Review



# Methods for Synthesis and Extraction of Resveratrol from Grapevine: Challenges and Advances in Compound Identification and Analysis

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*Review*

# Methods for Synthesis and Extraction of Resveratrol from Grapevine: Challenges and Advances in Compound Identification and Analysis

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**Abstract:** Resveratrol is the most important biopotential phytoalexin of the stilbene group (natural polyphenolic secondary metabolites), synthesized naturally by the action of biotic and abiotic factors on the plant. The yield of individual bioactive compounds isolated from grapevine components, products and by-products is directly dependent on the conditions of the synthesis, extraction and identification techniques used. Modern methods of synthesis and extraction, as well as identification techniques, are centred on the use of non-toxic solvents that have the advantages of the realisation of rapid extractions, maintenance of optimal parameters, and low energy consumption, being a challenge with promising results for various industrial applications. Actionable advances in identifying and analysing stilbenes consist of techniques for coupling synthesis/extraction/identification methods that have proven accurate, reproducible and efficient. The main challenge remains to keep resveratrol compositionally unaltered while increasing its microbiome solubility and stability as a nutraceutical in the food industry.

**Keywords:** resveratrol; grapevine components; products; by-products; synthesis; extraction; identification; stability

## 1. Introduction

Originating from grape skins, resveratrol is a phytoalexin, a compound produced by grapevine components that acts similarly to an antibiotic in response to the attack of stressors such as the fungus *Botrytis cinerea* [1,2]. *Cis-* and *trans*-isomer resveratrol is found both in grapevine components and in products and by-products resulting from applied technologies, with considerable attention in the biomedical literature being given to the t*rans*-resveratrol isomer [3,4,5'trihydroxyl-trans-stilbene (tR)]. Many publications attest to the presence of resveratrol in grape berries, skin, seeds, pulp, stems, stalks, leaves, vine shoots or roots. Resveratrol is also present in products resulting from the various technologies applied to grapes: wine and juice, grape skin powder, raisins, and by-products of the vine: grape pomace, grape canes, wine less, and various extracts. Recent studies show that the content of resveratrol is higher in the cut grape pomace than in other components (wine, grapes, raisins, etc.), varying depending on numerous intrinsic and extrinsic factors, with the synthesis and extraction methods applied to have a major role in its quantity and stability [3,4]. As early as [5] showed how the concentration of resveratrol during alcoholic fermentation increases in the must and decreases in the skins of black grapes while remaining constant in the seeds. The study shows that after malolactic fermentation, the amount of resveratrol is about twice the amount measured at the end of alcoholic fermentation, indicating a resveratrol amount probably in the form of glucosides or oligomeric form from which the enzymatic activity of malolactic bacteria could release free resveratrol. In the last 15 years resveratrol has become an important qualitative parameter of wine because of the several beneficial effects on human health revealed by biological and clinical studies [6]. The identification of resveratrol in grapevine [7] makes this plant of particular importance for industrial, medical and

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food research [8], with the demand for products based on resveratrol extracted from grapevine components, products and by-products increasing. Numerous types of research prove the beneficial role for health, the diseases covered being among those with increased incidence: anticancer activity [9], cardioprotection [10], neuroprotection via upregulation of endogenous antioxidant expression and activity [11], protection against diabetes [12] or reducing the effects of some neurological diseases, such as Alzheimer or Parkinson, [13,14], antioxidant activity [15–17], inhibition of platelet aggregation [18] of anti-inflammatory activity [19], etc (Figure 1).

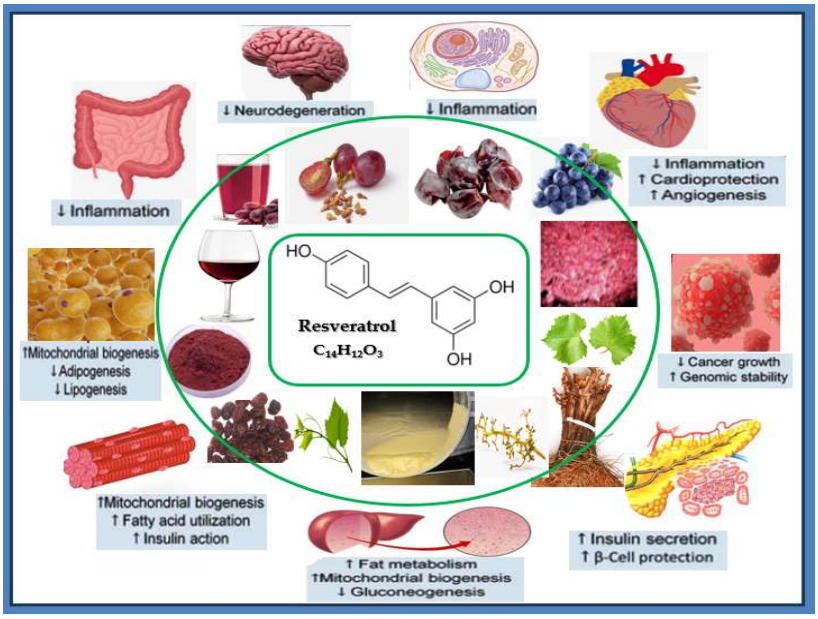


**Figure 1.** Biological effects of resveratrol from grapevine components, products and by-products.

In recent years, understanding the "French Paradox" has stimulated a new research interest, revealing that resveratrol synthesized in grapes and contained in wine plays a beneficial role in certain cardiovascular regulatory mechanisms [20,21]. Research in the food industry is interested in using resveratrol in products to increase their functionality [22,23]. Also, maintaining stability after extraction represents a particular interest of current research. In this context, several strategies for the biotic synthesis of resveratrol have been attempted, including yeast [24] and bacterial or recombinant plant engineering to ensure a constant supply of resveratrol [25]. However, continuous efforts are being made to find better sources or strategies for the production of higher and more stable amounts of resveratrol (green extraction with mixture formation [26], microencapsulation [27], etc. The progress made by researchers so far in the techniques for extraction and identification of resveratrol and, in particular, *trans*-resveratrol is evident. Thus, research in the last decade has focused on the modernization of synthesis and extraction methods in order to create premises in which the use of low-toxicity substances can have proven efficacy, decreasing extraction time by making the extraction methods more efficient with reduced energy consumption, the challenge of keeping intact the bioactivity of resveratrol is still topical due to its instability. This study presents the most important methods of synthesis and extraction, the progress made by researchers in terms of identification techniques, as well as aspects related to the use of several methods simultaneously (coupling of methods) so that the results obtained lead to the accurate determination of resveratrol under the most natural conditions, taking into account the current directions of its use.

