Review paper
10.7251/AGRENG2202110S
UDC 634.8:543.645

RESVERATROL IN GRAPES - BENEFITS AND POTENTIAL USE

Aleksandra ŠUŠNJAR, Dragana ŠUNJKA, Dragana BOŠKOVIĆ, Sanja LAZIĆ, Slavica VUKOVIĆ

The University of Novi Sad, Faculty of Agriculture, Trg Dositeja Obradovića 8, 21000 Novi Sad, Serbia
*Corresponding author: dragana.sunjka@polj.edu.rs

ABSTRACT

Resveratrol (3,4',5-trihydroxystilbene) is one of the most important polyphenol compounds present in the human diet. From the aspect of agricultural production, resveratrol is also an important component. Grapevine plants produce it as a secondary metabolite that is synthesized to the greatest extent in stressful conditions. These conditions include abiotic and biotic factors such as a lack or excess of water, the content of micro and macro elements in the soil, agrotechnical measures, infections caused by phytopathogenic microorganisms, the presence of chemical stressors such as heavy metals, intensive application of plant protection products (PPP), uncontrolled application of synthetic fertilizers, etc. The most important stressor is infections caused by phytopathogenic organisms, especially the fungus *Botrytis cinerea*, whose presence is a trigger for the synthesis of resveratrol. With the intensive resveratrol production, plants activate the induced defense system, which inhibits the growth and further progression of pathogens. Often, the concentrations of synthesized resveratrol in infected plants are not sufficient to completely suppress pathogens, but they certainly slow down and keep infections at a low level, to provide additional time for us to use adequate protection measures. In addition to the plants that produce it, its application is also possible in the form of a water solution of pure resveratrol that can be applied during the storage of agricultural products to preserve their freshness as long as possible and to reduce the use of PPP in storages. In this paper, an overview of the last references was given to gain an overall picture of how important resveratrol is and how much potential it has from the aspect of human health and plant protection.

Keywords: *resveratrol, phenols, grapevine, Botrytis cinerea Pers.*

INTRODUCTION

The grapevine (*Vitis* spp.) is considered one of the oldest plant species. It has a long history of cultivation of about 7000 years. Due to the method of cultivation, the nutritional value of the fruits, and the economic profitability it gained great importance in agriculture. According to the latest data, around 7.6 million ha are under vineyards in the world, with Europe accounting for 65% of those areas. The annual production of grapes reaches almost 78 million tons, and the largest producers of grapes and wine are Spain, France, and Italy (Korać et al., 2016). In the Republic of Serbia, a tendency to decrease the area under vineyards has been observed (in the past few decades, it decreased by almost 50%). The reason for this is an insufficiently developed market, insufficient competitiveness, and a changing assortment where autochthonous varieties have been neglected. All of this represents a major obstacle on the way to strong and modern viticulture in Serbia, and it can be overcome by returning to the old, autochthonous grape varieties and exploiting all their qualities. The content of nutritional components in grapes is at a high level. The mentioned components include vitamins, minerals, colors, sugars, tannins, and polyphenols as the most abundant compounds (Korać et al., 2016). The mentioned substances have a positive effect on human health with their anti-inflammatory and antimicrobial effects. In addition, they affect the properties of fruits and their products, giving them color, smell, taste, pungency, etc. Polyphenols are secondary plant metabolites present in cereals, vegetables, fruits, and their products (Pandey and Rizvi, 2009). In addition to affecting the physical properties of the fruits in which they are represented, they have multiple positive effects on human health such as anti-inflammatory action, inhibition of platelet aggregation, antimicrobial activity, and antioxidant activity the most important among them. They are the most widespread antioxidants in the plant world, and their consumption has a beneficial effect on the human body, protecting cells from oxidative stress (Đekić et al., 2008). The reason for this is their susceptibility to oxidation due to the presence of a hydroxyl group and an unsaturated double bond (Rice-Evans et al., 1997). Among the plants that contain large amounts of polyphenols, and which are present in a variety of human diets, the grapes stand out. The presence of polyphenols in grapes is influenced by many factors such as climatic conditions (De Pascali et al., 2014), physical and chemical properties of the soil, stress, and agrotechnical measures (irrigation, tillage), health status of the vine (Pantelić et al., 2016). Polyphenols in grapes can be roughly divided into four groups, depending on the number of phenolic rings they contain and based on the structural elements that connect these rings, namely: phenolic acids, flavonoids, stilbenes, and lignins (Pandey and Rizvi, 2009). In the non-flavonoid class of phenolic compounds, stilbenes (1,2-diarylethenes) stand out because of their defensive effect on plants. They contain two phenyl moieties connected by a methylene bridge of two carbon atoms (Moreno and Peinado, 2012). The synthesis of stilbene, which includes resveratrol, takes place in the skin and seeds of the berries, but it has also been detected in the stem, winter buds, shoot tips, petioles, roots, and leaves of the vine, in concentrations of 0.2-16.5 mg. /kg (Colica et al., 2018). Resveratrol stands out as the most important polyphenol (stilbene) in grapes. Over the past several decades, this compound has been the subject of much research in the fields of medicine, pharmacy, plant physiology, biochemistry, and agriculture. Its synthesis in vine shoots, especially in berries, is stimulated by stressful conditions such as infections with phytopathogenic microorganisms, unfavorable environmental conditions, mechanical damage to plants, UV radiation, etc. Economically significant phytopathogenic fungi such as *Botrytis cinerea* Pers, *Plasmopara viticola* Berk. & M. A. Curtis, Berl. & De Toni, *Uncinula necator* Schwein, *Guignardia bidwellii* Ellis stand out as the most intensive trigger of resveratrol synthesis. Therefore, it is of great importance to assume that resveratrol forms a significant part of the induced immune system of the grapevine, which is activated upon the occurrence of stressful conditions. In addition, its consumption has a beneficial effect on health, and all the mentioned benefits of resveratrol, discovered so far, speak in favor of the perspective of further study of this compound.

