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Detection, identification and determination of resveratrol in wine. Problems and challenges.

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Abstract

Resveratrol is a compound synthesized by plants in response to unfavorable conditions of growth like mechanical injury, siege of bacteria or fungi and UV exposure. It is concentrated mostly in grapes skin and further more in the products made from grapes especially red wines. Each wine is characterized by different amount of given stilbene since its occurrence is affected by many factors like: types of grapes, environment (climate, soil, region) and winemaking technologies. Due to its health beneficial effects, people are very interested in resveratrol and its activity to deal with some diseases.. Therefore, its determination and quantification is of high importance. However, the complexity of wine matrix makes its analysis very challenging. The study provides data of the resveratrol occurrence in different types of fruits and wines, regarding region they come from and comparison of analytical techniques and challenges taking into account their process and green assessment.

Key words: resveratrol, wine, gas chromatography, green assessment, GAPI

1. Introduction

Standards of living in many well-developed countries have increased across last decades, what then pushed people to put greater attention on the healthy life style and what is more quality of food products. Nowadays, people are more and more conscious, that products they eat may have positive or negative effects on their health. There is a general trend for the healthy life style in order to maintain good health conditions as well as to slow down the aging processes. Technology progress and scientific development have contributed to the discovery of dependence between diet and human health. Currently, it is known, that food products besides supplying of nutrients to human body are also valuable sources of compounds, acting prophylactically and sometimes even supportively in the treatment of civilization diseases, such as: heart diseases, nervous system diseases, digestive diseases and

cancer diseases [1]. This create opportunity for many scientist to broaden the topic and find new correlations between diet and health maintenance.

Recent studies showed, that more and more interest is focused on the biologically active compounds of the plant origin. Plants sometimes even called as a “biofactories” act as a source of numerous elements and also produce primary and secondary metabolites. Secondary metabolites are not always necessary for their basic life processes, but are fundamentally important in adaptations of plants to the environmental conditions. Biologically active, secondary metabolites have a huge potential, thus can be successfully applied in such areas like: medicine or dietitian. Valuable secondary metabolites include polyphenols [1-2].

Polyphenols are a wide group of compounds belonging to the phytochemicals, occurring naturally in overground part of plants. They are most abundant in fruits due to the fact, that they are responsible for their color. Polyphenols are secondary metabolites of plants fulfilling fungicide, antioxidative and building function [3-4]. They are characterized by very diverse chemical structures, having in common at least two hydroxyl group bonded to the acidic benzene ring. What diverse them more are: molar masses, properties and what is more biological functions. Their biologic activity strongly depends on the number and the position of the substituents in the compound molecule. The bigger the number of hydroxyl groups in the molecule the stronger the antioxidative properties and more powerful protection of organisms against free radicals [2,4]. Polyphenols classification, according to the number of hydroxyl groups and the way of bonding of aromatic ring, is based on four main groups presented on the Figure 1 [4].

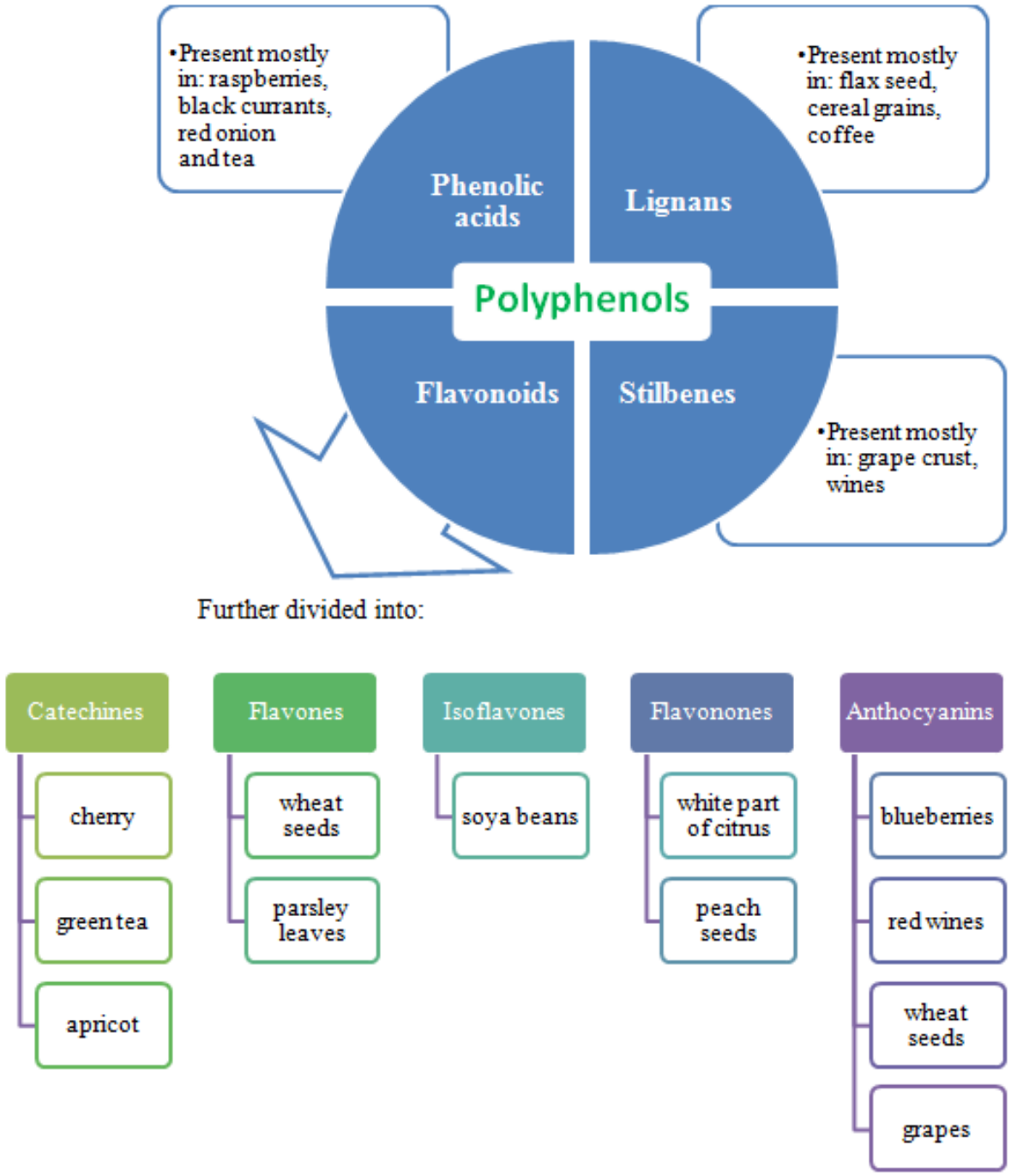


Figure 1 Polyphenols classification according to the number of hydroxyl groups and the way of bonding of the aromatic ring [4].

The primary dietary sources of resveratrol in the human diet are peanuts, peanut butter, blueberries, grapes, and wine. It has been proved, that red wine, which is produced by fermentation of juice on the crushed grapes, contains greater amount of resveratrol than white wine, which is produced by fermentation of the juice alone. Due to the fact, that recent research suggests, that consumption of resveratrol may reduce the risk of certain cancers, heart disease, and other age-related disorders, this compound is widely studied by analytical scientists.

Due to physicochemical properties of resveratrol as well as complex composition of the matrices, in which it occurs, determination of this compound is challenging and laborious. Many analytical methods are reported for determination of resveratrol in wine, which based on the application of high performance liquid chromatography (HPLC), capillary electrophoresis (CE), and gas chromatography (GC). Depending on the technique used for final determination, a chemical conversion of analyte is often needed due to properties of resveratrol. In addition, a pre-concentration step is required, because resveratrol occurs at low concentration level as well as, because wine is characterized by complex matrice composition. Another challenge is to couple analyte pre-concentration, extraction and derivatization into single process, what is in accordance with green chemistry and green analytical chemistry, which arise directly from the principles of sustainable development. The result of this approach is to reduce the amount of reagents used, waste generated and energy consumed. The application of microextraction techniques in conjunction with the chemical conversion of analytes perfectly meets the specified requirements. There are a large number of reports in the literature, relating to the determination of resveratrol in the wine industry, but they are generally based on the use of liquid-liquid extraction or solid phase extraction prior to final determination using liquid chromatography. The milestone of knowledge development in the field of resveratrol is presented on the Figure 2.