## 2. Methods of Synthesis and Extraction

The methods for synthesising and extracting resveratrol from grapevine components and products are diverse (chemical, natural, biotechnological), utilizing high-performance technology

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and high-purity gradients. Recently, alternative solvents (deep eutectic solvents - DES) have significantly increased the concentration of extracted polyphenols, and some methods, such as the ultrasound-assisted extraction method (UAE), provide higher extraction yields than classical methods. Current research is focused on the use of combined synthesis and extraction methods (chemical with natural or natural with biotechnological, etc.) which have proven the efficiency of the process.

### *2.1. Synthesis and Chemical Extraction Methods*

The best classical solvents for extracting stilbenes from grapevine cords are alcohols (methanol or ethanol) from the protic group [28]. One of the most well-known methods for the chemical extraction of polyphenols is the MeOH method developed by [29]. Thus, dried grape skin samples (approximately 2g) and dried seed samples (approximately 1g) were extracted three times with 20 mL MeOH containing 0.1% HCl (skin) and 10 mL MeOH/$H_2O$ (80/20) containing 0.1% HCl (seeds). The research by [30] shows that total polyphenols and RSA were higher for grape seed extracts, followed by grape skin and pulp extracts using MeOH/$H_2O$ mixture (70:30, v/v) as solvent. Also, [31] obtained good results for extracting stilbenes from grapevine compounds using resveratrol and MeOH and found that the other stilbenes were better extracted in acetone. The optimization of solvent (water, $C_2H_5OH$, acetone-$C_3H_6O$, MeOH and butanol) extraction on phenolic compounds from grapes must based on a central composite design was investigated by [32], concluding that acetone and $C_2H_5OH$ allow the extraction of phenolic compounds from grape must, $C_2H_5OH$ is more recommended because it is considered an environmentally friendly solvent. A good extraction was obtained with $C_2H_5OH/H_2O$ (80:20, v/v) by [33], showing that recovery (> 96%) and reproducibility (6.83-15.13%) were satisfactory. After extraction, the resveratrol isomers in grape skin were quantified by high-performance liquid chromatography coupled to a visible ultraviolet-visible diode-array detector. In order to improve the *trans*-resveratrol content (endogenous) in post-harvested grapes, several short anoxic treatments with dry nitrogen were tested, the results allowing the design of an anoxic treatment protocol for grapes prior to the vinification process, which resulted in *trans*-resveratrol enriched wines [34]. In another study, the skins of red and white grapes were separated from the other grape pomace residues and subjected to extraction with 1:1 $C_2H_5OH$-acidic water as an extractant to obtain as many phenolic compounds as possible from this material [35]. Combined methods to increase the efficiency of the synthesis and extraction processes are also used by [36], evaluating the effect of pressure (100, 400 bar), temperature (35, 55°C) and modifier addition (5% $C_2H_5OH$, v/v) to identify the optimal extraction of resveratrol from grape pomace obtained as a by-product in winemaking. The best results were obtained when combining high pressure with low temperature, using 5% $C_2H_5OH$, v/v as co-solvent. Another method involving pre-pressure, temperature and carbon dioxide is based on supercritical extraction and was developed by [37]. They use the SOX in which the pulp obtained from the grape skin was extracted with a supercritical $CO_2$ fluid (SFE) containing 10 WT% $C_2H_5OH$ 96% at 300 bar and 40°C, with a single separator (operating at 40 bar and 40°C), the extraction being carried out until the powder was completely exhausted (about 48 h), the $C_2H_5OH$ being removed by vacuum distillation.

### *2.2. Synthesis and Natural Extraction Methods*

Some of the most important extraction methods applied to grapevine products and by-products, in addition to conventional extraction by maceration (MAC), are represented by sustainable extraction techniques, such as microwave-assisted processes (MAE), ultrasound, pressurized supercritical fluids, hydrothermal fluids, in order to obtain safe, stable and high-quality extracts.

#### 2.2.1. Conventional Extraction (Maceration)

Carrying out dynamic MAC with hydroethanol solution on grape seed powder (30 mL to 1 g of powder sample) followed by simple solid-liquid organic extraction yielded good results in the

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research by [38]. The combination of cold MAC with thermomaceration (heating crushed grapes at 50°C for 60 minutes) and enzymatic maceration (1 mL/L of the pectolytic enzyme was added) performed by [39] increased the total phenolic compounds content (*trans*-resveratrol increases from 0.09 to 0.23 mg/100 g). The total phenolic compounds and antioxidant capacity were monitored during conventional fermentation (10 days) by [40], the main conclusion is that compared to conventional heat treatment, the phenolic compounds content must be doubled immediately after OH treatment (ohmic heating) at preset parameters (E = 55 V/cm, t = 60-90 s, T = 72°C).

Testing of using an alternative maceration technique (nitrogen maceration) instead of carbonic maceration by [41] resulted in increased polyphenols and anthocyanins in macerated wines. In another research, four environmentally friendly extraction methods were tested, obtaining 29 polyphenols, including stilbene, from grapevine stems, involving the use of water and polyethylene glycol (PEG) as environmentally friendly solvents, together with MAC, microwave, ultrasound and reduced pressure techniques, two of which had higher efficacy (water + microwave + ultrasound + atmospheric pressure (1121 ± 4.8 µg/g *trans*-resveratrol), water + microwave + ultrasound + reduced pressure (916 ± 1.9 µg/g *trans*-resveratrol)), the others yielding lower amounts (694 ± 1.0 µg/g *trans*-resveratrol) [42]. An interesting approach to the impact of prolonged MAC (6 months) on phenolic quality is found in the study by [43], which shows maintenance of this quality for 4 months, after which a decrease is recorded probably due to precipitation/reabsorption while the extraction of phenols from the seeds occurred during longer maceration periods, with differences from one variety to another.

### 2.2.2. Ultrasound-Assisted Extraction

Ultrasound-assisted extraction (UAE) has been increasingly used in recent times. It is also referred to as the 'green' or environmentally friendly method due to its use as a pre-treatment on plant matrices to facilitate polyphenol extraction. Compared to other extraction methods, the advantages of this method are clear: minimization of the number of solvents used, low execution time, and low investment with high yields.