RESVERATROL IN GRAPES

The history of resveratrol (3,4',5-trihydroxystilbene) can be traced back more than 2000 years since the grape extract was first used to treat heart disease and other health problems (Huang et al., 2019). It was isolated for the first time, as a pure compound, in 1939 from the roots of the plant *Veratrum grandiflorum* O. Loes (Takaoka, 1939; Pezzuto, 2019). Later, in 1963, it was isolated from the roots of *Polygonum cuspidatum* Siebold & Zucc., a plant used in traditional Chinese medicine (Yang et al., 2019; Huang et al., 2019). It is present in at least 72 plant species, including families such as *Vitaceae*, *Myrtaceae*, *Dipterocarpaceae*, *Cyperaceae*, *Gnetaceae*, *Fabaceae*, *Pinaceae*, *Moraceae*, *Fagaceae*, *Liliaceae*, and 31 genera of spermatophytes (Colica et al., 2018). Extraction of resveratrol can be successfully carried out with plant species such as *Arachis hypogeal* L., *Eucalyptus gunnii* Hook, *Morus rubra* L., *Vitis vinifera* L., *Veratrum grandiflorum* O. Loes, *Rheum rhaponticum* L., *Polygonum cuspidatum* Siebold & Zucc, *Gnetum montanum* Markgr., *Picea abies* L., *Pinus silvestris* L., and others. (Aggarwal et al., 2004; Colica et al., 2018; Huang et al., 2019). When it comes to the content of resveratrol, fruits, and vegetables that contain it in significant quantities, and are part of the everyday human diet should be especially highlighted. It is important to emphasize that grapes contain more resveratrol than their other natural sources (Hasan and Bae, 2017). Resveratrol is one of the most important polyphenolic compounds in grapes and wine (Đekić et al., 2008; Cvejić et al., 2010; Yang et al., 2019; Huang et al., 2019). It is a natural phytoalexin, one of the carriers of the induced defense mechanism of plants. In nature, this compound is present in two isomeric forms, trans and cis. The trans isomer has greater biological activity due to the presence of the 4'-hydroxystyryl group (Soleas et al., 1997). The cis form occurs as a consequence of the transformation of the trans isomer by UV radiation or throughout the processing of grapes during the vinification, and all due to the presence of a C—C double bond (Tian and Liu, 2019), whereby it never reaches the concentration of the trans isomer (Sato et al., 1997; Soleas et al., 1997). Both forms of resveratrol are present in grapes, with the cis form present in very small amounts that are often difficult to detect (Cvejić et al., 2010; Colica et al., 2018; Đekić et al., 2008; Yang et al., 2019). Resveratrol originates from the acetate-malonate and phenylpropanoid pathways of the plant's primary and secondary metabolism. Condensation of p-coumaroyl CoA with three molecules of malonyl

