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19 Detection of polyphenolic compounds (stilbenes and flavonoids) in natural products

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Summary

Stilbenes and flavonoids are poliphenolic compounds widely represented in nature and have become of particular interest to chemists and biologists because of their wide range of biological activities like prevention of heart disease and cancer. Resveratrol, is a stilbene compound present in grapes and other food products. Piceatannol and pterostilbene are two trans-resveratrol-like natural stilbenes endowed with anticancer activity higher than that of resveratrol; however, it is less diffused in nature than resveratrol. 3'-hydroxypterostilbene (3'-hpt) is a natural pterostilbene analogue, recently isolated from the whole herbs of Sphaerophysa salsula; it is 50-90 times more active as apoptotic agent in neoplastic cells than resveratrol. Flavonoids are a large family of ubiquitous secondary plant metabolites have been

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described as health-promoting, disease-preventing dietary supplements, and have activity as cancer chemopreventive agents. The cancer protective effects of flavonoids have been attributed to a wide variety mechanisms, including modulating enzyme activities resulting in the decreased carcinogenicity of xenobiotics.

In this work some Sicilian plants were analyzed by HPLC for the presence of stilbenes (resveratrol, piceatannol, pterostilbene and 3'-hpt) and flavonoids (quercetin, apigenin, kaempferol, (±) narigenin, chrysin, pinocembrin, and galangin). We observed that some Sicilian grapes were rich of free piceatannol; in these grapes we detected picetannol concentrations ranging from 0.18 ± 0.25 to 22.97 ± 3.01 mg/Kg. In 250 samples of grapes analyzed, pterostilbene and 3'-hpt were detected only in two grapes of Nero d'Avola variety. Sicilian pistachios is a nut containing high concentration of resveratrol ranged from 6.38 ± 0.05 to 8.27 ± 0.08 mg/Kg (av = 7.09 ± 0.54 mg/Kg); however, neither pterostilbene nor 3'-hpt were detected in twelve different pistachios samples examined. Interestingly, a high amount of 3'-hpt, in addition to flavonoids, was detected in propolis. Indeed, in Italian propolis the concentration for pterostilbene is 0.2 ± 0.01 mg/Kg, for 3'-hpt ranged from 0.1 ± 0.04 to 2.2 ± 0.12 mg/Kg, for total flavonoids ranged from 1.39 ± 0.08 to 98.80 ± 0.28 mg/Kg, but quercetin were not detected. Among Italian propolis samples analyzed, it was highlight the high amount of 3'-hpt only in a sample coming from Sicily (2.2 ± 0.12 mg/Kg). However, analyzing other samples of propolis from Japan, we detected the amount of stilbenes, for pterostilbene and 3'-hpt was 9.46 ± 0.05 mg/Kg and 5.06 ± 0.11 mg/Kg, respectively. The concentration for total flavonoids was 153.12 ± 0.50 mg/Kg. In conclusion, piceatannol is widely rapresented in Sicilian grapes and wines. It was also of interest the detection of high amounts of 3'-hpt and flavonoids, in particular chrysin, pinocembrin and galangin, in propolis, a finding that could explain, at least in part, the benefical effect of propolis for human health.

Introduction

Stilbene and flavonoids compounds are widely represented in nature. Flavonoids are part of family of naturally occurring polyphenolic compounds and represent one of the most prevalent classes of compounds in vegetables, nuts, fruits and beverages such as coffee, tea, and red wine as well as medical herbs. They have attracted the attention of many researchers due to their wide ranging of biological activities, including free radical scavenging, modifying enzymes that activate or detoxify carcinogens and inhibiting the induction of the transcription factor activetor protein-1 (AP-1) activity by tumor promoters (1-3). One of the most studied stilbenes is resveratrol (*trans*-3,4',5-trihydroxystilbene), a phytoalexin present in grapes and other foods, which seems to play a role in the prevention of heart diseases associated with red wine consumption because it inhibits platelet aggregation, alters eicosanoid synthesis and modulates lipid and lipoprotein metabolism (4-7). Resveratrol has recently been suggested as a potential cancer chemopreventive agent based on its striking inhibitory effects on cellular events associated with cancer initiation, promotion, and progression (8-10). Moreover, resveratrol has powerful growth inhibitory and pro-apoptotic effects on various cancer cell lines (11, 12).

