# Dietary Supplements with Resveratrol, Flavonoids and Phenolic Acids: in-depth HPLC Profiling and Antioxidant Capacity as Quality Markers

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*Dietary supplements containing natural compounds, including resveratrol, are increasingly used as health improving products. The present study had three objectives, namely: the quantification of resveratrol by HPLC-MS in nine dietary supplements, the qualitative and quantitative assessment of 18 phenolic acids and flavonoids in the same supplements, and finally the measurement of the antioxidant capacity of these products. The content of resveratrol in commercial samples ranged between 22.8 and 104.7 % of the declared amount. The highest number of polyphenols that could be quantified in a dietary supplement was nine. The values obtained for antioxidant capacity suggest that resveratrol supplements containing below 10 mg of the stilbene have, even in the presence of other components, a very low antioxidant capacity which may be insufficient for an attainment of the desired antioxidant status. To our knowledge, this is the first HPLC-analysis cumulating the quantification of resveratrol with that of eighteen other polyphenols in dietary supplements, giving an in-depth overview of their composition and health benefits from the viewpoint of antioxidant capacity.*

*Keywords: resveratrol, antioxidant capacity, HPLC-MS, dietary supplements*

Resveratrol (3,5,4'-trihydroxystilbene, fig. 1) is a phytoalexin that can be found in grapes, roots of *Polygonum cuspidatum*, some berries and peanuts [1, 2]. It became popular due to its presence in wine and the so-called *French paradox* [3]. Resveratrol is a pleiotropic molecule with tremendous therapeutic potential having antioxidant, cardioprotective, anti-inflammatory, anticancer, anti-aging [4], lipid-lowering, glucose lowering [5, 6] and neuroprotective effects [7]. The great interest in this compound led to the development of different analytical methods for its identification and quantification. These methods aimed to identify both *cis* and *trans* isomers, or only one of them, most often *trans* form which is more stable [8, 9]. High performance liquid chromatography (HPLC) with diode array detection [10], electrochemical and fluorescence detectors [11] or its hyphenation with mass spectrometry (MS) [12, 13] have been used to quantify resveratrol. Dietary supplements containing resveratrol are readily available under different brands, containing different doses of the compound. The presence of the actual content declared by the producers is crucial for the therapeutic benefits and an indicator of product quality. In the present study, we aimed to quantify resveratrol in 9 dietary supplements, which are readily available in pharmacies and drugstores. Within this frame, an HPLC-MS method targeting both *trans*- and *cis*-resveratrol was employed.

In most supplements, resveratrol is combined with various plant extracts containing polyphenols in order to enhance health-promoting effects, including antioxidative properties. Moreover, recent studies pointed to the synergistic antioxidant effect of red grape polyphenols and resveratrol [14]. Therefore, in the current work we investigated as well the presence of 18 further polyphenols in the dietary supplements containing resveratrol. The HPLC-UV-MS were employed to detect and quantify 7 phenolic acids (chlorogenic acid, caftaric acid, gentisic acid, *p*-coumaric acid, ferulic acid, caffeic acid, sinapic acid, fig. 2) and 11 flavonoids (hyperoside, isoquercitrin, rutin, myricetol, quercetrin, quercetol, luteolin, kaempferol, apigenin, fisetin, patuletin, fig. 3). The final aim of this study was the assessment of the antioxidant capacity of the dietary supplements by two different methods: Trolox equivalent antioxidant capacity (TEAC) and Electron Paramagnetic Resonance spectroscopy (EPR). Due to the combination of two efficient HPLC methods assessing resveratrol and other eighteen polyphenols in dietary supplements, with the evaluation of their antioxidant capacity, the present work is able to offer a thorough overview of their composition, quality and health benefits.