The ultrasound-assisted method for extracting resveratrol from grapevine cords with three choline chloride-based NaDES (deep natural solvent systems) was tested [44]. Complementarily, the Box-Behnken Experimental Design (BBD) was applied with water content (5-27.5-50), solid/liquid ratio (10-30-50 mg/500 µL of BCH), temperature (20-50-80 °C), extraction time (5-32.5-60 min) to improve both polyphenol levels and antioxidant capacity. The study concludes that the optimal extract contains high proportions of stilbene (*trans*-resveratrol and *trans*-ε-viniferin), demonstrating that NaDES, as an environmentally friendly alternative to classical organic solvents, are effective for the extraction of resveratrol from cords. Investigations on the effects of ultrasonic pretreatment (53 kHz, 300 W, 30 °C, 300 s, in a mixture of 5% $K_2CO_3$ + 1% OO solution) and drying air temperatures (40-60 °C) on the drying behaviour, colour values, physicochemical properties (moisture content, VCC, TPC and antioxidant capacity (DDPH)) and the hydration and rehydration capacity of grapes were re-performed by [45]. As a result of the study, it can be said that ultrasound application can be successfully used to obtain raisins while maintaining a higher degree of nutritional value of grapes compared to classical drying. The sonication (53 kHz frequency at 100% amplitude for 20 min) and thermosensation method was applied by [38] on crushed grape berries, and it was found that compared to the enzymatic technique, *trans*-resveratrol increased from 0.09 to 0.23 mg/100 g. To extract polyphenols from grapevine cuttings, [46] use UAE and solid-liquid extraction using DES - LA (levulinic acid) as an alternative to traditional chemical solvents. Using these methods, the extracts identified and quantified eleven polyphenols belonging to the proanthocyanins, stilbenes, hydroxycinnamic acids, and flavonols families. UAE is characterized as a grapevine stem extract (GSE). The main phenolic constituents were identified as stilbenoids; among them, trans-resveratrol was highlighted. GSE was administered to an animal model of isoproterenol-induced myocardial injury. The extract attenuated the symptoms associated with drug administration: the plasma lipid profile was improved, and the perturbed plasma concentration of ions, markers of cardiac

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dysfunction, DNA laddering and myocardial tissue necrosis were decreased. This effect could be related to the antioxidant potential of GSE associated with its antioxidant properties, increased levels of endogenous antioxidants (glutathione and enzymatic antioxidants) and diminished lipid peroxidant markers in the heart [47].

#### 2.2.3. Microwave-Assisted Extraction

In their study [48], utilize the environmentally friendly technologies MAE and UAE to recover compounds of interest from the grape pomace. The use of microwaves (600 W for 2 min for three cycles) on crushed grapes with obtaining different maceration temperatures in the product mass, supplemented with sonication, also gave results in the study of [39], the *trans*-resveratrol content having a significant increase when this treatment was applied. Compared with the enzymatic technique, microwave and microwave, together with sonication, increased the number of polyphenols with strong antioxidant power, such as *trans*-resveratrol, concluding that the microwave technique was more effective for antioxidant capacity. However, sonication, cold and thermosonication results were lower than enzymatic treatment [49]. Regardless of the extraction method used (dynamic MAC, UAE, and micro on-assisted extraction), extracts obtained from grape pomace and seeds showed relatively high concentrations of phenolic compounds [50].

#### 2.2.4. Membrane Extraction

Compared to classical techniques, membrane extraction reduces operating and maintenance costs, keeps temperature and pressure parameters unchanged, and obtains superior extracts quantitatively and qualitatively. Among the disadvantages encountered are the size and geometry of the pores and the size of the molecules that compose them [51]. The use of grapevine (*Vitis labruscana*) callus suspension cultures in a conditioned environment (pH, temperature, time, enzyme-biocatalyst) and by in vitro bioconversion transforms *trans*-resveratrol into δ-viniferin, the proposed method could be an alternative approach for in vitro bioconversion of valuable molecules with industrial impact [52]. The potential to produce concentrated fractions of bioactive compounds from wine yeast on nanofiltration membranes was studied by [53] following the performance of the three membranes used in terms of productivity, loading index and retention to target compounds (polyphenols, flavonoids, sugars) and antioxidant activity, thus the membranes used can be considered suitable for the production of a concentrated fraction of phenolic compounds from wine yeast extracts. The effect of cold plasma treatment on various factors: moisture content (MC), pH, hardness (H), antioxidant activity (AOA), total phenolic content (TPC), rehydration ratio (Rr), browning index (BI) and colour difference (ΔE) in black raisins and golden raisins were investigated by [54] resulting in improvement in H, Rr, BI, AOA and TPC parameters. Thus, the application of cold plasma treatment can be introduced in food processing due to the prospects of significantly improving food quality by modifying/maintaining physicochemical and nutritional characteristics.

Separation, purification and concentration of phenolic compounds from grapevine by-products by membrane processes are techniques of interest in current research.

#### 2.2.5. Supercritical Pressurized Fluid Extraction (SCFE)

The use of supercritical fluid extraction (SFE) and pressurized fluid extraction (PFE) to separate bioactive substances from various resources is a topical area [26,49,55]. Regarding phenolic compounds (they present polar water-soluble components, thus having high efficiency in SCFE), the main advantage of using supercritical and pressurized fluids in resveratrol extraction is the preservation of quality and purity as the process takes place under controlled conditions of light and air, parameters that raise the incidence of degradation reactions. On grape seeds, [56] performed SCFE extractions (temperature 80°C; $CO_2$ flow rate 69 g/min; pressure 250 bar; time 60 minutes) and found that total polyphenols did not change significantly. The potential of micellar solutions of nonionic surfactants Brij S20 (BS20) and poloxamer 407 (P407) for the extraction of polyphenols from

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grape pomace from the vinification of red grapes was studied by [26], resulting in a 19% increase in total polyphenol extracts when using these micellar solutions compared to those obtained by the action of pure surfactants. Also, [57] traced the potential of eleven nonionic surfactants belonging to the poloxamer, Brij, Triton and Tween subgroups with the result that aqueous solutions of nonionic surfactants are efficient media suitable for simple resveratrol extraction. Supercritical fluid extraction of polyphenolic compounds from grapevine components has advantages over traditional methods. An example of comparison can be the classical extraction by SOX method, in which parameters such as light, temperature, pressure, and working time cannot be controlled, compared to the SCFE method, which by improved selectivity, speed, versatility, automation and environmental safety becomes innovative, with qualitative and precise results. The negative aspect of SCFE remains the rather high cost. A possible solution to ensure cost-effectiveness is to use pre-treatment processes of grapes or other vine components to prepare the substrate for SCFE application. These may include advanced shredding precedes (e.g., the grapevine can be crushed and powdered, the skins, seeds, leaves, etc. can be dried and powdered, etc.) to facilitate the application of enzymatic pretreatment, UV-C signals, in combination with the use of MAE or UAE, which can increase the efficiency of extraction of biological compounds from the grapevine, including resveratrol.