CoA is achieved by stilbene synthase activity. Four molecules of CO_2 are released for every molecule of resveratrol synthesized. The synthesis of resveratrol in grapes is then catalyzed by the enzyme stilbene synthase, which uses p-coumaroyl-CoA and malonyl CoA as a substrate (Colica et al., 2018). Accumulation of resveratrol in grapes varies depending on the grape variety, genotype, location, environmental conditions, and ripening period. Different amounts of resveratrol have been detected in grape skin, seeds, shoots, buds, and roots, however, a relatively higher amount of resveratrol can be found in the skin of grapes, and less in the pulp and end products such as juice and wine (Hasan and Bae, 2017). Expressed as a percentage, the distribution of resveratrol in the berry is uneven, and about 60–70% of the total resveratrol is found in the seeds, 28–35% in the skin, and only 10% in the pulp (Gođevac et al., 2010). The synthesis of resveratrol was also monitored during the ripening of different vine varieties. The amounts of resveratrol were relatively high in unripe fruits, and low in ripe berries. It was observed that resveratrol is synthesized more intensively and to a greater extent in the skin cells of the berries, while it is almost absent in the mesocarp of the fruit. Furthermore, a clear negative correlation was established between the content of resveratrol in the grape skin and its stage of development (Jeandet et al., 1991). Although it is naturally present in grapevine plants in limited quantities, its synthesis can be induced by exposing plants to stress, i.e. various biotic and abiotic factors, among which the most prominent are ultra-violet (UV) radiation, ozone, anoxic treatment, mechanical damage, phytopathogenic infections organisms (Hasan and Bae, 2017), jasmonic acid (JA), salicylic acid (Tassoni et al., 2005), H2O2 and AlCl3 (Wang et al., 2013). In addition to the fact that resveratrol belongs to the chemical group of stilbenes, it is also included among phytoalexins (Pandey and Rizvi, 2009). The term phytoalexin is related to antimicrobial compounds of low molecular mass produced by plants, in response to infection with phytopathogenic organisms or other forms of stress. In the interaction with phytopathogenic microorganisms, they have an inhibitory effect and their intensive synthesis in plants begins with the interaction between the plant and the microorganism. This is the reason why their presence is always associated with the resistance of plants to phytopathogenic fungi, although they can also occur in conditions of abiotic stress. On the other hand, the term "metabolite of stress" introduced by Stoessl et al. (1976) includes antifungal and non-antifungal compounds produced in response to the presence of various stressors, which may or may not be involved in the plant's defense mechanism. Whichever group it belongs to, the importance of resveratrol in protecting plants and preventing the progress of established infections is not diminished (Langcake and McCarthy, 1979).

HEALTH BENEFITS OF RESVERATROL

At the beginning of the nineties of the last century, when during epidemiological studies it was discovered that resveratrol has a cardioprotective effect, the attention of scientists from the fields of medicine and pharmacology was increasingly directed towards this compound. Since then, interest in resveratrol and grapevine, as its most important source in human nutrition, has grown exponentially. Resveratrol is an activator of SIRT1, one of the forms of proteins from the sirtuin group, characteristic of mammals (Chung et al., 2010). SIRT1 deacetylates histone and non-histone proteins, and in addition functions as a transcription factor for many physiological processes. The pathway regulated by SIRT1 affects metabolism, stress resistance, cell lifespan, cellular senescence, immune system function in inflammation, endothelial function, and circadian rhythm. Resveratrol has been shown to activate SIRT1, which indicates the possibility of exerting positive effects in diseases caused by abnormal metabolic control, inflammation, and cell cycle defects (Berman et al., 2017). Resveratrol inhibits cellular events associated with tumor initiation, promotion, and progression. Resveratrol was also found to affect tumor initiation by dose-dependently inhibiting free radical formation when cells (HL-60) were treated with 12-O-tetradecanoylphorbol-13-acetate (Sharma et al., 1994). The inhibitory effect of resveratrol on the development of preneoplastic lesions in the mammary glands treated with a carcinogen and the tumorigenesis of skin cancer was proven in mice (Yang et al.,1997). This drew attention to the fact that resveratrol, as a common ingredient in human nutrition, has great potential in medicine and pharmacology as a potential chemopreventive agent in the treatment of cancer in humans, because it affects all three stages of carcinogenesis: initiation, promotion, and progression (Berman et al., 2017).Considering the positive effect of resveratrol against cancer (Jang et al., 1997), a great effort was made to investigate its biological and pharmacological properties and activities in more detail (Garg et al., 2005; Huang et al., 2019). Therefore, in addition to the anti-cancer activity of this compound, antioxidant, anti-inflammatory, immunomodulatory, regulatory, neuroprotective, and additional cardiovascular protective effects have been determined (Poulsen et al., 2013), and a positive effect in various chronic diseases such as liver diseases, obesity, diabetes, Alzheimer’s and Parkinson’s disease (Meng et al., 2020). Resveratrol has been shown to affect multiple molecular targets associated with cardioprotective effects. For example, resveratrol promotes endothelial function that may help prevent atherosclerosis and coronary artery disease (Cho et al., 2017; Berman et al., 2017). Also, in research conducted on mice, a positive effect in the treatment of hypertension was found, by causing oxidative activation of protein kinase 1-(PKG1), which leads to the normalization of blood pressure (Prysyazhna et al., 2019; Meng et al., 2020). Several neuroprotective effects of resveratrol have also been demonstrated, including protection against neuronal damage, improvement of cognitive dysfunction, and enhancement of learning and memory abilities (Weiskirchen and Weickirchen, 2016). When it comes to inflammatory processes in the body, resveratrol acts by inhibiting the production of pro-inflammatory cytokines and modifies the immune response against pathogens such as viruses, fungi, and bacteria (Liu et al., 2014; Meng et al., 2020). In the treatment of bacteria, resveratrol can change the expression of virulence factors, reduce biofilm formation, reduce motility and increase the sensitivity of bacteria to different classes of conventional antibiotics (Vestergaard and Ingmer, 2019). Based on all than mentioned, it can be concluded that resveratrol acts in several ways, namely: antioxidant (de la Lastra and Villegas, 2007), an inhibitor of cyclooxygenase and lipid modification, inhibitor of LDL oxidation and platelet aggregation, vasodilator and antiviral agent (Campagna and Rivas, 2010; Cvetković et al., 2015). Considering that it is a bioactive compound present in grapes (and its products), the consumption and utilization of resveratrol represented in the diet through natural sources are very interesting. A large number of in vitro studies have been performed by monitoring the consumption of resveratrol at concentrations that greatly exceed even the highest amount that could be ingested through the diet. Today, various dietary supplements of resveratrol can be found on the market, in which its content varies, and is expressed in milligrams or even grams. An example of this is the daily intake of resveratrol doses of a few grams, while it is known that e. g. a liter of wine contains very small amounts expressed in mg/L (Guilford and Pezzuto, 2011). However, there are doubts that the body cannot use the total amount of resveratrol introduced by supplements, but only a small part, which is a problem for further pharmacological research. This gives priority to the intake of resveratrol through natural sources and highlights the intake of resveratrol through resveratrol-rich foods. We should certainly not forget the fact that it is a very valuable natural compound that has a beneficial effect on several target sites and whose potential needs to be explored and used to the maximum (Pezzuto, 2011; Pezzuto, 2019).