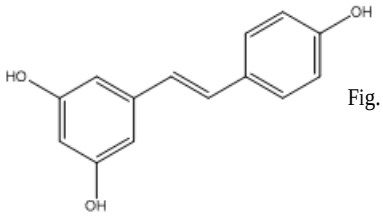

Fig. 1. Chemical structure of *trans*-resveratrol

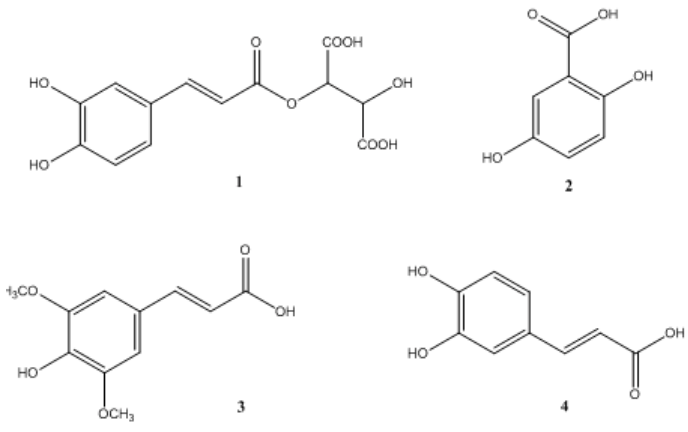

Fig. 2. Phenolic acids investigated in the current study: (1) caftaric acid, (2) gentisic acid, (3) sinapic acid,(4) caffeic acid

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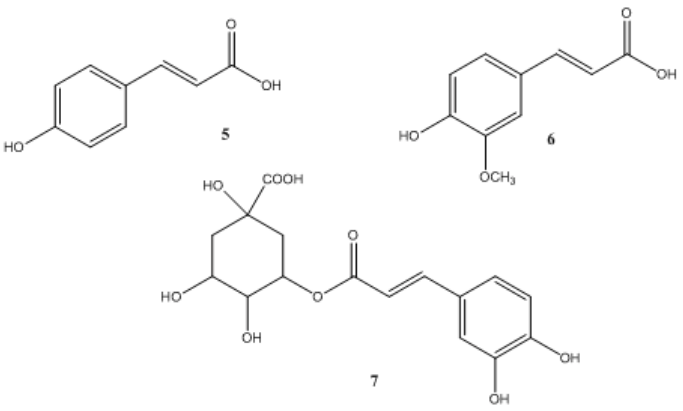


Fig. 2. Phenolic acids investigated in the current study: (5) *p*-coumaric acid, (6) ferulic acid, (7) chlorogenic acid