Piceatannol and pterostilbene are two *trans*-resveratrol-like natural stilbenes which have recently aroused interest due to their chemopreventive and anticancer properties.

Piceatannol has been isolated, together with resveratrol, in grapes and wine. As *trans*-resveratrol, piceatannol displays cytotoxic activity in acute leukemia and lymphoma cells and antiproliferative activity in colorectal cancer cell lines (13).

Pterostilbene (*trans*-3,5-dimethoxy-4'-hydroxystilbene) was first isolated from red sandalwood (*Pterocarpus santalinus*). Pterostilbene as been demonstrated to have a cancer chemopreventive activity similar to that of resveratrol and it is cytotoxic for a number of *in vitro* cancer cell lines (14).

Recently, 3'-hydroxypterostilbene (*trans*-3,5-dimethoxy-3',4'hydroxystilbene), a new natural pterostilbene analogue, has been isolated from whole specimens of the herb *Sphaerophysa salsula*, a shrub widely distributed in central Asia and northwest China (15). It was observed that 3'-hydroxypterostilbene (3'-hpt) was 50-97 times more potent than *trans*-resveratrol in inducing apoptosis in different leukemia cell lines (16).

In this work we analyzed some natural products for the presence of stilbenes (resveratrol, piceatannol, pterostilbene and 3'-hpt) and flavonoids (quercetin, apigenin, kaempferol, (±) narigenin, chrysin, pinocembrin, and galangin). Quercetin (3,5,7,3',4'-pentahydroxyflavone) is a flavonoid present in wine wich has a wide spectrum of anticancer properties including inhibition of the growth of cells derived from human cancers such as those of stomach, colon, prostate and breast (17). Apigenin, a 4',5,7-trihydroxyflavone, present in propolis which shows an antibacterial activity against oral microrganisms; it was the most effective inhibitor of activity of bacterium-derived glucosyltransferase and on the surface of saliva-cated hydroxyapatite beads (18). Chrysin (5,7-dihydroxyflavone) is a natural, biologically active compound extracted from many plants, honey and propolis. It possesses potent anti-inflammation, anti-cancer and anti-oxidation properties (19). Pinocembrin (5,7-dihydroxyflavanone) showed cytotoxicity against a variety of cancer cells and galangin showed antiproliferative effect on HL-60 human leukaemia cell (20, 21).

We observed that resveratrol and free-piceatannol, but not pterostilbene and 3'-hpt, are stilbenes widely represented in Sicilian grapes and Sicilian pistachios. Interestingly, a high amount of flavonoids as chrysin, galangin, pinocembrin and for the first time 3'-hpt was detected in propolis produced in Italy and Japan.

Materials and methods

Compounds

Trans-resveratrol and piceatannol (*trans*-3,3',4,5'-tetrahydroxy-stilbene) was purchased from Sigma (St. Louis, MO, USA); *trans*-resveratrol-3-O-β-glucoside (*trans*-piceid) was purchased from Apin Chemicals Ltd (Great Britain); *cis*-resveratrol and *cis*-piceid were obtained by UV irradiation of diluited solutions of their respective *trans*-isomers. Pterostilbene, 3'-hydroxypterostilbene (3'-hpt), apigenin, chrysin, galangin, kaempferol, (±) narigenin pinocembrin, and quercetin were provided by the Department of Pharmaceutical Science, the University of Bologna, Italy.