RESVERATROL AND PHYTOPATHOGENIC FUNGI

Phytopathogenic fungi represent the main threat to vine growing and achieving healthy and high yields. With their way of life, they limit the development of plants, cause degeneration of different plant organs, and cause changes in plant tissues during the growing season, thereby permeating all developmental stages of the vine. During evolution, as well as through genetic engineering, grapevine varieties with a certain level of resistance to certain phytopathogenic fungi have been developed, where autochthonous varieties stand out the most. A significant factor that affects the aforementioned resistance is the amount of resveratrol present in healthy plants, as well as the intensity of its synthesis during stressful conditions, which infections certainly are. The presence of infection encourages the creation of resveratrol in larger quantities than it is naturally present, where it acts on pathogens by limiting them and preventing the further progress of the infection until the environmental conditions become unfavorable for further development and reproduction of the pathogen. It is believed that resveratrol is directly involved in the resistance of the grapevine to some of the most economically important pathogens such as *Botrytis cinerea*, *Plasmopara viticola*, *Uncinula necator*, *Guignardia bidwellii*. The concentration of resveratrol in cases of infection with the mentioned pathogens increases around the spot of infection. Localized synthesis and accumulation of resveratrol help to some extent in limiting the infection and preventing its further spread. The synthesis of this compound begins immediately after recognizing the presence of the pathogen, and long before the formation of visible symptoms of infection (Hasan and Bae, 2017). Detection of infection includes the recognition of signaling molecules, i. e. elicitors (Montero et al., 2003). Elicitors are molecules capable of stimulating plant defense mechanisms, participating in various oxidative and physiological responses to abiotic stress including the activation of several secondary biosynthetic pathways such as the one leading to the synthesis of phenolic compounds (Gutiérrez-Gamboa et al., 2021). Salicylates, jasmonates, and ethylene play the role of elicitors in grapevine plants, and in response to their presence, plants synthesize phytoalexins, and among them resveratrol to the greatest extent (Montero et al., 2003). The phenomenon of the dependence of resveratrol synthesis on the presence of infections with phytopathogenic organisms is the subject of many studies conducted over the past decades, with a large number of them supporting the existence of a positive correlation. The established opinion is that resistant varieties of grapevines, in contrast to sensitive ones, initially contain more resveratrol and can produce it in greater quantity when they find themselves in stressful conditions. When it comes to infections with phytopathogenic fungi, they spread from the point of penetration into the plant to the surrounding tissues. In that situation, the concentration of resveratrol in the surrounding tissues increases simultaneously with the growth and spread of the pathogen, reaching several times higher concentrations than the initial one, present before the infection. In this way, resveratrol forms a chemical barrier to limit the progression of pathogens. Among the already mentioned phytopathogenic fungi, *B. cinerea* stands out the most and its influence on the synthesis of resveratrol in grapevine plants is the most studied. During research on the production of trans-resveratrol in grapes in response to infection with this fungus, was concluded that the grapevine in sensitive stages such as ripening in the presence of infection cannot synthesize the required amount of trans-resveratrol sufficient to inhibit the growth and development of the pathogen. However, it is certainly possible at earlier stages, especially during the first stages of berry development (Jeandet et al., 1995). In the period from BBCH 71 to BBCH 75 (from the "phase young fruits begin to swell" to "berries pea-sized") the concentration of trans-resveratrol decreases, indicating a decrease in resveratrol levels during ripening. Healthy fruits contain less resveratrol than infected ones. When comparing sensitive and resistant varieties of grapevine (Huxelrebe and Castor) to the mentioned pathogen, it is important to point out that a significantly higher amount of trans-resveratrol (up to 50% more) is synthesized in the berries of resistant varieties. Accumulation of this compound increased during the first four days after infection and then decreased until the sixteenth day. Also, it was found that leaves of less sensitive varieties produce higher total amounts of resveratrol per lesion in response to infection (Baveresco et al., 1997). By creating new, high-quality, wine and table grape varieties, the natural ability to defend against various stressors has been somewhat impaired. Therefore, today, more and more vine growers are returning to old, autochthonous varieties with high resistance to various types of stressors, in which synthesis of resveratrol is represented to a greater extent.