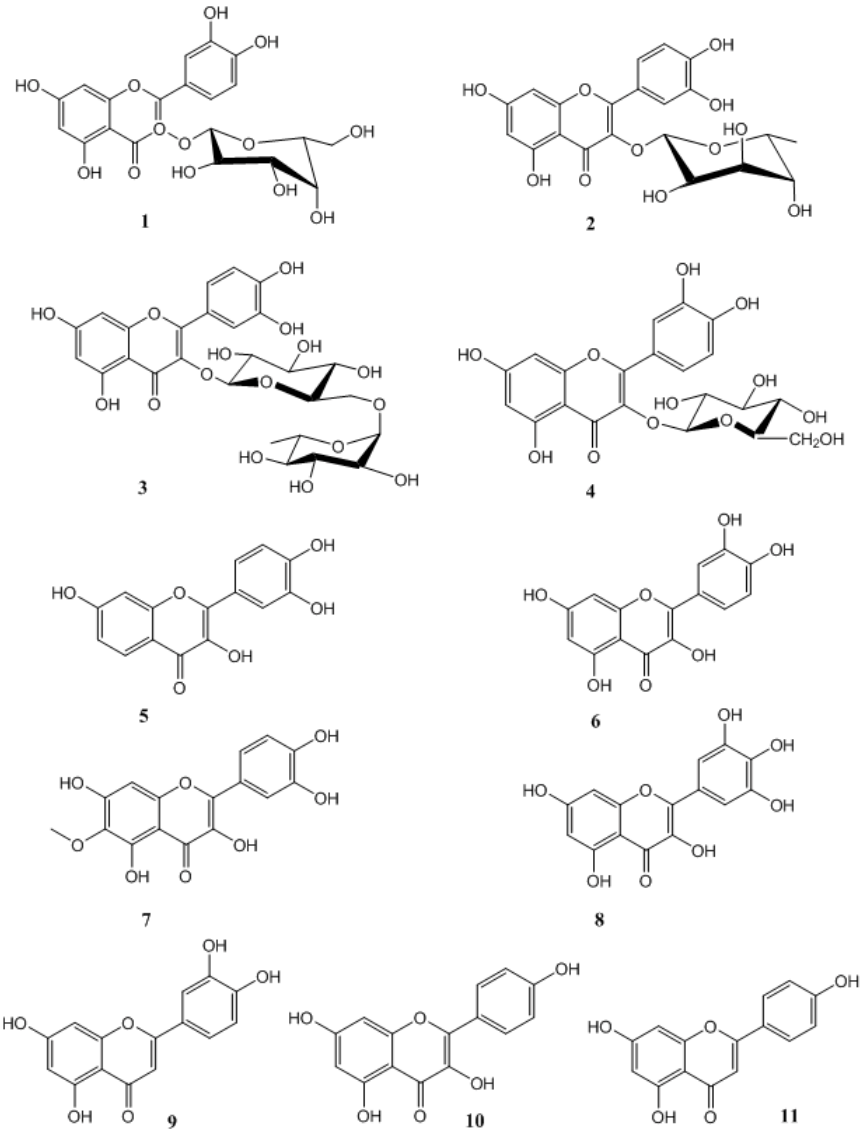


Fig. 3. Flavonoids investigated in the current study: (1) hyperoside, (2) quercitrin, (3) rutin, (4) isoquercitrin, (5) fisetin, (6) quercetol, (7) patuletin, (8) myricetol, (9) luteolin, (10) kaempferol, (11) apigenin

## Experimental part

### *Chemicals and standards*

The dietary supplements were purchased from pharmacies and drugstores. For all the supplements the content of resveratrol was mentioned by the producer and ranged between 10 and 300 mg. Six dietary supplements were capsules and three were tablets.

*Trans*-resveratrol, ABTS (2,22 -azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) diammonium salt), potassium peroxo-disulfate, potassium nitrosodisulfonate (Fremy's salt), trolox (6-hydroxy-2,5,7,8-tetramethylchromane-2-carboxylic acid) were purchased from Sigma (Sigma-Aldrich Chemie GmbH, München and Schnelldorf Germany). HPLC-grade solvents were purchased from Merck (Merck KgaA, Darmstadt, Germany). Eighteen standards of polyphenolic compounds were used. Chlorogenic acid, *p*-coumaric acid, caffeic acid, rutin, apigenin, quercetol, isoquercitrin, quercetrin, hyperoside, kaempferol, myricetol, and fisetin were purchased from Sigma (St. Louis, MO, USA), ferulic acid, sinapic acid, gentisic acid, patuletin, and luteolin from Roth (Karlsruhe, Germany) and caftaric acid was obtained from Dalton (Toronto, ON, Canada).

### *Sample preparation*

One unit of the pharmaceutical form was dispersed / disintegrated for 60 min in 50 mL water at 37°C. 45mL

methanol were added and the mixture was sonicated for 10 min. It was made up to volume with methanol (100 mL). A dilution 1:100 was prepared and the resulted solution was used for further investigations.

*Standard Solutions and Calibration Method*

The determination of resveratrol in dietary supplements was performed using the method previously described by Vlase et al [15]. Briefly, a standard solution of *trans*-resveratrol in methanol (10 mg/mL) was prepared. This stock solution was kept at 4°C, protected from daylight. Aliquots of this solution were diluted with bi-distilled water before use. For *cis*-resveratrol the solution was obtained by irradiation for 10 minutes of a *trans*-resveratrol standard solution using an UV lamp (254 nm). To obtain the calibration curves, two working solutions of *trans*-resveratrol were prepared. The first one was used to obtain the calibration curve for *trans*-resveratrol in the range of 184.3 - 2867.5 ng/mL ($R^2$=0.996). The calibration curve for *cis*-resveratrol was obtained with dilutions of a solution of *trans*-resveratrol after irradiation with UV light. The concentration of *trans*-resveratrol that was not converted from the second dilution series was calculated using the calibration curve previously obtained. The difference between the concentration of *trans*- resveratrol before and after irradiation represents the concentration of *cis*-resveratrol. The analytical signal obtained for *cis*- resveratrol was plotted against its calculated concentration generating the calibration curve or the *cis* isomer [15]. The conversion yield of the transformation *trans* to *cis*-resveratrol, was 90% after 10 min of irradiation. The calibration curve for *cis*-resveratrol was obtained in the range 187.5 -2895.8 ng/mL ($R^2$=0.996).

