018. Resveratrol: An overview of its anti-cancer mechanisms. *Life Sci.*, **207**, 340–349.

Fabjanowicz M., Płotka-Wasylka J., Namieśnik J., 2018. Detection, identification and determination of resveratrol in wine. Problems and challenges. *TrAC Trends Analyt. Chem.*, **103**, 21-33.

Fan E., Lin S., Du D., Jia Y., Kang L., Zhang K., 2011. Current separative strategies used for resveratrol determination from natural sources. *Anal. Methods*, **3,** 2454-2462.

Fernández-Marín M.I., Guerrero R.F., Puertas B., García-Parrilla M.C., Collado I.G., Cantos-Villar E., 2013. Impact of preharvest and postharvest treatment combinations on increase of stilbene content in grape. *OENO One*, **47**, 203-212.

Fernández-Marín M.I., Puertas B., Guerrero R.F., García-Parrilla M.C., Cantos-Villar E., 2014. Preharvest methyl jasmonate and postharvest UVC treatments: increasing stilbenes in wine. *J. Food Sci.*, **79**, 310-317.

Figueiredo E.A.D., Alves N.F.B., Monteiro M.M.D.O., Cavalcanti C.D.O., Silva T.M.S., Silva T.M.G., Braga V.D.A., Oliveira E.D.J., 2017. Antioxidant and antihypertensive effects of a chemically defined fraction of syrah red wine on spontaneously hypertensive rats. *Nutrients*, **9**, 10–23.

Filardo S., Di Pietro M., Mastromarino P., Sessa R., 2020. Therapeutic potential of resveratrol against emerging respiratory viral infections. *Pharmacol. Ther.*, **214**, 107613.

Flamini R., Zanzotto A., de Rosso M., Lucchetta G., Vedova A.D., Bavaresco L., 2016. Stilbene oligomer phytoalexins in grape as a response to *Aspergillus carbonarius* infection. *Physiol. Mol. Plant Pathol.*, **93,** 112–118.

Flores G., Del Castillo M.L.R., 2016. New procedure to obtain polyphenol-enriched grapes based on the use of chemical elicitors. *Plant Foods Hum. Nutr.*, **71**, 239-244.

Franco M.A., Coloru G.C., Del Caro A., Emonti G., Farris G.A., Manca G., Massa T.G., Pinna G., 2002. Variability of resveratrol (3, 5, 4′-trihydroxystilbene) content in relation to the fermentation processes by *Saccharomyces cerevisiae* strains. *Eur. Food Res. Technol.*, **214**, 221–225.

Fu Q., Cui Q., Yang Y., Zhao X., Song X., Wang G., Bai L., Chen S., TianY., Zou Y., Li L., Yue G., Jia R., Yin Z., 2018. Effect of resveratrol dry suspension on immune function of piglets. *Evid. Based Complement. Alternat. Med.*, 10.

Gaensly F., Agustini B.C., da Silva G.A., Picheth G., Bonfim T.M.B., 2015. Autochthonous yeasts with β-glucosidase activity increase resveratrol concentration during the alcoholic fermentation of *Vitis labrusca* grape must. *J. Funct. Foods,* **19**, 288–295.

Gao L., Chu Q., Ye J., 2002. Determination of trans-Resveratrol in wines, herbs and health food by capillary electrophoresis with electrochemical detection. *Food Chem.*, **78**, 255-260.

Garde-Cerdán T., Portu J., López R., Santamaría P., 2015. Effect of foliar applications of proline, phenylalanine, urea, and commercial nitrogen fertilizers on stilbene concentrations in Tempranillo musts and wines. *Am. J. Enol. Vitic.*, **66**, 542-547.

Geana E.I., Dinca O.R., Ionete R.E., Artem V., Niculescu V.C., 2015. Monitoring *trans*-resveratrol in grape berry skins during ripening and in corresponding wines by HPLC. *Food Technol. Biotechnol.*, **53**, 73–80.