Acetonitril, methanol and ethanol of HPLC-grade were obtained from Merck (Darmstadt, Germany). Water was purified using a Milli-Q system (Millipore, Bedford, MA, USA). Phosphate buffer was prepared with potassium di-hydrogen phosphate ACS-ISO for analysis (Carlo Erba Reagents, MI, Italy) at 0.02 M and adjusted a pH= 3.0 with orthophosphoric acid 85% ACS-ISO for analysis (Carlo Erba Reagents, MI, Italy), and

after it was filter with Nitrocellulose 0.45 μm, 47 mm gridded (Millipore, Bedford, MA, USA). **Figure 1** and **Figure 2** show molecular forms of stilbenes and flavonoids respectively.

Grape samples

Sicilian samples of grape, obtained from Assessorato Agricoltura e Foreste of Sicily, relative to vintage 2004 were analysed by HPLC. The analysis consisted in a first extraction fase of grape (20 g) with 30 ml of methanol/water (95:5; v/v), filtration and concentration in Rotavapor (Buchi) for 60 minutes; added to concentrate 5 ml of sodium carbonate follow a second extraction with 10 ml of ethyl acetate for three-time. The

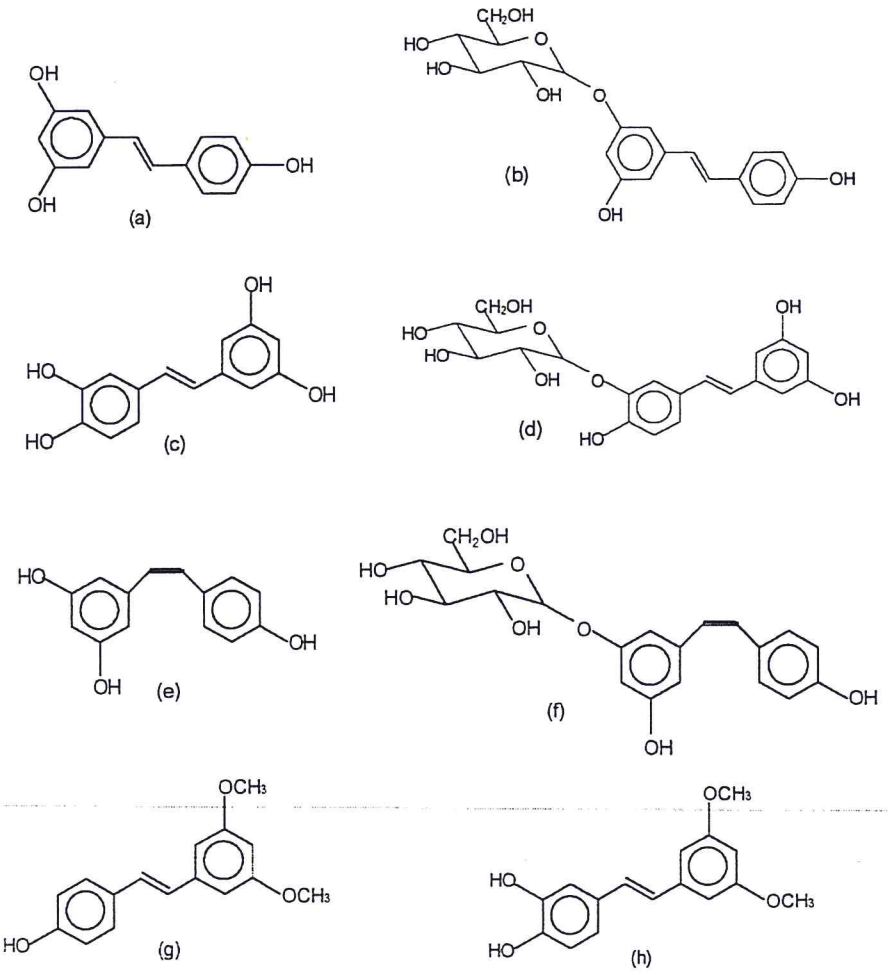

Figure 1. Molecular forms of (a) *trans*-resveratrol, (b) *trans*-piceid, (c) piceatannol, (d) astringin, (e) *cis*-resveratrol, (f) *cis*-piceid, (g) pterostilbene and (h) 3'-hydroxypterostilbene.