*Apparatus and Chromatographic Conditions*

An Agilent 1100 HPLC Series system (Agilent, SUA) equiped with an autosampler G1311A, degasser (G1322A) and a binary gradient pump (G1311A) were used. MS detection was performed using an Agilent Ion Trap VL mass spectrometer (Agilent, SUA). For the separation, a reversed-phase Zorbax SB-C18 analytical column (100 x 3.0 mm i.d., 3.5µm particles) was employed.

For resveratrol analysis an isocratic elution was performed using a mixture of 1 mM ammonium acetate/ acetonitrile (73/27, v/v). The flow rate was 1mL/min and the injection volume 10 µL. The column was operated in a G1316A oven at 40°C. All solvents were degassed in an ultrasonic bath and filtered using 0.5 mm (Sartorius) filters. The mass spectrometer was operated using an atmospheric pressure chemical ionisation (APCI) source in negative mode. The nebulising and dry gas was represented by nitrogen. The APCI heater was set at 350 °C, the nebulizer pressure 60 psi, dry gas flow was 7 L/min and was heated at 250 °C. The mass spectrometer operated in multiple reactions monitoring (MRM) mode and was set to monitor the transition m/z 227→m/z (184.8; 158.8; 182.8; 156.8; 142.8). Chromatographic and mass spectrometric data acquisition were performed using Chemstation software (Agilent Technologies, Palo Alto, CA, USA), version B.01.03 and LC/MSD Trap Control (Bruker Daltonik, GmbH, Brehmen, Germany), version 5.3, while data processing was performed using LC/MSD Data Analysis and Quant Analysis software (Bruker Daltonik, GmbH, Brehmen, Germany), version 1.7.

For analysis of polyphenols, the method was in accordance to the one described previously in the literature [16-19], with some slight modifications. The mobile phase was represented by methanol: acetic acid 0.1% (V/V). The elution started with a linear gradient from 5% methanol to 42% methanol at 35 min, then 42% methanol for 3 min. Injection volume was 5ìL, and a flow rate of 1 mL/min. The work temperature was 48°C. For the detection of compounds both UV and MS mode were employed. The UV detection was performed at 330 nm up to 17 min and then 370 nm for the next 21 min. For quantitative determination, a calibration curve was made for each compound in the range 0.5-5µg/mL ($R^2$=0.999). Due to peak overlapping, gentisic acid, cafeic acid, caftaric acid and chlorogenic acid could only be identified by MS but not quantified. The limit of detection was 0.1µg/mL, and the limit of quantification was 1.5 µg/mL. For the MS detection the mass spectrometer was fitted with an electrospray ionisation (ESI) interface, being operated in the negative mode. Conditions were the following: nebulising and dry gas was nitrogen, dry gas flow was 12 L/min and was heated at 360°C, the nebulising pressure was 70 psi and capillary voltage 3000V.

*Antioxidant tests*

The antioxidant capacity of the dietary supplements has been evaluated using the Trolox equivalent antioxidant capacity (TEAC) method and an Electron Paramagnetic Resonance (EPR) spectroscopy assay as previously described [20-23].

## Results and discussions

*Resveratrol content*

The development of adequate analytical methods for quality evaluation of dietary supplements is an increasing demand due to the relentless diversification of these products and their increasing number. Most dietary supplements contain plant products, and accidental substitutions of the plant material are a possibility [24]. Moreover, quality assessment is especially important for products with a high risk of being adulterated [25]. A further matter to consider is handling and stability of extracts along the production chain and storing, which may reduce the original quality of an extract [26]. Altogether, these issues underpin the need of qualitative assessments of the dietary supplements found on the market.

In the present study we analyzed the resveratrol content of nine dietary supplements available in pharmacies. The products included capsules and tablets of multi-ingredient formulations. Six out of nine brands declared to contain *Polygonum cuspidatum* root extract with resveratrol (table 1). Resveratrol was assessed as the sum of *cis*- and *trans*-isomers employing a previously validated HPLC-MS method [15]. Resveratrol was detected and quantified in all the analyzed samples and the measured amounts were subsequently opposed to the data provided by the producer (table 2).