RESVERATROL AS A FUNGICIDE

Nowadays when intensive agricultural production is at its peak, the application of synthetic fungicides is an inevitable step in protecting plants from diseases caused by phytopathogenic fungi. According to the Law on plant protection products (Službeni glasnik Republike Srbije, 41/09), their application is regulated and limited, due to the harmful effects on human health, non-target organisms, the environment, and the increasingly frequent development of resistant populations of various phytopathogenic fungi. Therefore, finding new solutions in the form of biological, natural fungicides is of great necessity. Resveratrol has proven to be a good partner in the fight against the most important phytopathogenic fungi of the grapevine. In case of infections of lower intensity, during unfavorable meteorological conditions for the development of pathogens, the effect of resveratrol is reflected in the limitation and inhibition of development, and therefore in the suppression of pathogens. When it comes to severe infections, the effectiveness of resveratrol is not enough to completely suppress the pathogens. In the mentioned situations, intensive synthesis limits the further progression of pathogens and provides the additional time necessary for implementing suitable protection measures. The non-specific antifungal effect of resveratrol and its accumulation in infected tissues makes it a suitable natural fungicide, which, with its natural presence in grapevine plants, contributes to its resistance to fungal infections. However, the problem of protecting the vine does not end after the harvest, because the grapes also need to be protected during storage. A special threat is *B. cinerea*, as the most destructive storage pathogen, not only of grapes but also of other agricultural products. Since resveratrol is a natural antioxidant, it is assumed that it may have positive effects when it comes to preserving stored products. Grapes naturally contain it, and additional, external applications could greatly enhance its effectiveness and prevent fruit decay. This is supported by the research of Montero et al. (2003) who reported the activity of trans-resveratrol and its correlation with ethylene released from grapes infected with *B. cinerea* at room temperature. Ethylene is an indicator of the ripening and aging of fruits, and if it is present in the atmosphere of the storage area, it can contribute to the faster decay of fruits. In this case, the content of trans-resveratrol and ethylene showed the opposite behavior, because the high content of trans-resveratrol corresponded to a low concentration of released ethylene. In grapes infected with *B. cinerea*, ethylene emission started to increase after 48 h when the content of trans-resveratrol started to decrease. The activity of trans-resveratrol as a natural fungicide was also tested by exogenous application on grapes. A short immersion of bunches in trans-resveratrol solution delayed the increase in ethylene emission for about 48 h and led to a decrease in its emission. The tested compound had a positive effect on the preservation of grapes during storage, doubling its usual shelf life at room temperature. During the other efficacy tests, the fruits of different plant species were immersed in an aqueous solution of trans-resveratrol of different concentrations. During the test carried out on grapes, after ten days the fruits treated with trans-resveratrol kept their freshness, while the untreated fruits were dehydrated and infected with phytopathogenic bacteria and fungi. Treated fruits kept freshness twice as long compared to untreated ones. Apart from the purpose of protecting grapes during storage, its effectiveness has also been tested during the storage of apple fruits, which today represents a significant challenge (Ureña et al., 2003). Considering a large number of chemical treatments of apples during the growing season, there is an increasing effort to find adequate solutions for the protection of fruits during storage, while avoiding as much as possible the use of synthetic PPP such as fungicides based on fludioxonil or thiophanate-methyl. By monitoring the condition of treated and untreated fruits of the Golden Delicious variety for 75 days, it was observed that the fruits treated with trans-resveratrol kept a freshness without damage and external signs of decay, while the untreated fruits were completely rotten after 75 days (Ureña et al., 2003). Also, it has been proven that in vitro conditions, the use of resveratrol in the concentration range of 60-140 µg/ml significantly reduces the growth of *B. cinerea* mycelia, while the concentration of 90 µg/ml inhibits the growth of *B. cinerea* mycelia by 50%. In addition, the mentioned concentrations of resveratrol cause cytological deformations of the mentioned pathogen, which results in the formation of secondary and tertiary germ tubes in conidia, cytoplasmic granulation, and the formation of deformed and curved germ tubes (Hoos and Blaich, 1990; Adrian et al., 1997). In addition to *B. cinerea*, agricultural products are exposed to other phytopathogenic fungi and bacteria during storage. During the research, when observing the treated fruits, no signs of infection with phytopathogenic bacteria that were present in the control were observed, which is in favor of resveratrol. When it comes to the action of resveratrol on phytopathogenic bacteria, its mechanism of action is based on damaging the bacterial cell membrane and preventing biofilm formation (Chen et al., 2016). In addition to its effect on *B. cinerea*, resveratrol also showed positive results when it comes to suppressing and inhibiting the fungus *Bipolaris oryzae* and the bacterium *Xylella fastidiosa* (Yu et al., 2013; Paulo et al., 2010). All of the results support the fact that resveratrol is a potential part of the antifungal and antibacterial strategy for the control of not only grapevines, but also other cultivated species, both in the field and during the storage.