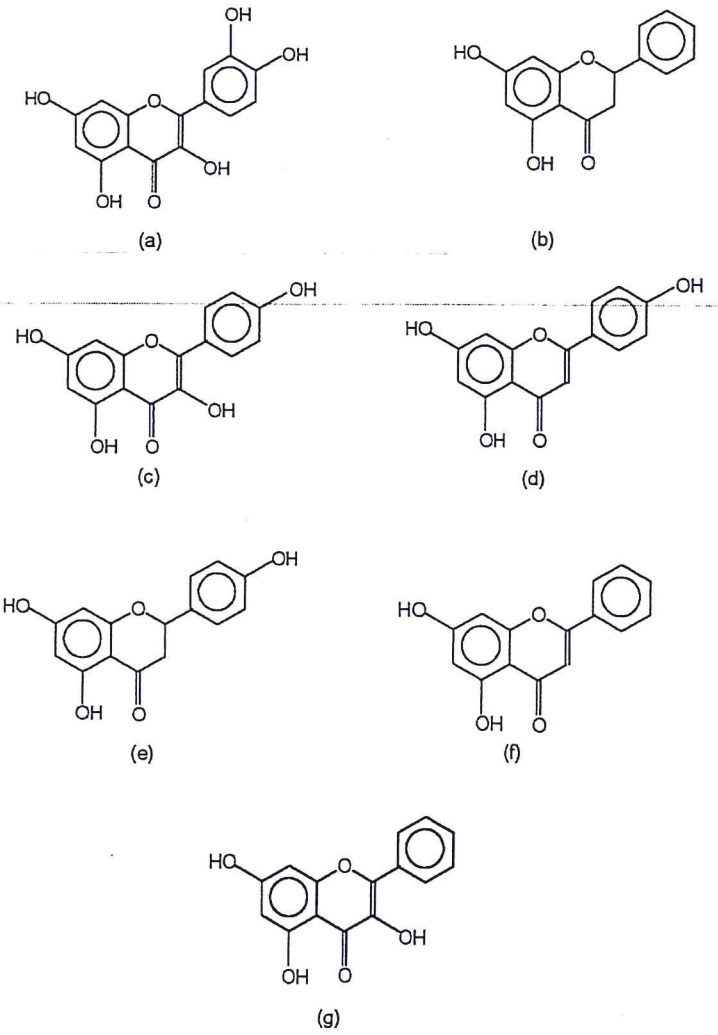

Figure 2. Molecular forms of (a) quercetin, (b) pinocembrin, (c) kaempferol, (d) apigenin, (e) (±) naringenin, (f) chrysin and (g) galangin.

organic layer extract were evaporated in Rotavapor and eluited in 1 ml of methanol/water (50:50; v/v), followed by filtration using 0.20 μm cellulose membrane filter (Minisart RC 25 Sartorius, Germany). Each sample was accompanied with a card which reported details relating to kind of tendril and cultivation place.

Pistachio samples

Pistachio samples comes from plants of pistachio belonging to the Anacardiaceae family, species *Pistacia vera* L., variety "Napoletana" or "White". A total of twelve

pistachio samples harvested impart in six samples caming from Sicilian farm situated in the Bronte area and six caming from the Agrigento area.

All twelve samples were harvested in September 2005 during the maturation phase and they were dried to the sun.

Pistachio's samples were shelled by hand and immediatly analysed. The extration procedure was carried out according, in part, to the method described by Sanders et al., 2000 (22). The quantification of stilbenes was made by HPLC.