#### 2.2.6. Applying Electric Fields

The use of advanced techniques such as electrospinning to produce ultrathin nanofibers and membranes is one of the best ways to create continuous nanomaterials with variable biological, chemical and physical properties, thus increasing the variability of the fields of use [58]. The application of pulsed electric fields (PEF) is an effective approach to enhance the extraction yield of bioactive compounds from black grape pomace [59], with positive results. Innovative use of electrospun nanofibers with grapevine leaf extract is a novel approach aiming to increase the synergistic biological action of the active compounds present in the extracts, with direct benefits for the development of nutraceutical products [60], attracting more and more interest from the food industry.

#### 2.2.7. Using the Box-Behnken Experimental Design (BBD) and Response Surface Methodology (RSM)

The use of BBD combined with RSM to determine the optimization of cold plasma treatment time and voltage on the quality characteristics of non-gold and golden raisins resulted in prolonged shelf life and, at the same time, increased freshness while maintaining the quality parameters during storage [54]. Also, [59] utilized RSM combined with applying PEF, obtaining a significant increase in the extraction yields of biologically active compounds from grape pomace from black grapes. In another study by [61], the impact of temperature, extraction time, solid/liquid (S/L) ratio and mixing speed on extraction efficiency was evaluated using a BBD n and response surface modelling. The extracted compounds were evaluated regarding physical properties (conductivity, total dissolved solids and pH) and chemical properties (total polyphenol content and antioxidant activity). BBD on grapevine strings with established parameters (water content (5-27.5-50), solid/liquid ratio (10-30-50 mg/500 μL of 1,4-butanediol - BCH), temperature (20-50-80 °C), extraction time (5-32.5-60 min) to improve the levels of polyphenols, including resveratrol as well as the antioxidant capacity was also applied with good results by [44]. The use of the BBD on grape pomace by [48] resulted in the best extraction conditions, resulting in the concentration of phenolic compounds (including *trans*-resveratrol), anthocyanins and increased antioxidant activity (using ABTS and DPPH assays). Also, [62] identified the antioxidant activity of polyphenolic compounds in the skins and seeds of some grape varieties by performing the ABTS assay; the result obtained regarding antioxidant activity is positive.

#### 2.2.8. Other Methods

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Finding different methods to treat grapes in the postharvest period with the possibility of extending their shelf life may lead to variations in resveratrol content. Thus, [63] evaluated the effect of postharvest coating with chitosan - CH 1.0%, ghatti gum - GG 1.0% and combinations (GG 0% + CH 0%; control-distilled water); GG (GG 1.0% + CH 0%); CH (CH 1.0% + GG 0%); CH + GG (GG 1.0% + CH 1.0%), on the nutritional properties, phenolic compounds and antioxidant capacity of 'Rishbaba' grapes (*Vitis vinifera* L.) during 60 days of storage at a set temperature and humidity conditions (0 ± 1°C and 85% relative humidity). During storage, these treatments decreased the resveratrol content from 11.9 μg/g$^{-1}$ FW to 9.4 μg/g$^{-1}$ FW. The only coating that inhibited mould incidence and delayed the changes in resveratrol content was the CH + GG combination, which was considered edible and biodegradable. The up-regulation of phenylalanine ammonia ligase, cinnamate-4-hydroxylase, coumaroyl-CoA ligase and stilbene has a positive and direct relationship with the process of resveratrol synthesis and accumulation [25]. The reduced pressure extraction (RPE) technique is one of the efficient methods for polyphenol extraction, having a dual role (by lowering the extraction temperature, it prevents the deterioration of stilbenes while increasing their purity) [64].

Emerging extraction methods offer a sustainable approach for producing bioactive compounds from grapevine components, products and by-products for nutraceutical use in industry (food, pharmaceutical, medical).

### *2.3. Biotechnological Synthesis and Extraction Methods*

Biosynthesis of stilbenes in grapevine occurs under the action of an enzyme package. The first step is the oxidative deamidation of L-phenanine to cinnamic acid by phenylalanine ammonia lyase to generate resveratrol [65], which is further metabolized by specific enzymes (phenylalanine/tyrosine ammonia lyase (PAL/TAL), cinnamate 4-hydroxylase (C4H), 4-coumarate-CoA ligase (4CL) and stilbene synthase (STS)), resulting in a diversity of stilbenes with different properties and stabilities. Also, identify 13 grapevine enzymes that can utilize resveratrol as a substrate, including ten peroxidases, two glycosyltransferases and one O-methyltransferase.

The testing of three possible types of enzymatic reactions of resveratrol hydroxylation in order to reveal hydroxylated resveratrol derivatives, in particular, a reaction catalyzed by an NADPH-dependent cytochrome P450 hydroxylase, a 2-oxoglutarate-dependent dioxygenase, and ortho-hydroxylation, similar to the activity of the polyphenol oxidase cresolase (PPO), PPO having the highest specific activity detected in the crude extract, was performed by [66]. The ultimate goal was the detection of piceatannol, a naturally occurring hydroxylated analogue of resveratrol with a higher bioavailability and health-beneficial properties than resveratrol. The hydroxylation of resveratrol to produce piceatannol has also been studied by other investigators being reported for cytochrome P450 CYP1B1-dependent hydroxylases human CYP1B1 [66,67], CYP1A1/2 [68,69] and bacterial CYP102A1 [70,71].