Gerogiannaki-Christopoulou M., Athanasopoulos P., Kyriakidis N., Gerogiannaki I.A., Spanos M., 2006. *trans*-Resveratrol in wines from the major Greek red and white grape varieties. *Food Control,* **17**, 700–706.

Goldberg D.M., Yan J., Ng E., Diamandis E.P., Karumanchiri A., Soleas G., Waterhouse A.L., 1995. A global survey of *trans*-resveratrol concentrations in commercial wines. *Am. J. Enol. Vitic.*, **46**, 159-165.

González-Barrio R., Beltrán D., Cantos E., GilM.I., Espín J.C., Tomás-Barberán F.A., 2006. Comparison of ozone and UV-C treatments on the postharvest stilbenoid monomer, dimer, and trimer induction in var. 'Superior' white table grapes. *J. Agric. Food Chem.*, **54**, 4222-4228.

González-Barrio R., Vidal-Guevara M.L., Tomás-Barberán F.A., Espín J.C., 2009. Preparation of a resveratrol-enriched grape juice based on ultraviolet C-treated berries. Innov. *Food Sci. Emerg. Technol.*, **10**, 374–382.

González-Candelas L., Gil J.V., Lamuela-Raventos R.M., Ramón D., 2000. The use of transgenic yeasts expressing a gene encoding a glycosyl-hydrolase as a tool to increase resveratrol content in wine. *Int. J. Food Microbiol.*, **59**, 179-183.

Grieco F., Carluccio M.A., Giovinazzo G., 2019. Autochthonous *Saccharomyces cerevisiae* starter cultures enhance polyphenols content, antioxidant activity, and anti-inflammatory response of Apulian red wines. *Foods*, **8**, 453.

Guerrero R.F., Puertas B., Fernández M.I., Piñeiro Z., Cantos-Villar E., 2010a. UVC-treated skin-contact effect on both white wine quality and resveratrol content. *Food Res. Int.*, **43**, 2179–2185.

Guerrero R.F., Puertas B., Jiménez M.J., Cacho J., Cantos-Villar E., 2010b. Monitoring the process to obtain red wine enriched in resveratrol and piceatannol without quality loss. *Food Chem.*, **122**, 195-202.

Guerrero R.F., Valls-Fonayet J., Richard T., Cantos-Villar E., 2020. A rapid quantification of stilbene content in wine by ultra-high pressure liquid chromatography–mass spectrometry. *Food Control*, **108**, 106821.

Guld Z.S., Rácz A., Tima H., Kállay M., Nyitrainé Sárdy D., 2019. Effects of aging in oak barrels on the *trans*-resveratrol and anthocyanin concentration of red wines from Hungary. *Acta Aliment*., **48**, 349–357.

Gutiérrez-Escobar R., Aliaño-González M.J., Cantos-Villar E., 2021. Wine polyphenol content and its influence on wine quality and properties: A review. *Molecules*, **26**, 718.

Hasan M.M., Bae H., 2017. An overview of stress-induced resveratrol synthesis in grapes: Perspectives for resveratrol-enriched grape products. *Molecules,* **22**, 294.

Hasan M.M., Baek K.H., 2013. Induction of resveratrol biosynthesis in grape skins and leaves by ultrasonication treatment. *Korean J. Hortic. Sci. Technol.*, **31**, 496–502.

Hasan M.M., Yun H.K., Kwak E.J., Baek K.H., 2014. Preparation of resveratrol-enriched grape juice from ultrasonication treated grape fruits. *Ultrason. Sonochem*., **21**, 729–734.

Hernández T., Estrella I., Pérez-Gordo M., Alegría E.G., Tenorio C., Ruiz-Larrrea F., Moreno-Arribas M.V, 2007. Contribution of malolactic fermentation by *Oenococcus oeni* and *Lactobacillus plantarum* to the changes in the nonanthocyanin polyphenolic composition of red wine. *J. Agric. Food Chem.*, **55**, 5260-5266.