Propolis samples

Samples of Japanese propolis (Akita propolis) and Italian propolis, among which two samples from Sicily, were analysed by direct inject in HPLC; the extration fase was carried out through the homogenization of solid propolis in dimethyl sulfoxide (DMSO). An aliquot of this solution equal to 1 mg of propolis was dissolved in 1 ml of methanol/water (50:50, v/v), followed by filtration with 0.20 µm cellulose membrane filter Minisart RC 25.

HPLC analysis

The liquid cromatograph was an HPLC system Agilent Technologies (Palo Alto, CA) Series 1100, constituted by a quaternary pump and DAD detector. The column was a reversed-phase Luna ODS C18 (Phenomenex), 250 x 4.6mm ID, 5 µm. The mobile phase was made with solvent A (acetonitrile) and solvent B (phosphate buffer), using two gradient mobile phase. The first gradient was used to separate among stilbenes piceatannol, *trans*-resveratrol, pterostilbene and 3'-hpt in pistachio and grapes samples; it was composed as in **Table 1**. Moreover this gradient was used to analyzed the stilbenes and flavonoids compounds in propolis. The second gradient was used to separate the *trans*-piceid in grape and pistachio samples and it was composed as reported in **Table 2**. The flow rate of mobile phase was 1 ml/min and the temperature of column was 25°C. The inject volume was 50 µl. Each sample was inject three time. For both gradients, the experimental conditions were the same, whereas the only different consisted in the ratio of the solvent (A and B) during the eluition. The wavelength was set at 325 nm, that was the maximum absorbance for all stilbenes except for the pterostilbene where the wavelength was set at 318 nm, for *cis*-resveratrol and *cis*-piceid which the wavelength was set at 285 nm. For flavonoids compounds the retention time (t_R) and the wavelenght of absorption (λ) is reported in **Table 3**. The identification of the different compounds was achieved by comparision of both t_R and spectra (obtained for each eluted peak) with those obtained for the standard. To check the peak purity, the eluates were monitored with a photodiode array detector (DAD), with a wavelength range λ=220-600 nm. The absorption spectra of each peak was compared with the absorption spectra of the standard and it was identified when the match factor was >995. The t_R of piceatannol is 16.59 ± 0.4 minutes, of *trans*-resveratrol is 18.00 ± 0.35 minutes, for pterostilbene and 3'-hpt the t_R is 33.52 ± 0.30 minutes and 30.51 ± 0.30 minutes respectively. This t_R obtained with the gradient eluition 1; for *trans*-piceid the t_R ranged from 17.93 to 18.09 minutes using the gradient eluition 2.

To increase the sensivity of the procedure, an Agilent 1100 Series fluorescence detector set at 325/390 nm (excitation/emission).

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Calibration

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Table 1. Gradient eluition 1.

Time (minutes)	Solvent A (%)	Solvent B (%)
5.00	10	90
8.00	20	80
10.00	20	80
13.00	40	60
25.00	40	60
27.00	60	40

Table 2. Gradient eluition 2.

Time (minutes)	Solvent A (%)	Solvent B (%)
5.00	10	90
8.00	20	80
19.00	20	80
30.00	40	60
33.00	60	40
50.00	60	40

Table 3. Retention time (t_R) and absorption wavelenght (λ) of flavonoids.

Flavonoids	t_R (minutes)	λ (nm)
Quercetin	18.98 ± 0.11	325
Apigenin	21.41 ± 0.17	325
Naringenin	21.97 ± 0.24	285
Kaempferol	22.33 ± 0.03	325
Chryisin	30.99 ± 0.01	285
Pinocembrin	31.71 ± 0.17	285
Galangin	31.78 ± 0.17	325

Calibration

Standards of piceatannol, *trans*-resveratrol, *trans*-piceid, pterostilbene, 3'-hpt, quercetin, apigenin, kaempferol, (±) naringenin, chrysin, pinocembrin and galangin were employed at different concentrations to construct calibration curve. All standards were diluted in methanol/water (50/50, v/v). For each standard it was made a calibration curve with a six different concentration level; all standard curves had a correlation coefficient > 0,997.