1939	• First mention of resveratrol in Japanese article [5].
1963	• Second mention of resveratrol in Japanese article [6].
1976	• Resveratrol origin investigation - synthesis by plants [7].
1979	• Factors affecting syntheses of resveratrol by plants [8].
1988	• Studies of enzymes involved in the resveratrol synthesis [9].
1992	• Determination of resveratrol from wine samples [10].
1993	• Begining of evaluation of new analytical methods for resveratrol determination [11].
2000	• Solid phase microextraction implementation for sample preparation [12].
2002	• Cardioprotective effects of resveratrol [13].
2007	• Cancer chemoprevention of resveratrol [14].
2008	• Neuroprotective effects of resveratrol [15].
2012	• Resveratrol supplementation [16].

Figure 2 Milestone in the field of development of knowledge in the field of resveratrol [5-16].

The aim of this review is to present the current knowledge regarding one of the most famous polyphenol – resveratrol - its origin, sources and to summarize the concentration of resveratrol in different types of wines. In addition, the absorption bioavailability and metabolism of this compound is discussed. Taking into account the physicochemical characteristics of resveratrol, an overview of the analytical methodologies, cleanup and pre-concentration techniques, a comparison between the derivatization agents and environmental assessment of the analytical methodologies have been made. The study concludes with a focus on the main issues, that should be further investigated, based on literature data from the last two decades and refers to different type of samples characterized by complex matrices composition. Databases like Web of Science, Mendeley and Scopus were used to select literature commented in the body. Such keywords as green analytical chemistry, green derivatization, enhanced parameters, microextraction techniques, green solvents, automation and connected to them were applied during literature searching.

2. Stilbene – resveratrol and its characteristic

One of the most famous polyphenol is resveratrol, having a molecular formula - $C_{14}H_{12}O_3$. It can be found also under the name 3,4',5 – stilbenetriol. Molecular weight of this compound is 228,25 Daltons. Resveratrol is synthesized by plants as a response to unfavorable or

stressful conditions, damage, mechanical injury, siege of bacteria or fungi or UV exposure [17-19].

It exists in two forms: trans- and cis- isomers (Figure 2). Both forms have similar properties however, cis-isomer with a lesser extent [20].

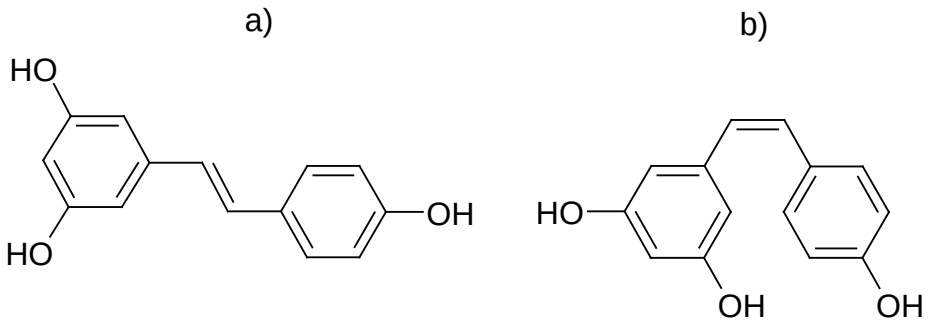


Figure 3 The chemical structures of resveratrol isomers. (A) – cis-resveratrol, (B) – trans-resveratrol.

Both forms are present in red wines examined in many researches published in different magazines [20]. Trans-resveratrol occurs naturally in grapes however, cis-resveratrol and its glucoside are present in wines of diverse origin, analyzed by different technology. It was detected, that vinification process causes, that some amount of trans-resveratrol transforms into its cis-form. Nevertheless, trans-form protected from light can be stable for months, except in high pH, while cis-resveratrol protected from light was stable only in neutral pH [21].

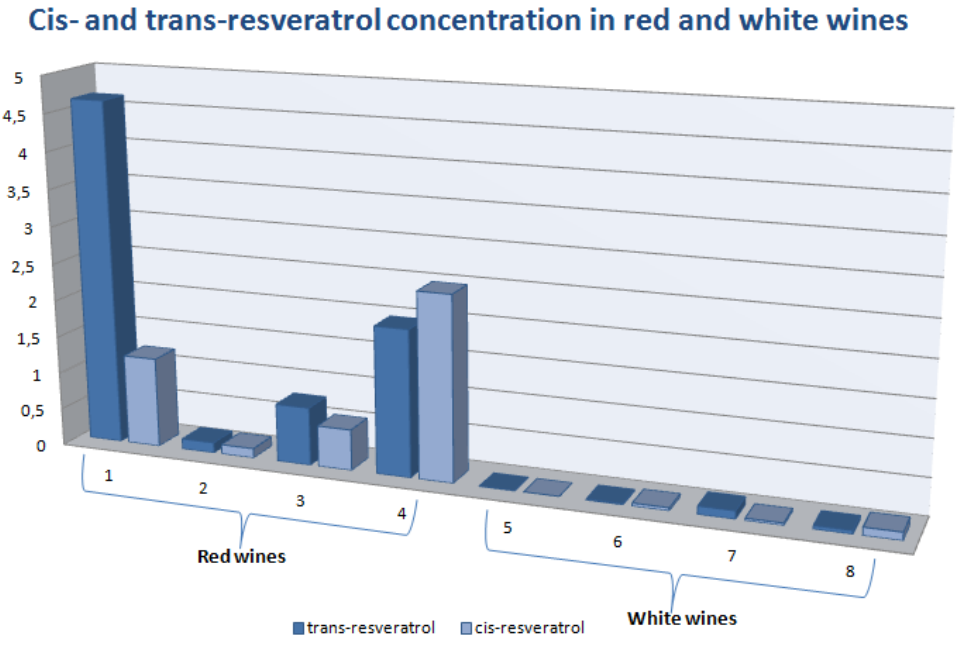


Figure 3 Resveratrol isomers concentrations in different types of wines [24-29].

Given phytoalexin is recognized by its biochemical and physiological properties including prevention and treatment of neurodegenerative diseases such as Alzheimer's and Parkinson's diseases, anti-inflammatory diseases such as rheumatoid arthritis. However, most widely known and widely applied are: inhibiting of cardiovascular disease and certain types of cancer [22,23].

3. Absorption Bioavailability and Metabolism of Resveratrol

Resveratrol is absorbed in a human body by intestinal villi of a small intestine. There is no correlation between the type of the food product consumed, the quantity of lipids in the meal and the assimilation of a given component. However, the food matrix may have an effect on bioavailability and an absorption of resveratrol in the human body, as well as sulfation, which is considered as the primary limitation factor of resveratrol bioavailability. There were many tests performed with human and animal participation, that showed very low absorption of resveratrol to the living tissues. This is due to the breakdown processes, that occur in the lumen in the intestine and in a liver. After absorption it is very quickly metabolized in hepatocytes with the half-decay time between 8–14 min. *In vitro* tests showed, that resveratrol in hepatocytes is almost completely metabolized under the influence of cytochrome P450 and converted to the form of piceatannol and tetrahydroxystilbene M1. Metabolites identified in human body are: resveratrol sulfate and resveratrol glucuronide. Then when it is transferred to the bloodstream, after 30 min it is transformed into sulfite derivatives. Following compounds

circulate in the blood to even 9 hours and then are excreted through the kidney and with faeces [30,31].

4. Effects of resveratrol to human body

It is well known, that increased consumption of monomeric resveratrol and/or resveratrol-containing foods may be associated with improved health. These health benefits are related to a diverse range of biological activities. In the following sub-sections, the positive effects of resveratrol on human body are discussed.

4.1.Cardioprotective effects of resveratrol

Coronary artery disease is the main reason of death in western countries. High intake of animal fat, mostly from meat, cheese and different dairy products results in occurrence of cardio-vascular disease. Moreover, the heavy use of tobacco products also impact on the coronary artery disease. Cardioprotective effects of resveratrol were detected on the basis of the researches, which showed inverse correlation between the consumption of a red wine and the incident of the coronary artery disease. French scientist discovered a phenomenon called "French paradox", which is based on the assumption, that moderate consumption of a red wine reduce the occurrence of the cardiovascular disease. Everything is due to the inhibitory effect on lipid peroxidation of a cell membrane. What is even more, protective action against oxidation of low density lipoproteins – LDL, (LDL oxidation influences the formation of fatty streaks in arteries, what further results in atherosclerosis development, what is dangerous for the human health.), what has influence on reducing the concentration of HDL cholesterol [2,4,30,32].

Additionally, resveratrol affects the metabolism of adenosine nucleotides in the vascular endothelium. It inhibits the activity of quinone reductase, which is responsible for the catalysis of the adenosine nucleotides reaction. This results in increasing activity of cellular antioxidant enzymes and increasing immunity of cells for oxidative stress. When the resveratrol is given to the cardiomyocytes, which are under the stress, the oxidative stress is reduced. Moreover, one may observe increasing enzyme activity, that prevent free radicals formation and increasing synthesis of NO. This mechanism protects organs against ischemia and its complication, which can occur like: arrhythmia, short-term mechanical dysfunction or even cell lysis [30].