CONCLUSION

Studying the metabolism of grapevine plants and their responses to stressful conditions has made it possible to discover another compound that has many positive properties. In addition to all the benefits for human health, which inevitably exist, many others have been discovered that make resveratrol a human ally. The problem of phytopathogenic fungi and the development of their resistance is one of the main limiting factors in growing vines, therefore any new option in their control is desirable, especially if it is natural and environmentally acceptable. Resveratrol is an initial compound of great potential which can improve vine protection in the future. All previous research on resveratrol provided a very significant contribution to the overall knowledge of this plant metabolite and opened the door for many new aspects of research.

ACKNOWLEDGEMENT

This study is a part of the project No. 451-03-68/2022-14/200117, funded by the Ministry of Education, Science and Technological Development of the Republic of Serbia.

REFERENCES

Adrian, M., Jeandet, P., Veneau, J., Weston, L. A., Bessis, R. (1997). Biological activity of resveratrol, a stilbene compound from grapevines, against *Botrytis cinerea*, the causal agent for gray mold. *Journal of Chemical Ecology, Vol. 23, No. 7,1689-1702.*

Aggarwal, B. B., Bhardwaj, A., Aggarwal, R.S., Seeram, N.P., Shishodia, S., Takada, Y. (2004). Role of resveratrol in prevention and therapy of cancer: preclinical and clinical studies, Anticancer Res. 24, 2783–2840.

Baveresco, L., Petegolli, D., Cantu, E., Fregoni, M., Chiusa, G., Trevisan, M. (1997). Elicitation and accumulation of stilbene phytoalexins in grapevine berries infected by *Botrytis cinerea*. *Vitis* 36 (2), 77-83 (1997).

Berman, A. Y., Motechin, R. A., Wiesenfeld, M. Y., Holz, M. K. (2017). The therapeutic potential of resveratrol: a review of clinical Trials. *NPJ Precision Oncology* (2017) 1: 35; doi:10.1038/s41698-017-0038-6.

Campagna, M. and Rivas, C. (2010). Antiviral activity of resveratrol. *Biochem. Soc. T.* 38 (2010) 50–53.

Chen, J., Yu, Y., Li, S., Ding, W. (2016). Resveratrol and Coumarin: Novel Agricultural Antibacterial Agent against Ralstonia solanacearum In Vitro and In Vivo. Molecules 2016, 21, 1501.

Cho, S., Namkoong, K., Shin, M., Park J., Yang, E., Ihm J., Thi Thu, V., Kyu Kim, H., Han, J. (2017). Cardiovascular protective effects and clinical applications of resveratrol. *J. Med. Food* 20, 323–334 (2017).

Chung, S., Yao, H., Caito, S., Hwang, J., Arunachalam, G., Rahman, I. (2010). Regulation of SIRT1 in cellular functions: role of polyphenols. *Arch.Biochem. Biophys*. 501, 79–90 (2010).

Colica, C., Milanović, M., Milić, N., Aielloc, V., De Lorenzo, A., Abenavolie, L. (2018). A Systematic Review on Natural Antioxidant Properties of Resveratrol. *Natural Product Communications* Vol. 13 (9), pp. 1195-1203.

Cvejić, J. M., Đekić, S. V., Petrović, A. V., Atanacković, M. T., Jović, S. M., Brceski, I. D., Gojković-Bukarica, Lj. C. (2010). Determination of *trans*- and *cis*-Resveratrol in Serbian Commercial Wines. *Journal of Chromatographic Science*, Vol. 48, 229-234.

Cvetkovic, Z. C., Nikolic, V. D., Savic, I. M., Savic-Gajic, I. M., Nikolic, Lj. B. (2015). Development and validation of an RP-HPLC method for quantification of *trans*-resveratrol in the plant extracts. *Hem. Ind.* 69 (6) 679–687 (2015).

De la Lastra, C. A., and Villegas, I. (2007). Resveratrol as an antioxidant and pro-oxidant agent: mechanisms and clinical implications. *Biochem. Soc. T.* 35 (2007) 1156–1160.

Đekić, S., Milosavljević, S., Vajs, V., Jović, S., Petrović, A., Nikićević, N., Manojlović, V., Nedović, V., Tešević, V. (2008). *Trans*- and *cis*-resveratrol concentration in wines produced in Serbia. *J. Serb. Chem. Soc. 73* (11) 1027–1037.