Resveratrol content ranged between 3.4 and 147.3 mg per pharmaceutical unit. Five of the dietary supplements contained more than 80% of the declared amount per capsule/tablet, but only one of these contain more that 90% (93.6%). One of the dietary supplements exceeded with 4.7 % the amount declared by the producer (DS9). For the other three products the amount of resveratrol that has been determined is lower that 60 % (22.8%, 49.1 % and respectively 58%). Altogether, these results show that only two of the nine analyzed products comply with general good manufacturing practices, where 95-105% of an active constituent is demanded.

Up to the present, a consensus over the optimum dose of resveratrol supplementation has not been reached. Therefore, the resveratrol content of market available food supplements varies in a wide range [4, 27]. The EFSA Panel on Dietetic Products, Nutrition and Allergies indicates that

**Table 1**
DESCRIPTION OF THE ANALYZED DIETARY SUPPLEMENTS

| Code | Dietary supplement composition according to the producer | Declared resveratrol amount per unit (mg) | Posology |
|---|---|---|---|
| DS1 | Resveratrol (from root of *Polygonum cuspidatum* 500 mg) 250 mg, grape skin extract 10 mg | 250 mg | 1 capsule/day |
| DS2 | Standardized extract of *Polygonum cuspidatum* 100 mg providing 50 mg *trans*-resveratrol | 50 mg | 1-2 capsules /day |
| DS3 | Resveratrol 20 mg (from *Polygonum cuspidatum* 20% resveratrol), green tea 150 mg (90% polyphenols), grape seed 250 mg (*Vitis vinifera* 5:1) | 20 mg | 2 tablets/day |
| DS4 | Resveratrol 10 mg, grape seed extract 50 mg, zinc 20 mg, chromium 200 µg, selenium 200 µg, conjugated linoleic acid (80%) 200mg | 10 mg | 2 capsules / day after meals |
| DS5 | Resveratrol 20 mg (from roots of *Polygonum cuspidatum*) (min. 18 mg *trans*-resveratrol), grape skin extract 100 mg (25% polyphenols), grape seed extract 50 mg (95% polyphenols), *trans*-pterostilbene (dimethyl-resveratrol) 5 mg, vitamin C 100 mg, green tea leaf extract 5:1 200 mg (50% polyphenols), quercetin 100 mg | 20 mg | 1 tablet/day |
| DS6 | Resveratrol from *Polygonum cuspidatum* extract 300 mg, red wine extract 67 mg(30% polyphenols), *Piper nigrum* extract 67 mg (95% piperine) | 300 mg | 1 capsule/day |
| DS7 | Resveratrol 20 mg, coenzyme Q10: 33.33 mg | 20 mg | 2-3 tablets / day |
| DS8 | Resveratrol 15 mg, coenzyme Q10: 60 mg vitamin B6: 3 mg, magnesium 150 mg | 15 mg | 1-2 capsules /day |
| DS9 | Root extract of *Polygonum cuspidatum* 102 mg (minimum 98% resveratrol), grape seed extract 100 mg (minimum 98% proanthocyanidins), coenzyme Q10 (minimum 59.98 mg) | 99.6 mg | 1 capsule/day |

| Dietary supplement | Amount measured (mg/unit) | % found compared to declared |
|---|---|---|
| DS1 | 144.9 | 58.0 |
| DS2 | 41.3 | 82.5 |
| DS3 | 18.7 | 93.6 |
| DS4 | 8.9 | 88.8 |
| DS5 | 16.2 | 80.9 |
| DS6 | 147.3 | 49.1 |
| DS7 | 19.4 | 96.8 |
| DS8 | 3.4 | 22.8 |
| DS9 | 104.3 | 104.7 |

**Table 2**
RESVERATROL CONTENT OF THE INVESTIGATED DIETARY SUPPLEMENTS

a dose of 150 mg/day of *trans*-resveratrol intended for adults, and the resveratrol intake at this dose is safe [28]. The dietary supplements that were analyzed did not exceed this amount of resveratrol, even if the producer indicated a higher content of this compound for some of them.

Several methods have been developed for the quantification of resveratrol in pharmaceutical formulations, trying to establish the optimum conditions [29]. The resveratrol content of such products has as well been evaluated by Rossi et al., who performed a study to evaluate the amount of this compound in 14 nutraceuticals purchased from online stores. Only five of these products respected the quality requirements of pharmaceutical grade [26].