In grapevine compounds, resveratrol can undergo isomerization processes mainly catalyzed by transferases (glycosyltransferases, methyltransferases), hydroxylases and pe-oxidases, resulting in various resveratrol derivatives, oligomers being the most prevalent [72,73]. The evidence of ACE inhibitory activity is found in the research by [47], which indicates the potential of GSE to ameliorate cardiovascular diseases. Thus, the research shows that not only the singular *trans*-resveratrol is protective of the cardiac system, but also GSE, through its stilbene and derivative content and improved lipid profile, had an- antioxidant role; the extract could be used in the creation of novel ingredients with functional character. Enzymatic bioconversion and plant callus and cell suspension cultures can produce stilbenes such as resveratrol and viniferin [52]. To further investigate and study the cell-wall architectural networks present in some grape varieties' skin and pulp tissues, different carbohydrate-active enzyme-active treatments were tested by [74], showing the very clear trend of cell-wall degradation in this context. In vitro tests have demonstrated the antifungal activity of several pure stilbenoids, extracts from annual and multiannual rootstocks have been proposed as an environmentally friendly alternative to classical fungicides in the context of sustainable viticulture [75]. The influence of stilbene content in the biotransformed extract obtained from multiyear wood

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and grapevine roots on Botrytis cinerea attack was studied by [1]. The formation of the active oligomerized stilbene system in the extract, including resveratrol, strongly reduced mycelial growth and spore germination of the fungal agent causing grey mould and also inhibited the production of *Botrytis lactazae*, despite the ability of the fungus to metabolise some stilbenes. How certain pathogens degrade grapevine wood was studied by [4]. This study investigates the presence of the fungi *Neofusicoccum parvum* and *Diplodia seriata* on the stump by determining the diversity of secreted proteins and extracellular enzyme activities involved in wood degradation and resveratrol metabolisation. It suggests that the activity of pathogenic fungal oxidase could form some resveratrol oligomers present in grapevine wood after pathogen attack.

A detailed study of the microbial community at the level of grapes is carried out by [76]. The results indicated that the natural microbial community changed significantly during the grape growth phase and was influenced by the growth stage, which can influence resveratrol biosynthesis (Figure 2). The edge represents the co-occurrence association between microbial genera, with red indicating a positive correlation and blue indicating a negative correlation.

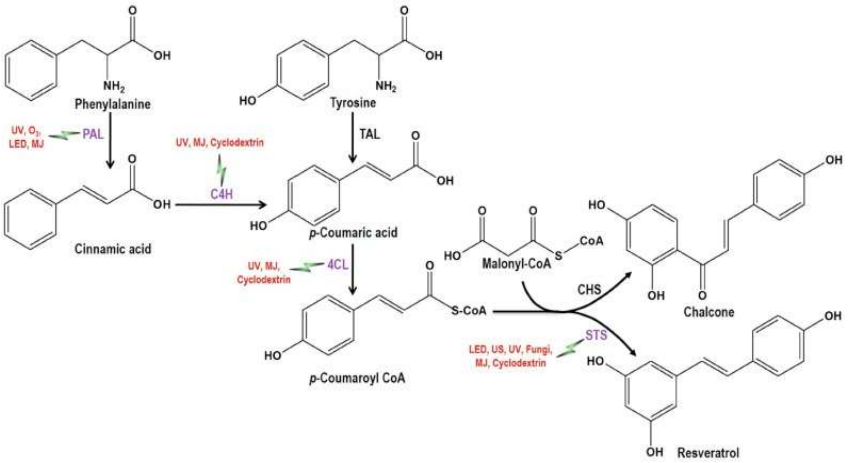


**Figure 2.** Biosynthesis of resveratrol in grapevine [25].

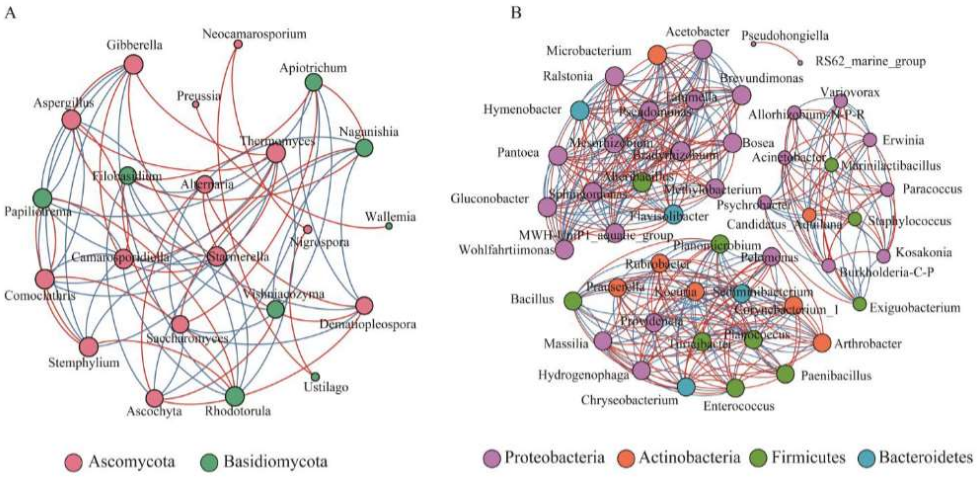


**Figure 2.** Co-occurrence networks of microbial genera at harvest stage. (A) Fungi; (B) bacteria by [76].

In vitro studies have shown that grape seeds and their extracts inhibit the growth of pathogenic *Enterobacteriaceae bacteria* while leading to the growth and survival of beneficial bacteria, including *Bifidobacterium* spp. and *Lactobacillus* spp. [77].

The biosynthesis of stilbenes is based on specific enzyme packages, and the action of these enzymes by hydroxylation or isomerization reactions on resveratrol leads to the formation of