Garg, A. K., Buchholz, T. A., Aggarwal, B.B. (2005). Chemosensitization and radiosensitization of tumors by plant polyphenols, Antioxidants Redox Signal. 7, 1630–1647.

Gođevac, D., Tešević, V., Veličković, M., Vujisić, M., Vajs, V., Milosavljević, S. (2010). Polyphenolic compounds in seeds from some grape cultivars grown in Serbia. J. Serb. Chem. Soc. 75 (12) 1641–1652.

Guilford, J. M., and Pezzuto, J. M. (2011). Wine and health: a review. *Am. J. Enol. Vitic.* 62, 471-486.

Gutiérrez-Gamboa, G., Mateluna-Cuadra, R., Díaz-Gálvez, I., Mejía, N., Verdugo-Vásquez, N. (2021). Methyl Jasmonate Applications in Viticulture: A Tool to Increase the Content of Flavonoids and Stilbenes in Grapes and Wines. Horticulturae 2021, 7, 133.

Hasan, M. M., Bae, H. (2017). An Overview of Stress-Induced Resveratrol Synthesis in Grapes: Perspectives for Resveratrol-Enriched Grape Products. *Molecules*, 22, 294.

Hoos, G., Blaich, R. (1990). Influence of Resveratrol on Germination of Conidia and Mycelial Growth of *Botrytis cinerea* and *Phomopsis viticola*.Journal of Phytopathology, 129 (2), 102-109.

Huang, X., Li, X., Xie, M., Huang, Z., Huang, Y., Wu, G., Peng, Z., Suna, Y., Ming, Q., Liu, Y., Chena, J., Xua, S. (2019). Resveratrol: Review on its discovery, anti-leukemia effects, and Pharmacokinetics. *Chemico-Biological Interactions 306, 29–38*

Jang, M., Cai, l., Udeani, G. O., Slowing, K. V., Thomas, C. F., C. W. W., Beecher, Fong, H. H. S., Farnsworth, N. R., Kinghorn, A. D., Mehta, R. G., Moon, R. C., Pezzuto, J. M. (1997). Cancer Chemopreventive Activity of Resveratrol, a Natural Product Derived from Grapes. *Science* 275, 218 (1997).

Jeandet, F., Bessis, R., Gautheron, B. (1991). The Production of Resveratrol (3,5,4'-trihydroxystilbene) by Grape Berries in Different Development Stages. Am. J. Enol. Vitic., Vol. 42, No. 1, 41-46.

Jeandet, P., Bessis, R., Sbaghi, M., Meunier, P. (1995). Production of the Phytoalexin Resveratrol hy Grapes as a Response to *Botrytis* Attack Under Natural Conditions. J. Phytopathology 143**,** 135-139.

Korać, N., Cindrić, P., Medić, M., Ivanišević, D. (2016). Voćarstvo i vinogradarstvo (deo vinogradarstvo). Univerzitet u Novom Sadu, Poljoprivredni fakultet, str. 1-2.

Langcake, P. and McCarthy, W. V. (1979). The relationship of resveratrol production to infection of grapevine leaves by *Botrytis cinerea*. *Vitis* 18, 244-253.

Liu, T.; Zang, N.; Zhou, N.; Li, W.; Xie, X.; Deng, Y.; Ren, L.; Long, X.; Li, S.; Zhou, L., Tu, W., Wang, L., Tan, B., Liu, E. (2014). Resveratrol inhibits the TRIF-dependent pathway by upregulating sterile _ and armadillo motif protein, contributing to anti-inflammatory effects after respiratory syncytial virus infection. *J. Virol*., 88, 4229–4236.

Meng, X., Zhou, J., Zhao, C. N., Gan, R. Y., Li, H. B. (2020). Health Benefits and Molecular Mechanisms of Resveratrol: A Narrative Review. Foods 2020, 9, 340.

Montero, C., Cristescu, S.M., Jimenez, J.B., Orea, J.M., te Lintel Hekkert, S., Harren, F.J.M., Gonzalez Ureña, A. (2003). trans-Resveratrol and Grape Disease Resistance. A Dynamical Study by High-Resolution Laser-Based Techniques. *Plant Physiology*, Vol. 131, pp. 129–138.

Moreno, J. and Peinado, R. (2012). Enological Chemistry, Chapter 5- Polyphenols, pp. 56.

Pandey, K. B., and Rizvi, S. I. (2009). Plant polyphenols as dietary antioxidants in human health and disease. *Oxidative Medicine and Cellular Longevity* 2:5, 270-278.

Pantelić, M. M., Dabić Zagorac, D. Č., Davidović, S. M., Todić, S. R., Bešlić, Z. S., Gašić, U. M., Tešić, Ž. Lj., Natić, M. M. (2016). Identification and quantification of phenolic compounds in berry skin, pulp, and seeds in 13 grapevine varieties grown in Serbia. *Food Chemistry* 211 (2016) 243–252

Paulo, L., Ferreira, S., Gallardo, E., Queiroz, J.A., Domingues, F. (2010). Antimicrobial activity and effects of resveratrol on human pathogenic bacteria**.** World J. Microbiol. Biotechnol., 26 (2010), pp. 1533-1538.