Another health beneficial effect of resveratrol is the influence on the process of platelet aggregation and thrombin metabolism. It was observed, that even small amount of a red wine

may decrease platelet aggregation and blood clots formation. It inhibits the lipopolisaccharides (LPS) and thrombin with lipopolisaccharide, that stimulate platelet adhesion to collagen and fibrinogen. There were comparison test performed on a red wine and gin consumption by men. It was found out, that both alcoholic beverages have positive effect on the reduction inflammation process, which is strongly correlated with the atherosclerosis development and cardiovascular diseases. Both groups of men (one, drinking red wine and the second drinking gin) had lowered level of fibrinogen (responsible for the blood clotting) and lowered level of interleukin-1 (marker of inflammation). However, only men drinking the red wine had decreased concentration of the C Reactive Protein (CRP). Researchers claim, that this is thanks to the resveratrol, which does not occur in gin [30,31].

4.2.Anticancer properties of resveratrol

At high concentrations and appropriate conditions polyphenols may act in an opposite way and despite being antioxygenative agent they become prooxidative. They may contribute to form ROS (reactive oxygen species) and apoptosis of already tumor-altered cells [33]. Resveratrol is a phytoalexins, that is able to inhibit the cycloxigenite-1 (COX-1) enzyme and what is more can reduce co-substrate for cycloxigenite-2 (COX-2) enzyme [33,34]. Tumor cell growth is driven by prostaglandins, pro-inflammatory substances, that comes from the conversion of arachidonic acid. Inhibitory activities of resveratrol in according to this enzyme, prevents formation of prostaglandins, what stimulates the cancer chemoprevention [35]. However, it is observed, that discussed stilbene compound is able to cleavage double-stranded and single-stranded DNA and further mediate in degradation of DNA into smaller pieces in the presence of copper (II) ions. It not always might cause adverse effects for humans. Since the ROS from the oxidative action of resveratrol are related with mediation of apoptotic DNA fragmentation. Resveratrol can bind to the copper ions as well as catalyze their redox cycling [20].

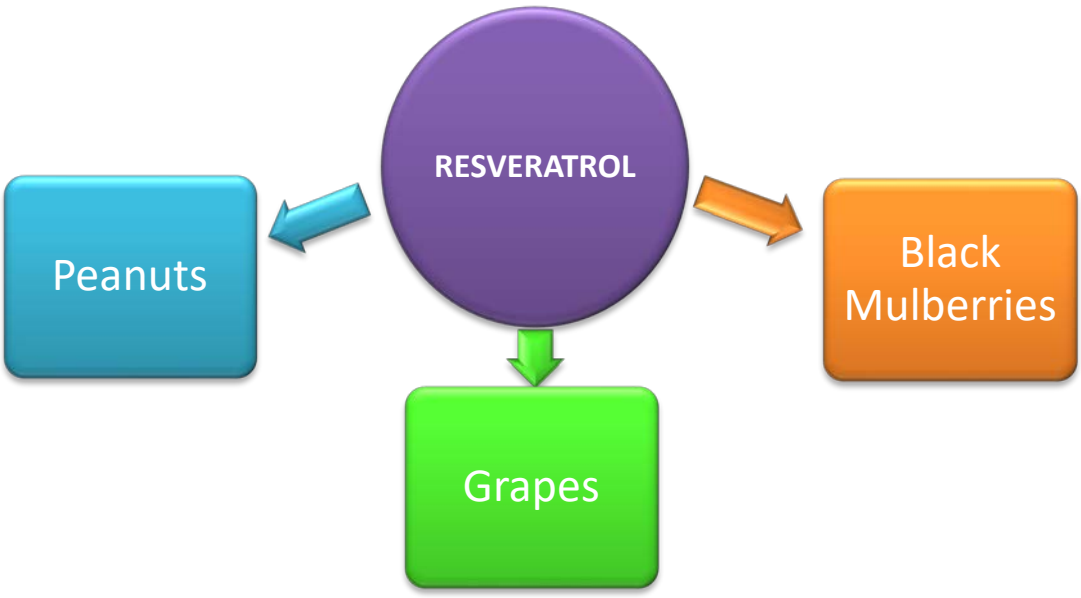
4.3. Resveratrol and the Nervous System Diseases

Diseases of nervous system affect many people and disturb normal function of the organism. Resveratrol thanks to its antioxidative properties can protect nervous system against degeneration. After rats examination, it is shown, that resveratrol attenuates β-amyloid toxicity in hippocampus cells by activation kinase C enzyme. It stimulates factors preventing free radicals action, including glutation, what further protects microglial cells against damage.

One of the reason of nervous system disease is deposition of β-amyloid in the brain, which enables proper work of nerve cells, impeding their communication. This leads to the memory loss or cognitive function disorder in human, what is commonly called Alzheimer Disease. There are several researches conducted to use resveratrol as compound helping in Alzheimer Disease treatment. Given compound limits the operation of proteins of β-amyloid and stimulates their decay to the form of short polypeptides and amino acids through the mechanism of proteasome. This promising result can help to inhibit or slow down the development of described disorder. Another reason of the nervous system degeneration is decreasing or inhibiting production of dopamine. This is the main factor of Parkinson Disease development. Following disorder disrupts the balance between cholinergics and dopaminergic neurons in the extra-pyramidal brain system causing necrosis of cells in a grey matter of brain, brainstem, cranial nerve nuclei and atrophy of the cerebral cortex. Resveratrol protects mesynchematic embryonic cells of mice against free radicals action by their removal. As well as it inhibits cyclooxygenase COX-2, factor catalyzing the reaction of compounds responsible for the inflammation process [30].

5. Sources of resveratrol

As the whole group of polyphenols thus resveratrol is most widely found in plants, both fruits and vegetables [2]. Figure 4 presented below, shows three main sources of resveratrol, based on the highest concentration of discussed stilbene.



224

225 **Figure 4 Three main sources of resveratrol in different plant species [36].**

226 Grapevines are especially rich in phenolic compounds, which are distributed with different
227 concentrations among the overground parts, present on the Figure 5.

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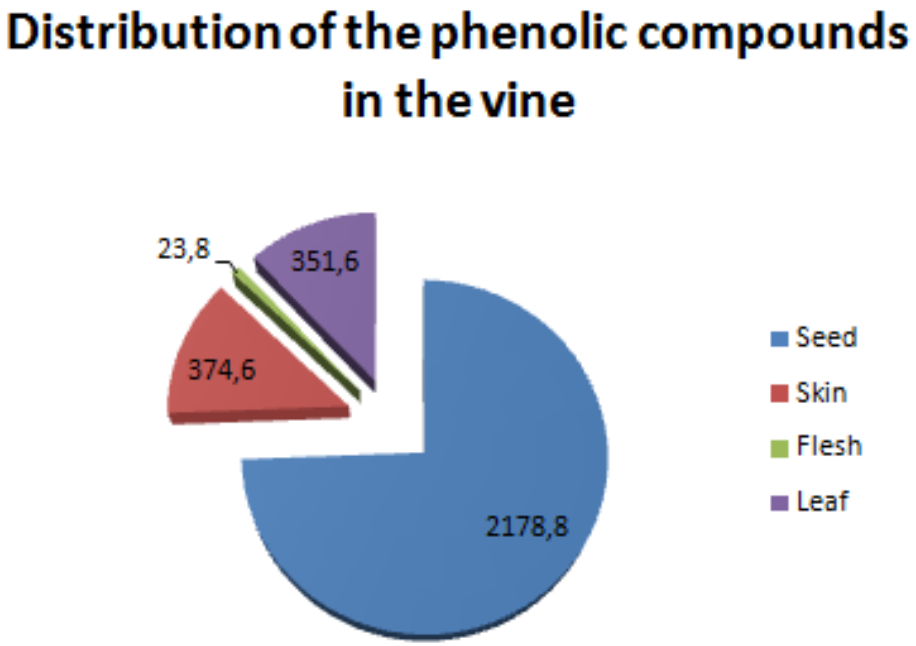

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230 **Figure 5 Distribution of the phenolic compounds in the vine, (Concentration is expressed**
231 **in mg/g GAE – gallic acid equivalent) [37].**

232

There are three main species of grapes, which are differentiated according to regions: *Vitis vinifera* – European grapes, *Vitis Labrusca* and *Vitis Rotundifolia* – grapes from North America and the third one French hybrids [37]. However, the level of investigated stilbenes in those fruits is highly correlated with the climate, soil, region etc. Favorable conditions for grapes cultivation are: moderate temperatures, long sunshine and moderate rainfall during summer. The quantity of every kind of this factor has significant impact on the amount of phenolic compound in grapes including resveratrol [38]. The concentrations vary also between dark and white grapes. The largest amount of resveratrol can be found in the skin of dark grapes. Furthermore, it results, that it is also present in products made from grapes like wines. There are lots of researches performed, in order to quantify the amount of resveratrol in the red and white wine, some of the results are presented on the Figure 6.