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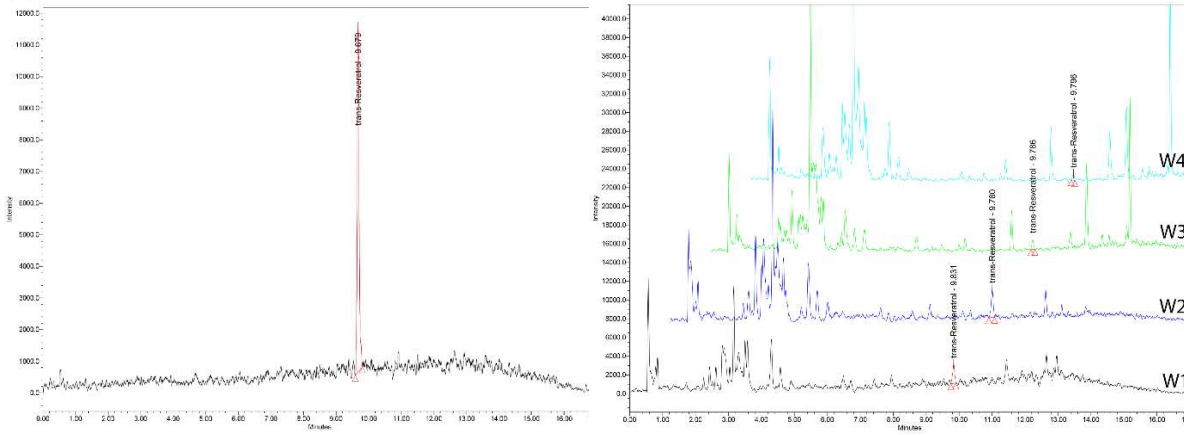
compounds similar in bioavailability and with beneficial properties for human health. The aim of using enzymatic bioconversion, various active enzymatic treatments and plant membranes is to produce resveratrol with high stability, which is imperative in the microbiome and the production of functional food products.

## 3. Identification Techniques

One of the most widely used techniques for the identification of the most important parameters in grapevine components, products and by-products is High-Performance Liquid Chromatography (HPLC) as well as Ultra-High-Performance Liquid Chromatography-UHPLC, and there is a wealth of valuable work of significant research importance. The UHPLC chromatogram shows a distinct peak corresponding to the pure *trans*-resveratrol reference sample, enhanced by MS detection of the m/z 227 molecular ion, characteristic of *trans*-resveratrol. The UHPLC-MS method thus provides high specificity, ensuring that the observed peak can be confidently attributed to *trans*-resveratrol without interference from other substances. Such specificity is essential for accurately quantifying complex matrices like wine [78], Figure 3 (a). The clean baselines and sharp peak shapes indicate a well-optimized UHPLC method, essential for accurate quantification and sample comparison - Figure 3 (b).




(**a**) (**b**)

**Figure 3.** (a) Chromatogram of a *trans*-resveratrol standard showing a prominent peak at 9.67 min, indicative of its purity and concentration in the reference sample; (b) Overlay of UHPLC chromatograms for Romanian wine samples, with the *trans*-resveratrol peak identified at the specific retention time across all samples. UHPLC: Ultra-high-performance liquid chromatography; W1: Fetească Regală; W2: Fetească Neagră; W3: Dry Muscat; W4: Cabernet Sauvignon. [78].

The resveratrol content in grapevine components, products and by-products can vary and is influenced by many factors (variety, processing methods applied, etc.). The positive results in increasing the content and stability of resveratrol have been observed following the coupling of synthesis, extraction or identification techniques, and these aspects have been the subject of numerous studies recently (Table 1).

**Table 1.** Data on the identification of resveratrol in grapevine components, products and by-products.

| Fractions | | Methods/ extracting substances | Detection technique* | Content in resveratrol | References |
|---|---|---|---|---|---|
| Grapevine components | Whole grape | $C_2H_3N/H_2O$ (40:60, v/v) | HPLC-UV | 0.09235 mg/L, DW | [79] |

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| | | $C_2H_3N$ - $CH_3COOH$ | HPLC-FL | 7–24 mg/L, DW | [80] |
| | | acidified water (0.1% H3PO4)/$C_2H_3N$ | HPLC-GC/MS | 13.9 ± 2.87 mg/L, DW | [81] |
| | | 70% $C_2H_5OH$ | LC-ESI-QToF-MS/MS | 227000 mg/L, FW | [82] |
| | | MeOH (70%) /$H_2O$ (8:2, v/v) | HPLC-DAD-ESI-MSn | 4.04 mg/L, DW | [83] |
| | Skin | MeOH | HPLC-ESI-MS/MS | 30.6 ± 1.7 mg/L, DW | [84] |
| | | 1% HCl in MeOH | HPLC | 3.13 ± 0.33 to 14.57 ± 1.34 mg/L, FW | [85] |
| | | incubation time - 24 h, US application method-(P01), US frequency - 20 kHz, US treatment time - 60 min and ultrasonic intensity (UI) - 1.15 W $cm^{-2}$ | HPLC | 180 ± 10 mg/L to 3580 ± 80 mg/L, DW | [86] |
| | | MeOH-deionized water (1:1) with 1 % $CH_2O_2$ (v/v) | UHPLC | 0.05 mg/L, FW | [87] |
| | | MeOH | HPLC | 0.065 to 7.119 mg/L, DW (*cis*-resveratrol) 0.633 to 9.152 mg/L, DW (*trans*-resveratrol) | [88] |
| | | MeOH/$C_4H_8O_2$ (1:1, v/v) | HPLC | 0.667 mg/L, DW | [89] |
| | | 70% MeOH | UPLC-MS-MS | 2.76 mg/L, FW | [90] |

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| | Seed | MeOH | HPLC-ESI-MS/MS | 20.4 ± 0.7 mg/L, DW | [84] |
| | | $H_2O$-$CH_2O_2$-$C_2H_3N$ (76.935/0.065/23, v/v/v) | UHPLC-MS/MS | 305.98 ± 0.23 mg/L, DW | [91] |
| | Pulp | MeOH | HPLC-UV | 45 to 1018.9 mg/L, DW | [92] |
| | Stem | $C_2H_5OH$ (5%, v/v) | HPLC | 680 to 1870 mg/L, DW | [36] |
| | | 1. ($H_2O$ + microwave + ultra sound + atmospheric pressure); 2 . ($H_2O$ + microwave + ultra sound + reduced pressure) | HPLC-ESI-MS/MS | 1121 ± 4 .8 mg/L, DW | [42] |
| | Leaf | MeOH | HPLC-ESI-MS/MS | 6.2 ± 0.1 mg/L, DW | [84] |
| | | The (DoE) approach, the red vine leaf extract (50% MeOH, temperature 70 °C, and three cycles per 60 min) | HPLC | 0.306 ± 0.009 mg/L DW | [60] |
| | | 10 mL of 0.1 m HCl 80% MeOH solution was extracted with two consecutive 15-min cycles of sonication at 4 °C in total darkness | UPLC | 30-40mg/L $FW^{-1}$ $\times10^{-1}$ | [93] |
| | | UV-C treatment/MeOH | LC-MS/MS | 0.01997718-0.35789 11798 mg/L, FW | [94] |
| | | 70% MeOH | UPLC-MS-MS | 4.22 mg/L, FW | [90] |
| | Shoot | EC50 Caco-2 /EC50 $HepG_2$-$H_2O_2$ | HPLC | 14.74 and 29.47 mg/L, DW | [95] |