Hoang T., 2021. An approach of fatty acids and resveratrol in the prevention of COVID-19 severity. *Phyther. Res.*, **35**, 2269-2273.

Hurst W.J., Glinski J.A., Miller K.B., Apgar J., Davey M.H., Stuart D.A., 2008. Survey of the *trans*-resveratrol and *trans*-piceid content of cocoa-containing and chocolate products. *J. Agric. Food Chem.*, **56**, 8374–8378.

Irnidayanti Y., Sutiono D.R., 2019. Tempeh & soybean seed coat: The alternative sources of *trans*-resveratrol as neuroprotective agents. *Int. J. Morphol.*, **37**, 1164–1171.

Jang M., Sheu S., Wan, C., Yeh Y., Sung K., 2009. Optimization analysis of the experimental parameters on the extraction process of Propolis. *Lect. Notes Eng. Comput. Sci.*, **2175**, 1295–1299.

Jeandet P., Delaunois B., Aziz A., Donnez D., Vasserot Y., Cordelier S., Courot E., 2012. Metabolic engineering of yeast and plants for the production of the biologically active hydroxystilbene, resveratrol. *J. Biomed. Biotechnol.,* **2012**, 579089.

Kalili K.M., de Villiers A., 2011. Recent developments in the HPLC separation of phenolic compounds. *J. Sep. Sci.,* **34**, 854-876.

Kammerer D., Carle R., 2009. Evolution of polyphenols during vinification and wine storage. *Funct. Plant Sci. Biotechnol.,* **3**, 46–56.

Keskin N., Noyan T., Kunter B., 2009. Health from grape with rResveratrol. *Turkey Clin. J. Med. Sci.,* **29**, 1273–1279.

Khoddami A., Wilkes M.A., Roberts T.H., 2013. Techniques for analysis of plant phenolic compounds. *Molecules,* **18**, 2328-2375.

Kontaxakis E., Trantas E., Ververidis F., 2020. Resveratrol: A fair race towards replacing sulfites in wines. *Molecules,* **25**, 2378.

Kostadinović S., Wilkens A., Stefova M., Ivanova V., Vojnoski B., Mirhosseini H., Winterhalter P., 2012. Stilbene levels and antioxidant activity of Vranec and Merlot wines from Macedonia: Effect of variety and enological practices. *Food Chem.,* **135**, 3003–3009.

Lambert M., Meudec E., Verbaere A., Mazerolles G., Wirth J., Masson G., Cheynier V., Sommerer N., 2015. A high-throughput UHPLC-QqQ-MS method for polyphenol profiling in rosé wines. *Molecules,* **20**, 7890-7914.

Li Y., Zhu W., Tao J.P., Xin P., Liu M.Y., Li J.B., Wei M., 2013. Resveratrol protects cardiomyocytes from oxidative stress through SIRT1 and mitochondrial biogenesis signaling pathways. *Biochem. Biophys. Res. Commun.,* **438**, 270–276.

Lin S.C., Ho C.T., Chuo W.H., Li S., Wang T.T., Lin C.C., 2017. Effective inhibition of MERS-CoV infection by resveratrol. *BMC Infect. Dis.,* **17**, 1–10.

Liu W., Liu C., Yang C., Wang L., Li S., 2010. Effect of grape genotype and tissue type on callus growth and production of resveratrols and their piceids after UV-C irradiation. *Food Chem.,* **122**, 475–481.

Malaguarnera L., 2019. Influence of resveratrol on the immune response. *Nutrients,* **11**, 1–24.

Marinella M.A., 2020. Indomethacin and resveratrol as potential treatment adjuncts for SARS-CoV-2/COVID-19. *Int. J. Clin. Pract.,* **74**, 25–27.