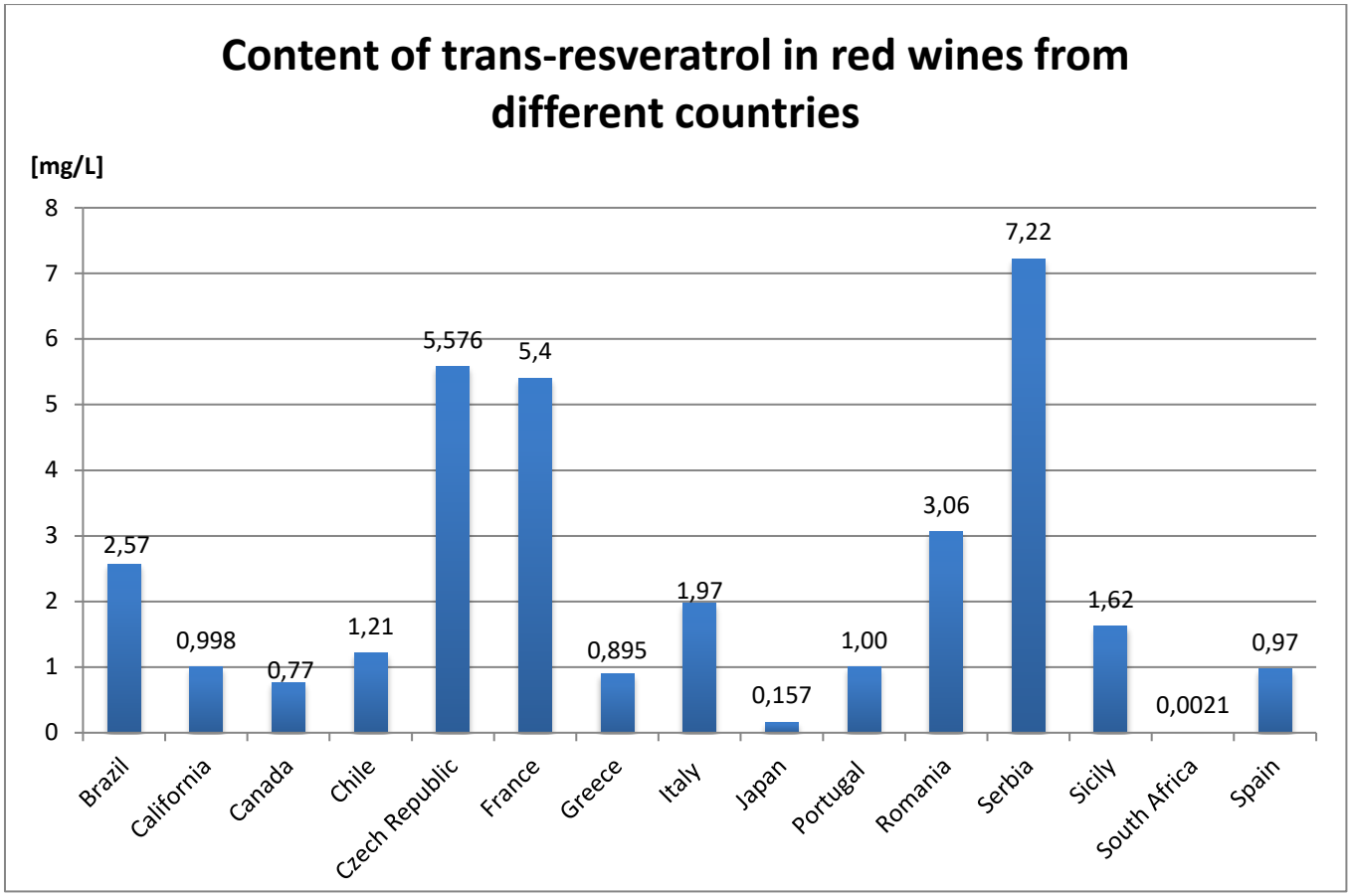

Figure 6 Trans-resveratrol concentration in red wines from different countries [24,36,39-41].

As it was discussed before, differences may result from the environmental conditions, that influence the production of trans-resveratrol by the grapevines like humidity or fungal diseases. Thus, the trans-resveratrol content may vary according to the harvesting date and

harvesting year [40]. The graph 2 presented above shows the highest concentration of trans-resveratrol in the Serbian wine and slightly lower, but still significant in wines from Czech Republic as well as France. This could be due to the fact, that the climatic condition of the year of the following wine production was very favorable. Warm and dry weather with a great number of sunny days has resulted in high resveratrol content. Moreover, grapes were probably at their best ripening stage having maximum resveratrol content in their structure. [24,40]. The worst results were obtained for the wine from South Africa. The environmental condition for the resveratrol production by grapes in this region (combination of temperature and humidity) were unfavorable and results in low the fungal pressure [28].

Despite grapes, there are lots of other fruits and vegetables, in which the resveratrol was determined and quantified. The highest amount was observed in black mulberries (*Morus nigra*). In general, berries are considered to be a good source of powerful antioxidants. They contain lots of phenolic compounds, mostly flavonoids and phenolic acids, but researches showed, that they are also a rich source of resveratrol [42]. Articles stated, that resveratrol content in a given fruit was on the level of 32,5 μg/g. [17]

Far lower amount, but still significant was observed in peanuts and resulting peanuts butter, which are one of the main source of resveratrol in the plant species. The quantity of the analyzed stilbenes were as follow:

- for peanuts it was approximately 5,1 ± 2,8 μg/g of fresh weight [18];
- for peanuts butter it was much lower and equaled approximately 0,3 ± 0,1 μg/g of fresh weight [18].
- for peanuts shell it was 91,0 μg/g of fresh weight [17].

Similarly, to the grapes, in which the highest content of resveratrol was detected in their skin, thus in many other fruits and vegetables, it is concentrated in high amount in their crust, what is presented on the Figure 7.

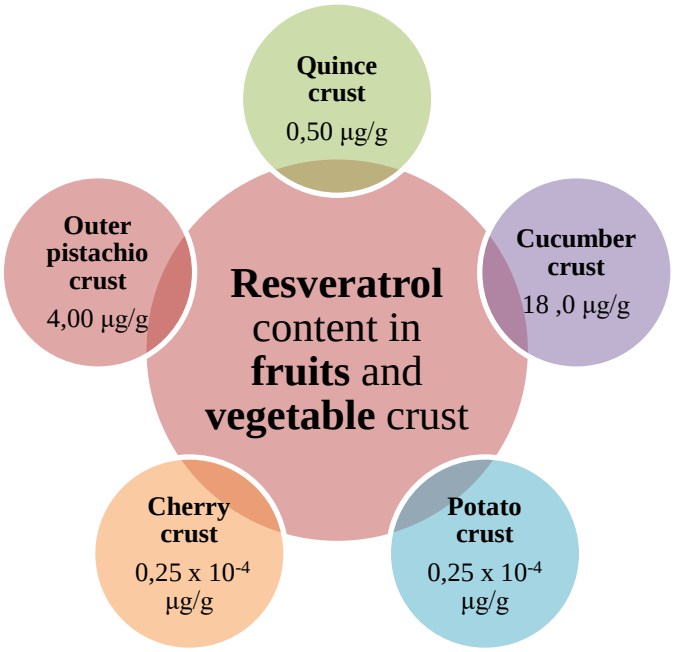

Figure 7 Concentration of resveratrol in crusts of selected fruits and vegetables [17].

6. Effects of Winemaking Technologies on Resveratrol Content

Due to the fact, that resveratrol has a numerous potential biological activities, it could contribute to the beneficial and health-promoting properties of wine [43]. Thus, knowledge on the factors impact on the amount of this compound in wine is important. It is well known, that resveratrol content in wine depends on different factors, including grapes variety, climatic conditions, harvest year, UV light, as well as winemaking technology, which is one among them, that can be controlled [43].