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| | | MeOH-$H_2O$ (80:20, v/v) | HPLC | 148.53 $mg/L^{-1}$, DW | [46] |
| | Root | MeOH | HPLC-ESI-MS/MS | 86.3 ± 2.5 mg/L, DW | [84] |
| | | COSMO-RS-NADES | UHPLC-UV | 520–2470 mg/L, DW | [96] |
| | Wood | *Botrytis cinerea* secretome | UHPLC-UV-DAD-MS | 9541 ± 16800 mg/L, DW | [1] |
| | Woody tissues | 80% MeOH | UPLC-MS | 69.1 to 436.5 $mg/L, DW^{-1}$ | [97] |
| | Bud | 80% MeOH | UPLC-MS | 150 $mg/L, DW^{-1}$ | [97] |
| Grapes product | Wine | $C_2H_3N/H_2O$ (40:60, v/v) | HPLC-UV | 0.1047 mg/L, DW | [79] |
| | | MeOH | UHPLC-orbitrap MS4 | 4.00 mg/L, DW (red wine) | [98] |
| | | Transepithelial diffusion | LC-MS | 0.361–1.972 mg/L, FW (red wine) 0–1.089 mg/L, FW (white wine) 0.29 mg/L, FW (rosé wine) | [99] |
| | | MeOH | UHPLC-MS/MS | 0.07-2.61 mg/L, DW (*cis*-resveratrol) 0.05-3.82 | [100] |

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| | | | | mg/L, DW (*trans*-resveratrol) | |
| | Juice | $C_2H_3N/H_2O$ (40:60, v/v) | HPLC-UV | 0.00009 1 mg/L, DW | [79] |
| | | $C_2H_6O$/water solution (60:40, v/v) | HPLC | 4.4 to 7.0 mg/L, DW | [101] |
| | Concentrated Juice | $C_2H_6O$/water solution (60:40, v/v) | HPLC | 12.4 to 21.3 mg/L, DW | [101] |
| | Grape Skin Powder | $C_2H_6O/H_2O$ (50%, v/v) | GSP/UV-A/HPLC | 250 mg/L, DW | [102] |
| | Raisin | HCl/MeOH/$H_2O$, 1:80:19, v/v/v) | UPLC-VION-IMS-QToF | 16544000 ± 44000 mg/L, DW | [103] |
| | Jam | UP200S ultrasonic system optimised with: solvent composition (10–70% and 30–90% MeOH in $H_2O$; solvent-to-solid ratio (10:1 - 40:1); ultrasonic probe diameter | UPLC-FD | 0.027 ± 0.01 to 1.760 ± 0.04 mg/L, DW | [104] |
| | Marmalade | BBD optimised with: solvent composition (60 - 100% and 10 - 70% MeOH in $H_2O$); microwave power (250 - 750 W); solvent-to-solid ratio (20:5 - 60:5) | UHPLC-FD | 1.74 $mg/L^{-1}$, DW | [105] |
| By-products | Grape canes | $C_2H_6O/H_2O$ (80:20, v/v) | HPLC-DAD-Q-ToF | 227.07 $mg/L^{-1}$, DW | [106] |
| | | The microencapsulation (by spray drying) using maltodextrin (MD) (10% w/v) and UV irradiation (254 nm) | HPLC | 679.6 ± 51.6 mg/L, DW | [27] |
| | | Sonicate/macerate -96% $C_2H_6O$ (v/v) | HPLC-MS | 815.9 ± 153 mg/L, DW | [107] |

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| | COSMO-RS-calculations for NADES extraction combined with HPCC biphasic solvent | UHPLC-UV | 1.50 mg/L, DW | [108] |
| | HPLC-UV-DAD | HPLC-ESI/MS | 890± 20 mg/L$^{-1}$, DW (dormant bud) 610±10 mg/L$^{-1}$, DW (second extended leaf) 200±70 mg/L$^{-1}$, DW (sixth extended leaf and visible inflorescence) | [109] |
| Grape pomace | $C_2H_6O$ (5%, v/v) | HPLC | 190 to 1073 mg/L, DW | [36] |
| | Extracted by SOX and MAC in IPA | HPLC-DAD/MS | 0.042–0.653 mg/L, DW (*trans*-resveratrol) 0.05–0.35 mg/L, DW (*cis*-resveratrol) | [110] |
| | 100 mL of MeOH 80% acidified with $CH_2O_2$ 0.1% for one hour in an ultrasonic bath | HPLC/DAD/ToF | 100 ± 20 mg/L. DW | [111] |
| Wine lees | Conventional aqueous (CE) and non-conventional UAE | HPLC | 36360 mg/L, DW | [112] |
| | Enzyme-assisted extraction based on the hydrolysis of WL proteins | UHPLC-(ESI+)-Q-ToF-MS | 164.00 ± 0.80 mg/L, DW | [113] |

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| | Grapevine extracts | MeOH/$H_2O$ (50:50, v/v) | HPLC-DAD(UV)/CAD | 36.75 $mg/L^{-1}$, DW (CAD) 211.25 $mg/L^{-1}$, DW (DAD/UV) | [114] |

* Abbreviations.