*Content in phenolic acids and flavonoids*

In addition to the quantification of resveratrol, the current analysis investigated as well the presence and/or content of eighteen other polyphenols (table 3). The scope was to have an original in-depth overview of the composition of marketed resveratrol dietary supplements and their health benefits. Polyphenol-rich dietary supplements, including resveratrol, are recommended together with lifestyle changes to improve the antioxidant status of persons given that oxidative stress is a fundamental player in all major pathologies. The quality and analytical parameters of the currently employed method for polyphenol identification and quantification has been verified in previous studies [20, 21, 30]. The following targeted compounds were identified in the tested dietary supplements: chlorogenic acid, gentisic acid, caftaric acid, p-coumaric acid, ferulic acid, hyperoside, isoquercitrin, rutin, myricetol, quercitrin, quercetol, luteolin and kaempferol. Quercetol was identified in 6 dietary supplements, kaempferol in 5, p-coumaric acid and ferulic acid in 4, hyperoside, isoquercitrin, rutin, myricetol and quercitrin in 2 and luteolin in one dietary supplemment. Among the phenolic acids, p-

**Table 3**
THE POLYPHENOL CONTENT OF THE DIETARY SUPPLEMENTS (µg/unit)

| Polyphenols | *m/z* | $R_T$ (min) | DS1 | DS2 | DS3 | DS4 | DS5 | DS6 | DS7 | DS8 |
|---|---|---|---|---|---|---|---|---|---|---|
| Chlorogenic acid | 353 | p.o. | - | - | +, p.o. | - | +, p.o. | - | - | - |
| Caftaric acid | 311 | p.o. | - | - | - | - | +, p.o. | - | - | - |
| Gentisic acid | 179 | p.o. | +, p.o | - | - | - | +, p.o. | - | - | - |
| p-coumaric acid | 163 | 8.5 | 73.204 | +, <LOQ | 49.130 | - | 103.297 | 1743.359 | - | - |
| Ferulic acid | 193 | 11.9 | 70.824 | - | 15.210 | - | 15.210 | 310.977 | - | - |
| Hyperoside | 463 | 18.2 | - | - | 97.921 | - | 46.091 | - | - | - |
| Isoquercitrin | 463 | 19.2 | - | - | 117.688 | - | 133.099 | - | - | - |
| Rutin | 609 | 19.8 | - | - | 13.161 | - | 109.653 | - | - | - |
| Myricetol | 317 | 20.4 | - | - | 21.912 | - | 121.339 | - | - | - |
| Quercitrin | 447 | 23 | - | - | 93.031 | - | 74.335 | - | - | - |
| Quercetol | 301 | 26.1 | 19.689 | 6.476 | 41.712 | 11.431 | 27655.153 | 33.453 | - | - |
| Luteolin | 285 | 28.5 | - | - | - | - | - | 116.709 | - | - |
| Kaempferol | 285 | 31.1 | 90.445 | 20.797 | 17.481 | - | 216.473 | 34.063 | - | - |

- – not detected; +, <LOQ - detected, but under the limit of quantification; p.o. – peak overlapping

coumaric acid and ferulic acid were quantified, while chlorogenic acid, caftaric acid and gentisic acid were determined only qualitatively.

The highest amount determined for a polyphenolic compound per pharmaceutical unit in these supplements was for quercetol in DS 5, where it was declared by the producer as an active ingredient. Supplements DS 3 and DS 5 afforded the highest number of polyphenols that could be identified with the current method, each containing 9 polyphenols that have been quantified.

*Antioxidant activity*

The antioxidant activity has been well established for large variety of polyphenols [31, 32]. The dietary supplements containing these compounds claim an antioxidant effect that determines their beneficial activity. For this reason, the measurement of their actual antioxidant capacity appeared to be of relevance and was subsequently performed by two different methods: TEAC and EPR. All studied dietary supplements presented antioxidant properties, but with wide variations, according to their composition. The observed activities followed a similar trend with both methods. The highest antioxidant effect has been observed for DS 5 and DS 3, the products where were quantified 9 polyphenols (beside resveratrol, table 4).