In general, it is well established, that prolonged time of maceration as well higher ethanol content positively affect the extraction of resveratrol and piceid. This is due to their better solubility. Several works have been established to present the impact on maceration time on the content of resveratrol [44]. It has been shown, that the highest concentrations of resveratrol and piceid were observed in wines produced with 10 days of maceration than those produced with 3 or 6 days [44]. In other hand, wines with relatively low concentration level of these compounds reached maximal concentrations after shorter periods of time, what could be due to the possibility of resveratrol metabolism by yeasts and enzymatic cleavage of the glycosidic bond of piceid [44]. Moreover, it was observed, that longer time of maceration increased the antioxidant activity of wines, which could results from the higher content of other phenolics. In another study [45], it was presented, that prolonged maceration did not

affect resveratrol concentration in wines made from the Castelao variety. Thus, it can be concluded, that the influence of maceration time could vary depending on the grape cultivar used. Concentration of resveratrol can increase during fermentation on the skins, however, it is important to note, that the final concentration of this phenolic compound in wine depends also on the ecological conditions and on grape variety. Another wine making parameter, that impact on resveratrol content in wine is thermovinification process, which requires intact or crushed grape to be heated (50°C to 87°C) for a short time [46]. Influence of two different thermovinification methods (60°C for 30min and 80°C for 3min) on resveratrol content in four different grape varieties was studied [47] and it was concluded, that content of resveratrol depends mainly on the grape variety. However, in comparison with control samples, used processes impacted on increasing of resveratrol content only in the Pinot Noir variety. In another study [48], Therefore, it can be suggested, that thermovinification could be responsible for the enhancement of concentration of resveratrol in wine, but this effect, as shown in some studies, may also differ according to grape variety [43].

Yeast selection is also an important factor, which can influence content of resveratrol in wine and only few works discussing this topic are reported. It was presented, that yeasts applied for must fermentation are among the factors responsible for the decrease of concentration level of resveratrol in wines [48], what was explained by the resveratrol absorption on cell walls or absorption/metabolism by the yeast cells. Moreover, the fact, that different types of yeast could affect the resveratrol content was also confirmed [44, 49]. It was also shown, that increase of resveratrol and piceid (up to four and two times, respectively) in Merlot wines produced using French yeast in comparison to Macedonian yeast [44]. Another suggestion was given by Vrhovsek et al. [50], who stated, that yeasts' β-glucosidase activity is depending on time of maceration Therefore, it can be concluded, that the final resveratrol and piceid concentration level is a result of yeast selection and maceration period.

7. Analytical challenges of resveratrol determination in wine

Wine is a very complex matrix containing except polyphenols many other chemical compounds like: sugars, dyes, tannins, minerals, vitamins, nitrogen compounds, organic acids, aromatic substances – compounds, having esters and aldehydes characteristics. All of the components play an important role in perceived aroma and flavor of the wine, but at the same time makes analysis more challenges and difficult. The structure of the wine matrices may

vary across wine from different winery. What is even more, the complexity of the structure of this alcoholic beverages may influence the interactions between volatile and nonvolatile compounds via different mechanisms. Due to this fact, the comparison between the concentration of resveratrol between different wines and other product should not take under consideration only the statistical parameters, but also the method of sample preparation and sample analysis [51,52]. Sample analysis can be performed using different method the most widely used and described in the literature are: liquid chromatography, gas chromatography, electrochemical method and spectrophotometry what is also shown on the Figure 8.

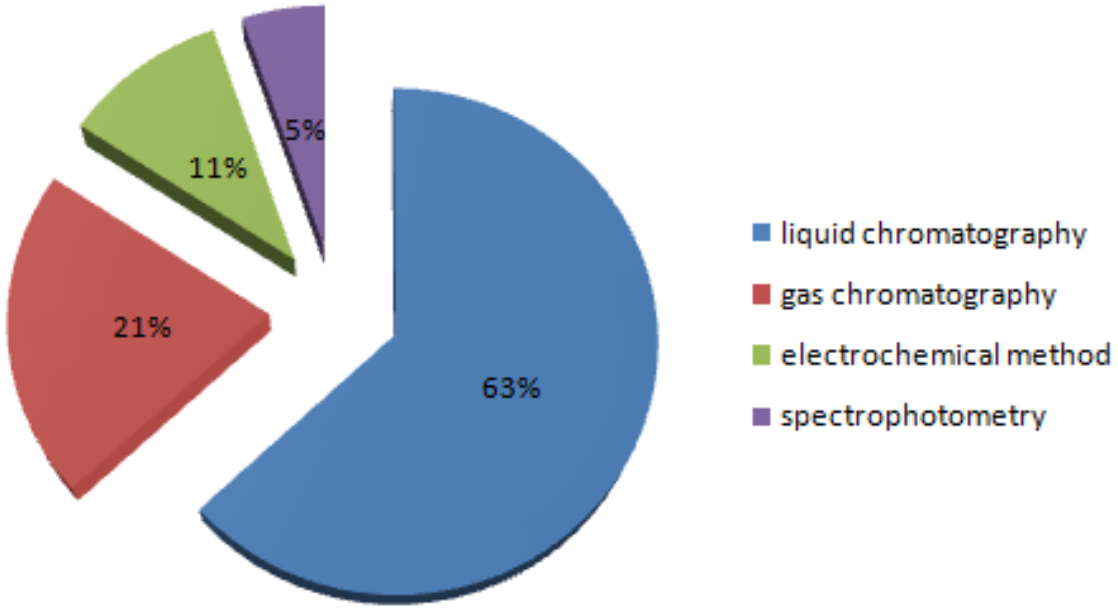

Figure 8 Percentage share of main methods used for determination and quantification of resveratrol from wine matrixes [Data base: Web of Science, Mendeley, Scopus].

However, due to the matrix complexity, the sample must be properly prepared to enable the analysis processes to take place. This is commonly performed by derivatization process, which:

- increase volatility, thermal stability of the analyzed sample, improve resolution as well as detection parameters when the gas chromatography is applied;
- improve sensitivity and separation properties when the liquid chromatography is utilized;
- as well as give charge to a specific components, while using electrophoresis [53].

In the literature the most commonly derivatization agents used for resveratrol determination are:

- bis(trimethylsily)trifluoroacetamide (BSTFA) (when GC is used as a separation technique);
- acetic anhydride (while using GC separation technique);
- dansyl chloride (when HPLC is used as a separation technique) [25,26,54,55,56].

Nevertheless, derivatization is a seconds step, firstly the extraction needs to be done. There are several different types of extraction methods, the most frequently mentioned in the literature are:

i) Solid Phase Extraction (SPE) in which the sample is passed through the C_{18} extraction cartridges after conditioning by methanol acting as a elution solvent. The SPE process is performed off-line and after pre-treatment, the extracted sample is further passed for the analysis [52,54,57].

ii) Solid Phase Microextraction (SPME); for the trans-resveratrol determination the fibers made from polydimethylsiloxane, polyacrylate, polymethylsiloxane/divinylbenzene can be used. Since resveratrol is a very polar compound with low vapor pressure the sample agitation is helpful, what in literature was noted with the speed of 500 rpm. This pre-treatment method is also done off-line [55].

iii) Liquid-liquid Extraction (LLE) to extract resveratrol by this technique, a methanol is used to obtain first extracts and then the precipitates are washed by the same elution solvent. After, that the sample is evaporated and the solid residue is dissolved in ethyl acetate and sodium bicarbonate solution. Once upon the sample are dried and dissolved in ethanol, it can be injected to the HPLC [40].

iv) Microextraction by Packed Sorbent (MEPS***)*** there are several factors affecting extraction by this technique like: type of sorbent material (C2, C8, C18, SIL, M1), number of extraction sample and sample volume. Once it was checked, that the most optimal conditions for resveratrol extraction is when the C8 sorbent is used, sample are small between 50 to 250 μL and there is one extraction cycle. What is more, the entire preparation sample set should last 3 min [58].

v) Stir Bar Sorptive Extraction (SBSE) together with SPME belong to the green preparation technique. Both use stir bars coated usually with a polydimethylsiloxane (PDMS) absorbent phase. However, SBSE use larger volume of PDMS. This results in higher recovery of compounds of researchers' interest. Moreover with combination of thermal desorption units the hyphenation between GC and SBSE can be achieved, what results in higher repeatability and sensitivity.[17]

vi) Dispersive liquid-liquid microextraction (DLLME) it is a technique considered as environmentally friendly, since it is characterized by the reduced consumption of organic solvents. Equilibrium conditions may by achieved within few seconds and high sample throughputs can be provided. Moreover, it is simple in use and low cost technique with high recovery and enrichment factor. However, before its implementation the acetylation is required [59].

All the extraction processes described above are usually performed off-line – samples are pretreated and then analyzed giving results, that can be collected and compared, what is showed on Figure 9.