Mattivi F., Vrhovsek U., Malacarne G., Masuero D., Zulini L., Stefanini M., Mose C., Velasco R., Guella G., 2011. Profiling of resveratrol oligomers, important stress metabolites, accumulating in the leaves of hybrid *Vitis vinifera* (Merzling × Teroldego) genotypes infected with *Plasmopara viticola*. *J. Agric. Food Chem.,* **59**, 5364–5375.

Moreno-Labanda J.F., Mallavia R., Pérez-Fons L., Lizama V., Saura D., Micol V., 2004. Determination of piceid and resveratrol in Spanish wines deriving from Monastrell (*Vitis vinifera* L.) grape variety. *J. Agric. Food Chem.,* **52**, 5396–5403.

Naiker M., Anderson S., Johnson J.B., Mani J.S., Wakeling L., Bowry V., 2020. Loss of *trans*-resveratrol during storage and ageing of red wines. *Aust. J. Grape Wine Res.,* **26**, 385–387.

Pannu N., Bhatnagar A., 2019. Resveratrol: from enhanced biosynthesis and bioavailability to multitargeting chronic diseases. *Biomed. Pharmacother.,* **109,** 2237–2251.

Pappalardo G., Di Vita G., Zanchini R., La Via G., D'Amico M., 2019. Do consumers care about antioxidants in wine? The role of naturally resveratrol-enhanced wines in potential health-conscious drinkers' preferences. *Br. Food J.,* **122,** 2689–2705.

Pastor R.F., Restani P., Di Lorenzo C., Orgiu F., Teissedre P.L., Stockley C., RufJ. C., Quini C.I., Garcìa Tejedor N., Gargantini R., Aruani C., Prieto S., Murgo M., Videla R., Penissi A., Iermoli R.H., 2019. Resveratrol, human health and winemaking perspectives. *Crit. Rev. Food Sci. Nutr.,* **59**, 1237–1255.

Pérez-Navarro J., García Romero E., Gómez-Alonso S., Izquierdo Cañas P.M., 2018. Comparison between the phenolic composition of Petit Verdot wines elaborated at different maceration/fermentation temperatures. *Int. J. Food Prop.,* **21**, 996-1007.

Pezet R., Cuenat P., 1996. Resveratrol in wine: extraction from skin during fermentation and post-fermentation standing of must from Gamay grapes. *Am. J. Enol. Vitic.,* **47**, 287-290.

Poklar Ulrih N., Opara R., Skrt M., Košmerl T., Wondra M., Abram V., 2020. Part I. Polyphenols composition and antioxidant potential during 'Blaufränkisch' grape maceration and red wine maturation, and the effects of *trans*-resveratrol addition. *Food Chem. Toxicol.,* **137**, 111-122.

Poussier M., Guilloux-Benatier M., Torres M., Heras E., Adrian M., 2003. Influence of different maceration techniques and microbial enzymatic activities on wine stilbene content. *Am. J. Enol. Vitic.,* **54**, 261-266.

Prazeres E.S., dos Santos M.B., Barreto A.D.A., Coutinho J.P., da Silva E.G.P., Melo S.C., de Jesus R.M., Lôbo I.P., 2021. Use of hexamethyldisilazane as a silanizing agent in microwave-assisted derivatization for determining phenolic compounds in wine by gas chromatography. *Microchem. J.,* **161**, 105785.

Preti R., Vieri S., VinciG., 2016. Biogenic amine profiles and antioxidant properties of Italian red wines from different price categories. *J. Food Compos. Anal.,* **46**, 7-14.

Ramdani L.H., Bachari K., 2020. Potential therapeutic effects of resveratrol against SARS-CoV-2. *Acta Virol.,* **64**, 276–280.

Rathburn H., Bell P., Cook S., Mayberry D.D., Geye E., Goodric R., 2020. A statistical analysis of *trans*-resveratrol in grape cane from ten varieties of cultivated wine grapes (*Vitis* spp.). *Texas J. Sci.,***72**.