Pezzuto, J. M. (2011). The phenomenon of resveratrol: redefining the virtues of promiscuity. *Ann. N.Y. Acad. Sci.* 1215, 123-130.

Pezzuto, J. M. (2019). Resveratrol: Twenty Years of Growth, Development, and Controversy. Biomolecules & Therapeutics; 27 (1): 1-14.

Poulsen, M. M. Jorgensen, J. O. Jessen, N. Richelson, B. Pedersen, S. B. (2013). Resveratrol in metabolic health: an overview of the current evidence and perspectives, Ann. N. Y. Acad. Sci. 1290, 74–82.

Prysyazhna, O.; Wolhuter, K.; Switzer, C.; Santos, C.; Yang, X.; Lynham, S.; Shah, A.M.; Eaton, P.; Burgoyne, J.R. (2019). Blood pressure-lowering by the antioxidant resveratrol is counterintuitively mediated by oxidation of cGMP-dependent protein kinase. *Circulation* 140, 126–137.

Ribera, A. E., Zuñiga, G. (2012). Induced plant secondary metabolites for phytopathogenic fungi control: a review. *Journal of Soil Science and Plant Nutrition*, 12 (4), 893- 911.

Rice-Evans, C. A., Sampson, J., Bramley, P. M. (1997). Why do we expect carotenoids to be antioxidants in vivo? *Free Radical Research*, 26, 381–398.

Sato, M., Suzuki, Y., Okuda, T., Yokosuka, K. (1997). Contents of Resveratrol, Piceid, and Their Isomers in Commercially Available Wines Made from Grapes Cultivated in Japan, Bioscience, Biotechnology, and Biochemistry, 61:11, 1800-1805.

Sharma, S, Stutzman, J. D., Kelloff, G. J., Steele, V. E. (1994). Screening of potential chemopreventive agents using biochemical markers of carcinogenesis. *Cancer Res*; 54 (22): 5848-55.

Soleas, J. G., Diamandis, E. P., Goldberg, D. M. (1997). Resveratrol: A Molecule Whose Time Has Come And Gone? Clinical Biochemistry, Vol. 30, No. 2, pp. 91-113.

Sovak, M. (2001). Grape Extract, Resveratrol, and Its Analogs: A Review. Journal of Medicinal Food, Vol. 4, 2, pp 93-105**.**

Stoessl, A**.,** Stothers, J. B. and Ward, E. W. B. (1976). Sesquiterpenoid stress compounds of the Solanaceae. *Phytochemistry* 15, 855-872.

Takaoka M. J. (1939). Of the phenolic substances of white hellebore (*Veratrum grandiflorum* Loes. fil). *J Fac Sci, Hokkaido Imperial University*, 3:1-16.

Tassoni, A., Fornalè, S., Franceschetti, M., Musiani, F., Michael, A. J., Perry, B., Bagni, N. (2005). Jasmonates and Na-orthovanadate promote resveratrol production in Vitis vinifera cv. Barbera cell cultures. New Phytol. 2005 Jun;166(3):895-905.

Tian, B., Liu, J. (2019). Resveratrol: a review of plant sources, synthesis, stability, modification, and food application. *J Sci Food Agric* 2020; 100: 1392–1404

Vestergaard, M., Ingmer, H. (2019). Antibacterial and antifungal properties of resveratrol. *International Journal of Antimicrobial Agents* 53 (2019) 716–723.

Wang, L. J.; Ma, L.; Xi, H. F.; Duan,W.; Wang, J. F.; Li, S. H. (2013). Individual and combined effects of CaCl2 and UV-C on the biosynthesis of resveratrol in grape leaves and berry skins. J. Agric. *Food Chem*., 61, 7135–7141.

Weiskirchen, S., and Weiskirchen, R. (2016). Resveratrol: How Much Wine Do You Have to Drink to Stay Healthy? Advances in Nutrition, Volume 7, Issue 4, Pages 706–718.

Yang, W., Li, F., Xing, X., Wang, Z., Yu, X. (2019). Study in Pesticide Activities of *Polygonum cuspidatum* Extracts and its Active Ingredient Resveratrol. *Natural Product Communications,* Original article pp. 1-6.

Yu, S.M., Lee, H.K., Jeong, U.S., Baek, S.H., Noh, T.H., Kwon, S.J., Lee, Y.H. (2013). Inhibitory effects of resveratrol and piceid against pathogens of the rice plant, and disease resistance assay of transgenic rice plant transformed with stilbene synthase gene. Res. Plant Dis., 19 (2013), pp. 177-182.

Zakon o izmenama i dopunama Zakona o sredstvima za zaštitu bilja (2021). ,,Službeni glasnik RS”, broj 41/09.