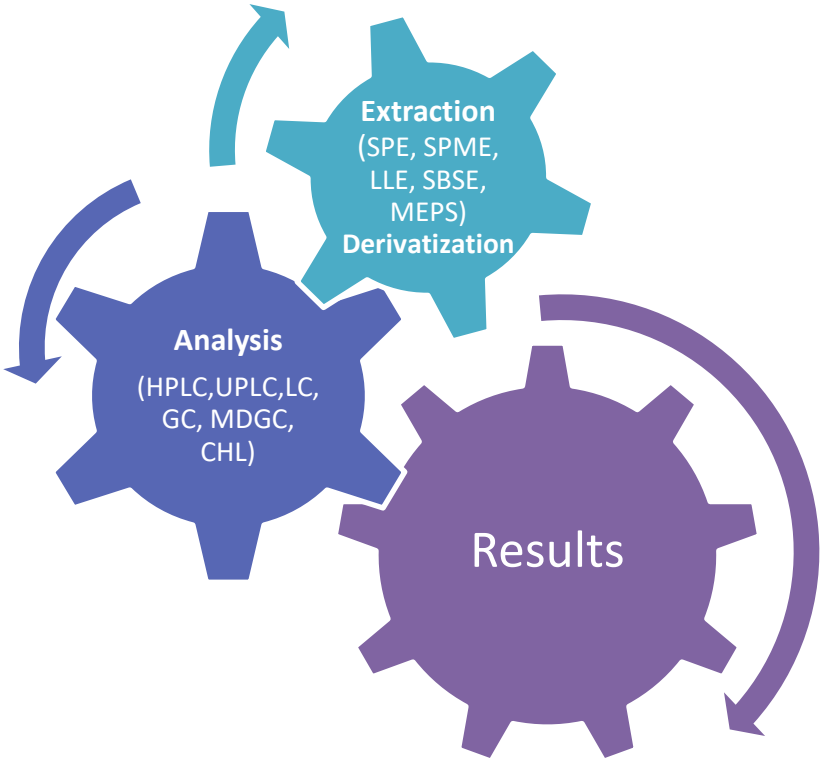

Figure 9 Graphical representation of the three main parts of analysis performance.

There are many methods described in literature used for determination and quantification of a given stilbenes. Information on analytical methodologies developed for resveratrol determination in wine samples are presented in Table 1.

7.1. Liquid chromatography

For determination of resveratrol in wine, the most commonly technique used is high-performance liquid chromatography (HPLC) coupled with different detection modes such as UV diode array detection (DAD), electrochemistry, fluorimetry and mass spectrometry. The detections based on fluorimetry, electrochemistry and mass spectrometry can offer higher sensitivity and selectivity than DAD. Initial studies, in which HPLC technique was employed as resolution technique, multi-step extractions prior to separation were carried out, while the sensitivity of detection in HPLC was enhanced significantly using fluorimetric or electrochemical detection. Moreover, only the *trans* form of resveratrol was measured. More recently, improved HPLC methods for detection and quantification of cis- and trans-resveratrol and piceid have been reported. The constituents of the mobile phase employed generally consisted of various mixtures of methanol (MeOH) [58,60] or acetonitrile (ACN) [24, 29, 38, 41] with water and electrolytes such as acetic acid [38], formic acid [41, 58] or ammonium acetate [29]. Generally, HPLC methods use a C18 normal phase- or a reverse phase column. Resveratrol can be easily determined in wines by means of direct injection into HPLC system (when the separation was coupled with photodiode array detection), however, sometimes the extraction and/or derivatization procedures need to be performed [39, 61]. In that cases, SPE or LLE are commonly used as extraction techniques and dansyl chloride as derivatizing agent.

Nowadays, ultra-performance liquid chromatography (UPLC) has become a wide-spread technique as well as new trend in separation sciences being regarded as a new direction for LC [58]. By application of sub-2μm particles, mobile phases at high linear velocities, and instrumentation that operates at higher pressures than those applied in HPLC, dramatic increases in sensitivity, resolution, and analysis speed can be obtained. This solution can also be applied for resveratrol determination in wine. For example, an ultra-fast and improved analytical methodology based on MEPS combined with UPLC was developed and validated for determination of resveratrol in wines by Gonçalves et al. [58]. Important parameters affecting the performance of MEPS including sorbent material type, cycles extraction number, and sample volume were examined. Validation experiments revealed very good recovery rate

(95±5.8% RSD), good linearity with R2 values >0.999 within the established concentration range, excellent repeatability and reproducibility values (RSD: 0.52% and 1.67%, respectively), thus demonstrating the robustness and accuracy of the MEPS(C8) /UPLC-photodiode array (PDA) method. On the basis of the analytical validation, the MEPS(C8)/UPLC-PDA methodology shows to be an improved, sensitive, and ultra-fast approach for determination of (E)-resveratrol in wines with high resolving power within 6 min.

7.2. Capillary electrophoresis

Capillary electrophoresis (CE) is an important tool for the determination of resveratrol in wine samples due to the potential for rapid and highly efficient separations. Moreover, high resolution power is achieved with low sample and reagent requirements. In contrast to GC, CE is suitable for thermal instable compounds. Furthermore, CE provides more rapid separations than LC. In spite of the advantages of CE, some drawbacks are observed, such as lower sensitivity and reproducibility of migration times than LC. From the other side, these disadvantages may be overcome by using a suitable pre-concentration method or highly sensitive detection systems. Several reports applied CE for the analysis of flavonoid compounds, however, only a few were specifically focused on resveratrol (Table 1). In fact, two major differences can be observed in the analytical approaches used. These are: the differences concern sample preparation (direct injection or SPE) and mode of separation, capillary zone electrophoresis (CZE) or micellar electrokinetic chromatography (MEKC). Some works described the direct analysis approach for determining resveratrol level in wines and only filtration of samples was carried out prior to final analysis by CE [62]. Direct analysis has two main advantages: reduction of time required for sample preparation and minimize the opportunity for *trans* to *cis* izomeration. From the other side, other compounds can co-migrate with one izomer form of resveratrol, thus, extraction is many often required. In that case, solid phase extraction is the technique most commonly used. Such solution allow to obtain cleaner and more concentrated samples [63]. Moreover, the procedure facilitated identification of analyte by altering sample conditions and removing interfering materials. However, major differences in the effectiveness of the SPE procedure could be seen depending on the mode of separation subsequently employed.

The main limitation of CE in the analysis of phenolic compounds including resveratrol, as compared to HPLC, is its low sensitivity. Application of LLE [64] or SPE [65] to concentrate

the sample is one of the alternatives to solve this problem. However, strategies for sample on-line pre-concentration in CE (e.g. LVSS, large-volume sample stacking) are of great importance due to the fact that they have shown advantages such as an increase in sensitivity without loss in separation efficiency [65]. These techniques can increase the detector signal by 10 to 1000 times through simple procedures, without the need to alter the instrumentation used. A capillary zone electrophoresis method was optimized to simultaneously separate resveratrol and other phenolic compounds present in wines, as well as to evaluate sample on-line preconcentration for detectability improvement by Ballus et al. [65]. The developed method showed excellent applicability due to the simple extraction procedure and the low volume of reagents used, reducing expenses for reagents and technicians.

7.3. Gas chromatography

Another approach for resveratrol determination, which is not as frequently used as HPLC, is application of gas chromatography. However, some studies are reported, mainly with the application of mass spectrometer as a detection technique. Nevertheless, since these compounds are non-volatile, the need for a chemical derivatization reaction, such as acetylation [54, 59] or silylation [55], prior to GC separation has long been considered the main drawback to this technique. Different type of derivatizing agents can be applied for chemical konversion of resveratrol what depends on the detection technique used for final determination, however, the most popular are: acetic anhydride and BSTFA. The derivatives obtained are characterized by such properties which are useful for application of analytical procedures based on GC techniques at the mixture separation, detection, and quantitative determination stages.

Recently, several works focused on determination of resveratrol in wine by application of derivatization process coupled with microextraction techniques are reported. The most popular microextraction technique used prior to final determination of this analyte in wine ia dispersive liquid-liquid microextraction [DLLME], however, also SBSE or SPME are often applied (Table 1). Reported methods were efficient and highly reproducible, allowing the accurate identification and quantification of resveratrol. Furthermore, the derivatization procedure and the overall analysis time were faster than in some LC methods, reaching LODs of the same order.

Table 1. Information on analytical methodologies developed for resveratrol determination in wine samples.