As early as [115] showed that fluorimetric detection is much more sensitive than UV detection, and its specificity allows a simple pre-purification of grape berries and direct injection of wines. The RP-HPLC method, described by [116], allows the separation of several types of phenolic compounds present in grapes and wines by directly injecting samples using a binary gradient with salt-free solvents and photodiode array detection. *trans*-resveratrol was isocratically separated on Nucleosil 100-5 C18 column using a mobile phase containing acetonitrile: water (40:60, v/v), detected by UV detector at 306 nm and the flow rate was 0.3 ml/min [79]. The concentrations of *trans*-resveratrol were evaluated using high-performance liquid chromatography-diode array detection in red wines obtained from Aglianico, Piedirosso and Nerello Mascalese grapes [117] with the observations that during MAC, the maximum extraction of *trans*-resveratrol was reached after 12 days for Aglianico and Piedirosso, after which a decline was observed. Another method with positive results for quantifying free *cis*- and *trans*-resveratrol is HPLC coupling (binary gradient) with fluorescence detection [80]. The grapes (7-24 mg/L) results indicated that the wines elaborated from the Mencía variety could be present with important amounts of *trans*-resveratrol. And, [118] detail the composition of phenols (anthocyanins, flavonols, hydroxycinnamic acid derivatives, stilbene and flavan-3-ols) in the skin and pulp of seedless table grapes (BRS Clara and BRS Morena varieties) using HPLC-DAD-ESI-MS/MS. These results suggest that the entire grapes, including the skin, may potentially possess beneficial properties to human health; the BRS Morena grape can be considered a high resveratrol producer. The identification of resveratrol in some grape varieties using the HPLC-DAD technique, after fractionation of *trans*-resveratrol through a 500 mg C18 column (SPI - Solid Phase Isolation technique). A continuous decrease in *trans*-resveratrol content was observed in all cultivars during ripening [119]. In their study, [38] determine the phenolic profile of grape seeds by liquid chromatography (Dionex Ultimate 3000 UPLC, Thermo Scientific, San Jose, CA, USA) with a diode-array detector (wavelengths of 280, 330 and 370 nm) equipped with an ESI source. In another research, [120] identified an appreciable amount of phenolic compounds in raisins and established that raisins are an important source of polyphenols and that there may be significant differences between species or cultivars. And [48] on grape pomace under similar conditions. An HPLC system (Waters, Milford, MA, USA) was used for polyphenol analysis, with which polyphenols such as querce-tin-3-O-glucoside, 5-O-caffeoylquinic acid, cyanidin-3-O-glucoside and resveratrol were identified in grape pomace [46]. High-performance liquid chromatography (HPLC) chromatograms showed that the highest concentration of *trans*-resveratrol in grape skins was detected in the early period of the ripening stage [121]. The identification and quantification of different phenolic classes in grape pulp using HPLC-DAD by [122], showed that the quantitative profile of individual and total phenolic compounds is closely related to the extraction method. Using high-performance liquid chromatography coupled to electrospray ionization mass spectrometry-mass spectrometry (HPLC-ESI-MS/MS), [42] identified 29 polyphenolic substances, including resveratrol. By LC-ESI-QTOF-QTOF-MS/MS, [82] identified 78 phenolic compounds consisting of flavonoids (36), phenolic acids (31), lignans (3), stilbene (Resveratrol 5-O-glucoside) and other polyphenols (7) in five grape samples. The use of UHPLC has found its applicability for the analysis of phenolic compounds in grape samples, the method being of great interest, among others, because it allows the phenolic characterization of grape varieties accurately in a short time [123]. The quantification of stilbenoids

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in powder from grapevine cork powder was performed with the UHPLC system at λ 306. HPLC-ESI-MS was used to qualify and identify *trans*-resveratrol peaks [108].

The identification techniques are diverse, high-throughput, and capable of identifying and quantifying an increasing number of polyphenolic compounds, including resveratrol. The couplings between techniques are of interest, increasing the accuracy of phenolic characterization in grapevine components, products and by-products, with shorter turnaround times. At the same time, separation and identification techniques are under continuous innovation to find the optimal solution to increase the stability of resveratrol.

## 4. Conclusions

Research on resveratrol over the last decade in terms of its synthesis, extraction and identification in order to increase its bioavailability in grapevine components and, at the same time, to enrich products and by-products obtained from the applied technologies with *trans*-resveratrol, is focused on the technique of combining methods. The results of the combination of synthesis, extraction or identification techniques indicate potential applications on grapevine components, products and by-products as a source of phenolic compounds that can be used in the food industry as antioxidants, nutraceuticals, activators of ripening processes or food colourants.

In the future, the development and validation of rapid separation methods for the characterization of polyphenolic fractions may lead to increased stability of resveratrol in grapevine components, products and by-products for use in various industrial applications such as functional food, pharmaceuticals, cosmetics, medical products, soil and plant bio-fertilizers, animal feed fortification, bioenergy or biofuel. Some of the ideas and practices developed and implemented in current research have the potential to contribute to industrial development and, at the same time, to improve quality of life.

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## Abbreviations

The following abbreviations are used in this manuscript:

| | |
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| HPLC | Hyght Performance Liquid Chromatography |
| HPLC-MS | HPLC- Mass Spectrometry |
| HPLC-UV | HPLC-Ultraviolet |
| HPLC-GC/MS | HPLC-Gass spectrometry/Mass spectrometry |
| HPLC-DAD(UV)/CAD | HPLC-Diode Array Detection (Ultraviolet)/charged aerosol detector |
| HPLC-ESI-MS/MS | HPLC-Electrospray Ionization-Mass Spectrometry-Mass Spectrometry /Mass Spectrometry |
| HPLC-DAD-ESI-MSn | HPLC-Diode Array Detection-Electrospray Ionization-Mass Spectrometry |
| HPLC-DAD-QToF | HPLC-Diode Array Detection-quadrupole-time of flight Mass Spectrometry |
| UHPLC | Ultra-Performance Liquid Chromatography; |
| UPLC-FD | UPLC-Fluorescence Detection |
| UPLC-MS | UPLC-Mass Spectrometry |
| UHPLC-UV | UHPLC-Ultraviolet |

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| UHPLC-UV-DAD-MS | UHPLC-Ultraviolet-Diode Array Detection-Mass Spectrometry |
| UHPLC-(ESI+)-QToF-MS | UHPLC- (Electrospray Ionization-+)-quadrupole-time of flight Mass Spectrometry |
| UHPLC-Orbitrap MS4 | UHPLC-Orbitrap mass spectrometry |
| UPLC-VION-IMS-QToF | UPLC-VION-IMS- quadrupole-time of flight Mass Spectrometry |
| LC-MS | Liquid Chromatography-Mass Spectrometry |
| LC-ESI-QToF-MS/MS | Liquid Chromatography-Electrospray Ionization-quadrupole-time of flight Mass Spectrometry/Mass Spectrometry |
| GSP/UV-A/HPLC | GSP/Ultraviolet-A/HPLC |
| DW | Dry weight |
| FW | Fresh weight |
| SOX | Soxhlet extraction |
| DoE | Design of Experiment |
| RSA | Radical scavenging activity |
| ACE | Angiotensin-converting enzyme |
| VCC | Vitamin C |
| TPC | The phenolic content |
| IPA | Isopropyl alcohol |

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