Rayne S., Karacabey E., Mazza G., 2008. Grape cane waste as a source of *trans*-resveratrol and *trans*-viniferin: High-value phytochemicals with medicinal and anti-phytopathogenic applications. *Ind. Crops Prod.,* **27**, 335–340.

Robles A.D., Fabjanowicz M., Płotka-Wasylka J., Konieczka P., 2019. Organic acids and polyphenols determination in Polish wines by ultrasound-assisted solvent extraction of porous membrane-packed liquid samples. *Molecules,* **24,** 4376.

Rocchetti G., Ferrari F., Trevisan M., Bavaresco L., 2021. Impact of climatic conditions on the resveratrol concentration in blend of *Vitis vinifera* L. cvs. Barbera and Croatina Grape Wines. *Molecules,* **26,** 401.

Rodríguez-Cabo T., Rodríguez I., Ramil M., Silva A., Cela R., 2016. Multiclass semi-volatile compounds determination in wine by gas chromatography accurate time-of-flight mass spectrometry. *J. Chromatogr. A,* **1442**, 107-117.

Roldán A., Palacios V., Caro I., Pérez L., 2010. Evolution of resveratrol and piceid contents during the industrial winemaking process of sherry wine. *J. Agric. Food Chem.,* **58,** 4268–4273.

Salehi B., Mishra A.P., Nigam M., Sener B., Kilic M., Sharifi-RadM., Fokou P.V.T., Martins N., Sharifi-Rad J., 2018. Resveratrol: A double-edged sword in health benefits. *Biomedicines,* **6**, 1–20.

Sartor S., Toaldo I.M., Panceri C.P., Caliari V., Luna A.S., de Gois J.S., Bordignon-Luiz M.T., 2019. Changes in organic acids, polyphenolic and elemental composition of rosé sparkling wines treated with mannoproteins during over-lees aging. *Food Res. Int.*, **124**, 34–42.

Segade S.R., Vincenzi S., Giacosa S., Rolle L., 2019. Changes in stilbene composition during postharvest ozone treatment of 'Moscato bianco'winegrapes. *Food Res. Int.*, **123**, 251-257.

Sener H., Yildirim H.K., 2013. Influence of different maceration time and temperatures on total phenols, colour and sensory properties of Cabernet Sauvignon wines. *Food Sci. Technol. Int*., **19**, 523–533.

ShrikantaA., Kumar A., Govindaswamy V., 2015. Resveratrol content and antioxidant properties of underutilized fruits. *J. Food Sci. Technol.*, **52**, 383–390.

Sinha D., Sarkar N., Biswas J., Bishayee A., 2016. Resveratrol for breast cancer prevention and therapy: Preclinical evidence and molecular mechanisms. S*emin. Cancer Biol.*, **40**, 209–232.

Sorrentino A., Boscaino F., Cozzolino R., Volpe M.G., Ionata E., La CaraF., 2012. Autochthonous fermentation starters for the production of Aglianico wines. *Chem. Eng. Trans*., **27**, 211–216.

Spanilá M., Pazourek J., Farková M., Havel J., 2005. Optimization of solid-phase extraction using artificial neural networks in combination with experimental design for determination of resveratrol by capillary zone electrophoresis in wines. *J. Chromatogr. A*, **1084**, 180-185.

Sun B., Ferrão C., Spranger M. I., 2003. Effect of wine style and winemaking technology on resveratrol levels in wines. *Ciência Téc. Vitiv.*, **18**, 77-91.

Sun B., Ribes A.M., Leandro M.C., Belchior A.P., SprangerM I., 2006. Stilbenes: quantitative extraction from grape skins, contribution of grape solids to wine and variation during wine maturation. *Anal. Chim. Acta*, **563**, 382-390.

Sun C., Wu Z., Wang Z., Zhang H., 2015. Effect of ethanol/water solvents on phenolic profiles and antioxidant properties of Beijing propolis extracts. *Evid. Based Complement. Altern. Med.*, **2015**, 595393.