Separation technique	Sample preparation	Derivatization: Type of derivatizing agent	LOD/LOQ	Recovery	RSD	Detection	Number of other analytes	Sample throughput	Time of analysis	Ref
HPLC	SPE	No	**LOD**: 0.4 mg/L **LOQ**: 1.32 mg/L	99.3%	5.0%	UV	0	8	7 min	52
DI-HPLC	-	No	**LOD**: 0.005 mg/L **LOQ**: 0.015 mg/L	78%	3.1-5.2%	DAD-UV-Vis	1	2	25 min	39
MDGC	SPME	Yes: BSTFA	**LOD**: 2.85 x 10^(-6) mg/L **LOQ**: 9.41 x 10^(-6) mg/L	83.6%	7.1%	MS-O	0	2	25 min	55
RP-HPLC	-	No	**LOD**: 0.003 mg/L **LOQ**: 0.01 mg/L	2.3%	97.2%	UV-electrochem	1	2	30 min	24
GC	SBSE-TD	Yes: acetic anhydride	**LOD**: 4.40 x 10^(-6) mg/L **LOQ**: 1.46 x 10^(-5) mg/L	94%	8.4%	MS	5	3	16 min	25
CHL	SPE	No	**LOD**: 0.002 mg/L **LOQ**: 0.005 mg/L	100.2 %	3.80%	Photomultipler tube	0	6	10 min	57
GC	SPE-DLLME	Yes: acetic anhydride	**LOD**: 1.51 x 10^(-6) mg/L **LOQ**: 5 x 10^(-6) mg/L	106%	5%	TOF-MS	38	3	20 min	26

GC	SPE	Yes: acetic anhydride	**LOD**: 0.24 x 10^(-6) mg/L **LOQ**: 0.8 x 10^(-6) mg/L	100%	4.1-7.8%	MS	1	1	33 min	54
DI-HPLC	-	No	**LOD**: 0.033 mg/L **LOQ**: 0.1 mg/L	89%	199%	UV	0	3	19 min	36
DI-HPLC	-	No	**LOD**: 0.12 mg/L **LOQ**: 0.3 mg/L	98.29%	0.85-2.13%	ESI-MS	1	2	25 min	41
ERGO/GC - electrode	-	No	**LOD**: 32 x 10^(-6) mg/L **LOQ**: 105,6 x 10^(-6) mg/L	98%	7.3%	DPV - SEM	0	6	10 min	67
HPLC	LLE	Yes: Dansyl chloride	**LOD**: 0.13 mg/L **LOQ**: 0.41 mg/L	96%	4%	FED	2	5	11 min	56
HPLC	LLE	No	**LOD**: 0.1 mg/L **LOQ**: 0.33 mg/L	89%	5%	PDA	0	3	16 min	40
HPLC	-	No	**LOD**: 0.2 mg/L **LOQ**: 0.66 mg/L	100.42%	10%	UV	0	3	19 min	68
LC	-	No	**LOD**: 0.15 mg/L **LOQ**: 0.495 mg/L	92%	5.8%	MS	1	2	30 min	27
UPLC	MEPS	No	**LOD**: 0.21 mg/L **LOQ**: 0.68 mg/L	99.4%	5.8%	PDA	0	4	13 min	58
TFC-LC	-	No	**LOD**: 18000 mg/L **LOQ**: 60000 mg/L	95%	5.5%	MS	5	1	40 min	28

LC	-	No	**LOD**: 8.8 x 10^(-5) mg/L **LOQ**: 0.003 mg/L	102.4 %	3.5%	UV/VIS-MS	1	12	5 min	29
CE	-	No	**LOD**: 0.06 mg/L **LOQ**: 0.2 mg/L	97.92%	2.07%	ED	0	3	17 min	62
DI-HPLC	-	No	**LOD**: 0.032 mg/L **LOQ**: 0.1 mg/L	?	5.26%	UV-vis	3	3	20 min	69
HPLC	SPE	No	**LOD**: 0.0007 mg/L **LOQ**: 0,02 mg/L	99%	2.85%	UV-vis	0	3	18 min	70
UPLC	SPE	Yes: acetic acid	**LOD**: 0.00048 mg/L **LOQ**: 0.0016 mg/L	105.1%	7.93%	MS/MS	12	60	1 min	71
CZE	SPE	No	**LOD: 0.26 mg/L**	-	-	UV	0	3	4 min	[65]
CZE	LVSS	No	**LOD: 0.06 mg/L LOQ: 0.2 mg/L**	96.5 %	0.93%	UV	15	4	20 min	[66]
GC	DLLME	Yes: TCE	**LOQ: 0.6 ng/mL**	97 %	3.4 %	MS	2	4	30 min	[59]
CZE	SPE	No	**LOD:** 0.03 mg/L LOQ: 0.06 mg/L	-	-	UV –VIS	0	4	7 min	[72]

CZE, capillary zone electrophoresis; HPLC- high-performance liquid chromatography; DI-HPLC – direct injection HPLC; MDGC – multi-dimension gas chromatography; RP-HPLC – riversed phase HPLC; GC – gas chromatography; LC – liquid chromatography; LVSS - large-volume sample stacking; UPLC – ultra-performance LC; TFC – LC – turbulent flow chromatography – LC; CHL – chemiluminescence; CE – capillary electrophoresis; CZE - capillary zone electrophoresis; SPE – solid phase extraction; SPME – solid phase microextraction; SPE-DLLME – SPE-dispersive liquid-liquid microextraction; SBSE-TD – stir bar sorptive extraction-thermal desorption; LLE – liquid-liquid extraction; MEPS – microextraction by packed sorbent; UV – ultra violet; DAD – UV-Vis – diode array UV-Vis detector; MS – mass spectrometry; MS-O – MS-olfactometry; TOF – MS – time-of-flight-MS; ESI-MS – electrospray ionization – MS;

DPV-SEM – differential pulse voltammetry-scanning electron microscopy; FED – fluorescence detection; PDE – photodiode array detector; ED – electrochemical detection; TCE - 1,1,1-trichloroethane

7.4. Green Assessment of selected analytical procedures applied for determination of resveratrol in wine samples

Although, the emissions from analytical laboratories are generally low, they are also more dispersed than industrial emissions, making them more difficult to control. Therefore, to remove or at least to reduce the side effects of analytical practices on operators as well as the environment, ideology of green analytical chemistry (GAC) was introduced in 2000 [73]. Activities of GAC are focused on several issues of which the most important are: the reduction of negative impact of chemical analyses on the environment; instrumentation and methodologies developments; and enabling analytical laboratories to be sustainable in terms of energy and costs. Due to the fact that it is a great challenge to reach an acceptable compromise between increasing the quality of results as well as improving environmental friendliness of analytical procedures, it is important to follow the principles and guidelines of GAC [74]. From the other side, some problems with GAC exist and one of the most pressing is the lack of well established methods of "greenness" assessment. And although, there are numerous analytical protocols examples reported in the literature, that claim to be green, these statements are very rarely supported by any evidence in the form of applied greenness metrics, or comparison with previously developed analytical or standard procedures [75]. Therefore, calculations or visual presentations, that provide an answer as to whether an analytical methodology can be regarded as green should be performed utilizing tools that serve such assessment.

In this section several analytical methodologies applied for resveratrol determination in wine [24, 25, 26, 36, 56, 58, 59, 62, 65, 66, 72] , samples by application of different type of methods (GC, LC and CE), that are mentioned in this paper are assessed in respect to the green character. To evaluate these selected protocols, Analytical Eco-Scale as well as recently published GAPI index (Green Analytical Procedure Index) were used.

Eco-Scale is a tool based on penalty points (PPs) subtracted from a base of 100, and these PPs are assigned for each compound/reagent relating to the amount, utilization of the chemicals, occupational hazards, high energy consumption, and waste generation [76]. The higher the score, the greener and more economical the analytical procedure is. The Analytical Eco-Scale has several advantages but also many drawbacks including: ease of score calculation; inclusion of different aspects of environmental impact; and ease of comparison of analytical procedures [76, 77]. The main drawbacks of this tool include: no information about the structure of the hazards is obtained; lack of information on the causes of environmental

impact of the analytical procedure, such as the use of solvents, other reagents, occupational hazard or generation of waste.

Considering the penalty points (PPs), calculated for each procedure used for wine analysis (Table 2), it can be concluded, that Procedure 1 based on SBSE-TD-GC-MS [25] can be assigned as green (Score: 93 PPs). Also all procedures based on capillary electrophoresis technique gives satisfactory results (Score: 84-88). The worst evaluated here procedures in term of "green" profile are Procedure 3 [55], Procedure 6 [56] and Procedure 7 [24].

Without a doubt, this Analytical Eco-Scale is a good semi-quantitative tool for laboratory practice and educational purposes. It is simple and fast to use, has well-defined criteria of evaluation and can be applied to any known and new methodologies.