Labels of dietary supplements do not always provide complete information regarding the chemical composition of the products, or enough information about their antioxidant activity. Supplements without declared antioxidant properties could also present this kind of activity due to the presence of polyphenols in their composition. A standardization of the polyphenol content in dietary supplements is important to establish the efficient doses

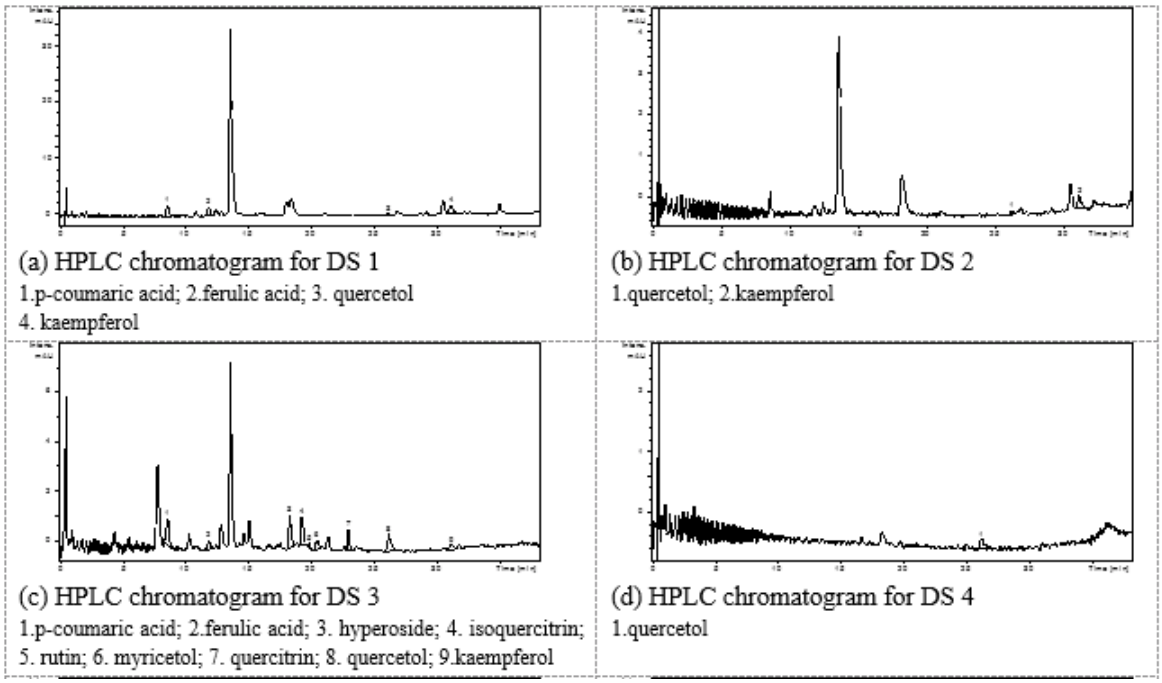
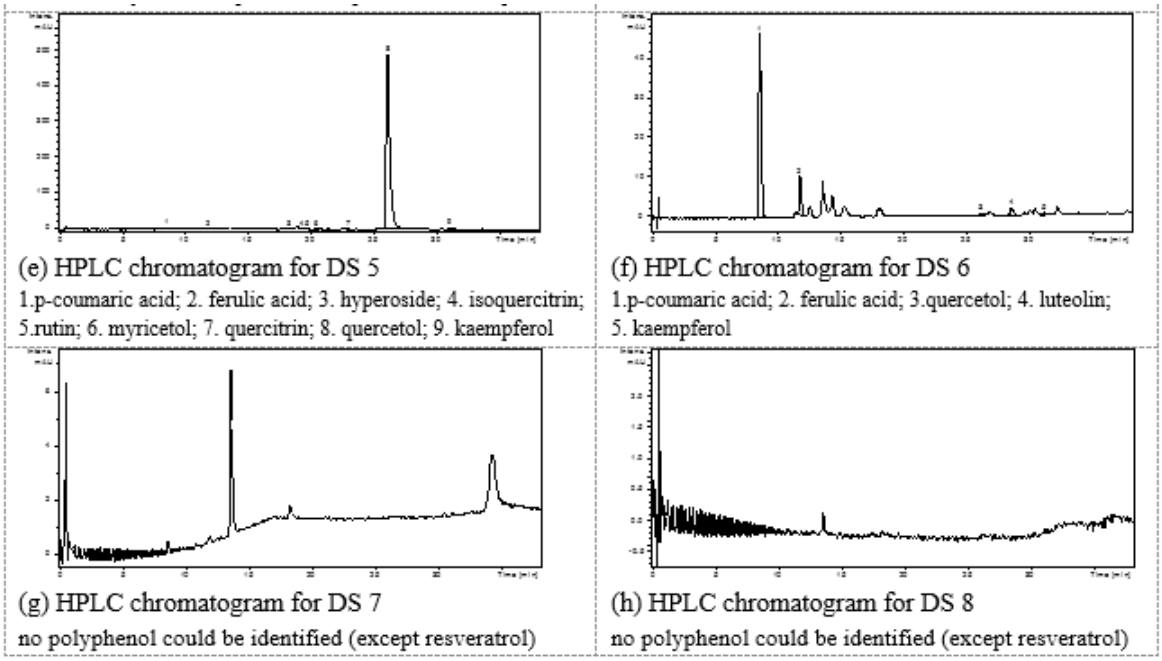