Surguladze M.A., Bezhuashvili M.G., 2017. Impact of wine technology on the variability of resveratrol and piceids in Saperavi (*Vitis vinifera* L.). *Ann. Agrar. Sci*., **15**, 137–140.

Suzuki M., Nakabayashi R., Ogata Y., Sakurai N., Tokimatsu T., Goto S., Suzuki M., Jasinski M., Martinoia E., Otagaki S., Matsumoto S., Saito K., Shiratake K., 2015. Multiomics in grape berry skin revealed specific induction of the stilbene synthetic pathway by ultraviolet-C irradiation. *Plant Physiol.*, **168**, 47-59.

Szkudelska K., Szkudelski T., 2010. Resveratrol, obesity and diabetes. *Eur. J. Pharmacol*., **635**, 1–8.

Tao Y., García J.F., Sun D.W., 2014. Advances in wine aging technologies for enhancing wine quality and accelerating wine aging process. *Crit. Rev. Food Sci. Nutr.*, **54**, 817–835.

Tian B., Liu J., 2020. Resveratrol: a review of plant sources, synthesis, stability, modification and food application. *J. Sci. Food Agric.*, **100**, 1392–1404.

Tokusoglu O., Unal M.K., Yemis F., 2005. Determination of the phytoalexin resveratrol (3,5,4′-Trihydroxystilbene) in peanuts and pistachios by High-Performance Liquid Chromatographic Diode Array (HPLC-DAD) and Gas Chromatography-Mass Spectrometry (GC-MS). *J. Agric. Food Chem.*, **53**, 5003–5009.

Tomić A., Zulj M.M., Andabaka Z., Tomaz I., Jakobović S., Jeromel A., 2018. Influence of pectolytic enzymes and selected yeast strains on the chemical composition of blackberry wines. *Polish J. Food Nutr. Sci.*, **68**, 263–272.

Valls J., Millán S., Martí M.P., Borràs E., Arola L., 2009. Advanced separation methods of food anthocyanins, isoflavones and flavanols. *J. of Chromatogr. A*, **1216**, 7143-7172.

Vernhet A., 2019. Red wine clarification and stabilization. *In: Red Wine Technology*. 237-251. Morata A. (ed.), Academic Press, Madrid.

Vries K., de Strydom M., Steenkamp V., 2018. Bioavailability of resveratrol: Possibilities for enhancement. *J. Herb. Med.*, **11**, 71–77.

Vuong Q.V., 2017. Utilisation of bioactive compounds from agricultural and food waste. 405 p. CRC Press, Boca Raton, FL.

Wang Y., Halls C., Zhang J., Matsuno M., Zhang Y., Yu O., 2011. Stepwise increase of resveratrol biosynthesis in yeast *Saccharomyces cerevisiae* by metabolic engineering. *Metab. Eng.*, **13**, 455–463.

Weiskirchen S., Weiskirchen R., 2016. Resveratrol: How much wine do you have to drink to stay healthy? *Adv. Nutr. An Int. Rev. J.*, **7**, 706–718.

Wu N., Clausen A.M., 2007. Fundamental and practical aspects of ultrahigh pressure liquid chromatography for fast separations. *J. Sep. Sci.*, **30**, 1167-1182.

Yunoki K., Yasui Y., Naito A., Masanori K., Ohnishi M., 2001. Comparative analysis of concentration of *trans*- and *cis*-resveratrol in must and wine from eleven different grapevines grown in Hokkaido, Northern Japan. *J. Oleo Sci.*, **50**, 895–903.

Zhang K., Li W., Ju Y., Wang X., Sun X., Fang Y.,Chen K., 2021. Transcriptomic and metabolomic basis of short-and long-term post-harvest UV-C application in regulating grape berry quality development. *Foods*, **10**, 625.