To evaluate three the best procedures based on GC. LC and CE techniques, GAPI tool was applied. In GAPI, a specific symbol with five pentagrams could be used to evaluate and quantify mainly from green to yellow and red - the low, medium and high impact to environment involved for each step of analytical methodology [78]. Each field reflects different aspect of the described analytical procedure and the field is filled green if certain requirements are met.

Taking into consideration evaluated Procedures 1, 8 and 10 applied for determination of resveratrol in water samples, it is visible at first glance, that the Procedure 8 does not require advanced sample preparation meaning extraction and derivatization procedure and from this point of view it can be considered greener than the other two methodologies. From the other side, this procedure obtained worst results in case of consideration reagent and solvents used for the procedure as well as occupational hazards. Here, the best results are obtained for Procedure 1 based on gas chromatography technique.

Taking into account results obtained by application of Eco-Scale and GAPI, it can be concluded, that the "greenest" procedure is the Procedure 1. This procedure is also characterized by very low limit of determination. In addition, good recovery and precision are declared.

Table 2. Calculated PPs for evaluated analytical procedures for resveratrol determination in wine

PROCEDURE 1 [25]		**PROCEDURE 2 [59]**		**PROCEDURE 3 [55]**		**PROCEDURE 4 [26]**	
Reagents	**PPs**	**Reagents**	**PPs**	**Reagents**	**PPs**		**PPs**
Na_2HPO_4	0	Acetone	4	Water	8	Water	0
Water	0	Internal standard	1	Internal standard	1	Internal standard	1
Internal standard	1	1,1,1-trichloroethane	2	BSTFA + TMS	6	Ethanolic solution	2
Acetic anhydride	1	Acetic anhydride	1	Ethanol	8	Methanol	4
		K2HPO4	0			K_2HPO_4	0
		CCl_4	4			Acetic anhydride	1
						Acetone	4
						Toluene	4
	Σ 2		Σ 12		Σ 23		Σ16
Instruments	**PPs**	**Instruments**	**PPs**	**Instruments**	**PPs**	**Instruments**	**PPs**
Transport	1	Transport	1	Transport	1	Transport	1
·GC-MS	3	GC-MS	2	GC–MS-olfactometry	3	GC-EI-QTOF-MS	3
upational hazard	0	Occupational hazard	0	Occupational hazard	0	Waste	2
ste	1	Waste	1	Agitation	1	Centrifugation	1
				Waste	1	Occupational hazard	1

	Σ 5		Σ 4		Σ 6		Σ 8
Total PPs: 7 **Score:** 93		**Total PPs:** 16 **Score:** 84		**Total PPs:** 29 **Score:** 71		**Total PPs:** 24 **Score:** 76	
PROCEDURE 5 [58]		**Fish analysis: PROCEDURE 6 [56]**		**PROCEDURE 7 [24]**		**PROCEDURE 8 [36]**	
Reagents	**PPs**	**Reagents**	**PPs**	**Reagents**	**PPs**	**Reagents**	**PPs**
Formic acid	2	Diethyl ether	2	Water	0	Water	0
Ethanol	12	Methanol	8	Internal standard	1	Acetonitrile	8
Acetic acid	1	Formic acid	2	Ethanolic solution	2	H_3PO_4	0
Internal standard	1	Dansyl chloride	8	Ethanol	8		
Water	0			Acetonitrile	8		
				H_3PO_4	1		
				NaCl	1		
	Σ 16		Σ 20		Σ 21		Σ 8
Instruments	**PPs**	**Instruments**	**PPs**	**Instruments**	**PPs**	**Instruments**	**PPs**
Transport	1	Transport	1	Transport	1	HPLC-UV-VIS	2
LC-PDA	2	HPLC-fluorimetric detection	2	HPLC-UV-ED	3	Storage temperature	1
upational hazard	1	Occupational hazard		Occupational hazard	0	Occupational hazard	0
ste	3	Waste	1	Storage temperature	1	Waste	3
ume	1		3	Waste	2		

	Σ 8		Σ 7		Σ 7		Σ 6
Total PPs: 24 **Score:** 76		**Total PPs:** 27 **Score:** 73		**Total PPs:** 28 **Score:** 72		**Total PPs:** 14 **Score:** 86	
PROCEDURE 9 [62]		**PROCEDURE 10 [65]**		**PROCEDURE 11 [66]**		**PROCEDURE 12 [72]**	
Reagents	**PPs**	**Reagents**	**PPs**	**Reagents**	**PPs**	**Reagents**	**PPs**
H_3BO_3–$Na_2B_4O_7$	2	Methanol	4	Boric acid	1	Sodium tetraborate	0
Ethanol	4	Internal standard	1	Internal standard	1	Methanol	4
Internal standard	1	Formic acid	1	NaOH	1	Ethanol	4
Water	0	Borate buffer	0	Ethanol	4	Sodium carbonate	0
		Water	0			Potassium peroxodisulfate	1
		NaOH	1			Gallic acid	1
	Σ 7		Σ 7		Σ 7		Σ 10
Instruments	**PPs**	**Instruments**	**PPs**	**Instruments**	**PPs**	**Instruments**	**PPs**
Transport	1	Transport	1	Transport	1	CE-UV-VIS	2
CE-ED	2	CE-UV	2	CE-DAD-UV	2	Storage temperature	1
upational hazard	1	Occupational hazard	0	Occupational hazard	0	Occupational hazard	0
ste	2	Waste	2	Storage temperature	1	Waste	3
age temperature	1			Waste	2		
	Σ 7		Σ 5		Σ 6		Σ 6

Total PPs: 14 **Score:** 86	**Total PPs:** 12 **Score:** 88	**Total PPs:** 13 **Score:** 87	**Total PPs:** 16 **Score:** 84
BSTFA, N,O-Bis(trimethylsilyl)trifluoroacetamide; CE, capillary electrophoresis; ED, electrochemical detection; GC, gas chromatography; HPLC, high performance liquid chromatography; PDA, photodiode aray detector; TMS, trimethylsilyl; UV, ultraviolet detector			

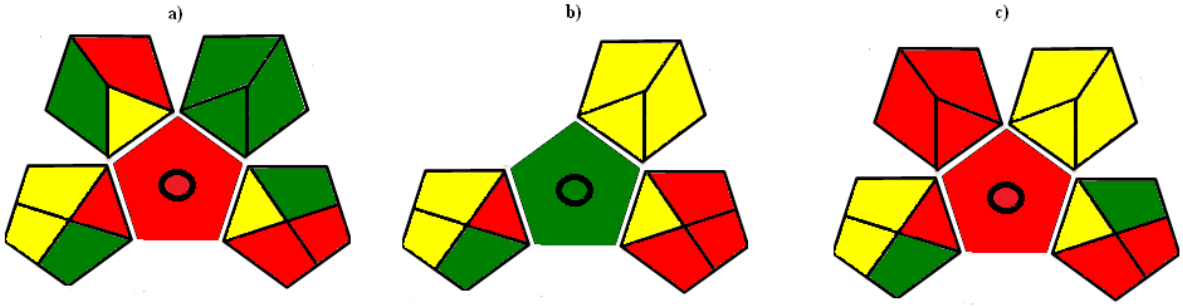

Figure 10. Assessment of the green profile of evaluated procedures (Procedure 1 [25], Procedure 8 [36] and Procedure 10 [65]) applied for resveratrol determination in wine samples using GAPI tool.

Conclusions

Increasing interest in resveratrol, as a compound, that can positively influence the human health. However, the absorption of resveratrol is very low due to the breakdown processes, that occur in the human body. It is quickly metabolized to resveratrol sulphate and resveratrol glucuronide, which in the blood stream are transformed to the sulphite derivatives and excreted. This force researches to examine different food products to find those with the highest resveratrol content. It is proved, that grapes especially grapes skin are characterized by the high content of a given stilbene. Furthermore, products made from them like wines mostly red wines, in which production not only juice, but also skins are used, are also characterized by high resveratrol content. Wine matrix except polyphenols includes sugars, dyes, tannins, minerals, vitamins, nitrogen compounds, organic acids, aromatic substances – compounds, having esters and aldehydes characteristics. Given matrix complexity makes the analysis more challenging. Sample preparation is a crucial aspect and different types of extraction was compared together with separation and detection techniques. The comparison was based upon several factors like: LOD/LOQ, recovery, RSD, number of analytes, sample throughputs and the time of analysis. Taking into account the green assessment using the Eco-Scale the best methods were those based on SBSE-TD-GC-MS and those used capillary electrophoresis, but in the presented review also GAPI tool was used to evaluate best method from GC, LC and CE technique. According to this tool the best result was obtained for gas chromatography which obtained good results in case of sample preparation, recovery and precision. As well as it is characterized by very low limit of detection.

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