Fig.4. HPLC chromatograms of dietary supplements samples (the peak at 13.5 min is represented by resveratrol) - a,b,c,d -



(e) HPLC chromatogram for DS 5
1.p-coumaric acid; 2. ferulic acid; 3. hyperoside; 4. isoquercitrin; 5.rutin; 6. myricetol; 7. quercitrin; 8. quercetol; 9. kaempferol

(f) HPLC chromatogram for DS 6
1.p-coumaric acid; 2. ferulic acid; 3.quercetol; 4. luteolin; 5. kaempferol

(g) HPLC chromatogram for DS 7
no polyphenol could be identified (except resveratrol)

(h) HPLC chromatogram for DS 8
no polyphenol could be identified (except resveratrol)

Fig.4. HPLC chromatograms of dietary supplements samples (the peak at 13.5 min is represented by resveratrol) - e, f, g, h -

| Dietary supplement | TEAC (mg TE/g dw) | EPR (mg FSE/g dw) |
|---|---|---|
| DS5 | 81.3 ± 4.12 | 182 ± 12.4 |
| DS3 | 77 ± 4.01 | 140 ± 4.53 |
| DS9 | 65.24 ± 5.21 | 101.24 ± 9.74 |
| DS6 | 63.42 ± 3.01 | 99.13 ± 5.7 |
| DS1 | 62.64 ± 1.25 | 100.01 ± 6.52 |
| DS7 | 50.65 ± 6.25 | 75.24 ± 4.25 |
| DS2 | 43.5 ± 6.52 | 72.5 ± 3.52 |
| DS4 | 21.7 ± 1.52 | 33.4 ± 2.58 |
| DS8 | 14.2 ± 1.23 | 28.7 ± 3.18 |

*mg TE/g dw*- milligrams of trolox equivalents (TE) per gram of dry weight;
*mg FSE/g dw* - milligrams of Fremy's salt (FSE) equivalents per gram dry weight

**Table 4**
ANTIOXIDANT PARAMETERS BTAINED WITH THE TWO METHODS FOR THE STUDIED SAMPLES, IN DECREASING ORDER

for these products [33]. The highest antioxidant activity (81.3±4.12 mg TE/g dw and 182±12.4 mg FSE/g dw for DS 5 and respectively, 77±4.01 mg TE/g dw and 140±4.53 mg FSE/g dw for DS 3) was measured in the supplements which afforded the identification of the most flavonoids and phenolic acids. These figures show that resveratrol supplements containing below 10 mg of the stilbene have, even in the presence of other components, a very low antioxidant capacity which may be insufficient for an attainment of the desired antioxidant status.

## Conclusions

Dietary supplements are numerous, widely advertized and easy to be accessed. Their quality assessment is mandatory in order to ensure their claimed health benefits. In the present study nine dietary supplements have been investigated for their content in resveratrol and 18 further polyphenols (phenolic acids and flavonoids). Resveratrol content in the 9 dietary supplements ranged between 22.8 and 104.7 % of the declared amount, and only two of them presented a higher content than 95%. The highest number of polyphenols that could be quantified in a dietary supplement with the employed target HPLC method was nine. The measurement of antioxidant capacity by TEAC and EPR ranged between 14.2 - 81.3 TE/g dry weight, and 28.7-182 mg FSE/g dry weight, respectively. To the knowledge of the authors, this is the first analysis associating the HPLC fingerprint with the assessment of antioxidative capacity as a marker of polyphenol-containing dietary supplements.

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