Recovery analysis and analytical precision

The recovery factor for all compounds were determined at four different concentration spiking the samples with pure standards. Each concentration was tested six

times before and after addition. The mean *trans*-resveratrol recovery averaged was 75.5% and for *trans*-piceid averaged 91.0%. The mean piceatannol recovery averaged was 80.0% and for pterostilbene and 3'-hpt were 90.0% and 92.0% respectively.

The mean recoveries for flavonoids were >100%. The precision of the analytical method for all molecules was determined spiking one sample at five different concentration by performing for each level six replicated.

Statistical analysis

The statistical analysis were applied by using MedCalc statistical program.

Results

Detection of stilbenes in grapes samples

In 250 samples of grapes analyzed we observed an amount of *trans*-resveratrol ranging from 0.13 ± 0.04 to 1.12 ± 0.18 mg/Kg, and *trans*-piceid ranging from 0.75 ± 0.05 to 7.10 ± 0.50 mg/Kg. Of interest, several Sicilian grapes were rich of free piceatannol; the concentration of this stilbenes ranged from 0.18 ± 0.25 to 22.97 ± 3.01 mg/Kg. The means concentrations were reported in **Table 4**. Moreover, pterostilbene and 3'-hpt were detected only in two Nero d'Avola grapes variety.

Table 4. Mean concentration and S.D. of piceatannol, *trans*-resveratrol and *trans*-piceid in grape samples of Sicily.

Compound	Mean (mg/Kg) ± S.D.
Piceatannol	23.15 ± 1.32
trans-piceid	4.00 ± 0.12
*trans*resveratrol	0.62 ± 0.05

Detection of stilbenes in pistachio samples

Twelve pistachio samples were analysed for their content in *trans*-resveratrol and *trans*-piceid. We observed that all samples examined contained *trans*-resveratrol and its glucoside. The concentration of *trans*-resveratrol ranged from 0.07 ± 0.03 to 0.18 ± 0.05 mg/Kg, the *trans*-piceid content were in the range of 6.20 ± 0.05 to 8.15 mg/Kg and the content of total resveratrol from 6.38 to 8.27 mg/Kg (**Table 5**).

No *cis* isomers of both stilbenes were detected in the samples analysed. The mean content of stilbenes was 0.12 ± 0.03 mg/Kg for *trans*-resveratrol, 6.97 ± 0.55 mg/Kg for *trans*-piceid and 7.09 ± 0.54 mg/Kg for total resveratrol. The concentration of *trans*-piceid was markadely higher than that of *trans*-resveratrol in all samples examined ($P<0.01$). Similar results are observed in red grapes and its derivates (wine, juice) (23, 24). In fact, the amount of *trans* piceid in red wine can be more than ten times greater than its aglycone *trans*-resveratrol (25). No significant difference in stilbenes content was observed comparing the samples of pistachio of Bronte and Agrigento areas.

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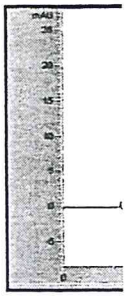

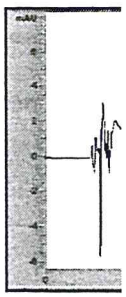

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Table 5. Concentration means and S.D. of *trans*-resveratrol and *trans*-piceid in pistachio samples of Bronte and Agrigento areas.

Compounds	Bronte Mean (mg/Kg) ± S.D.	Agrigento Mean (mg/Kg) ± S.D.
trans-piceid	6.68 ± 0.37	7.27 ± 0.56
trans-resveratrol	0.13 ± 0.04	0.10 ± 0.02
Total resveratrol	6.82 ± 0.36	7.36 ± 0.57

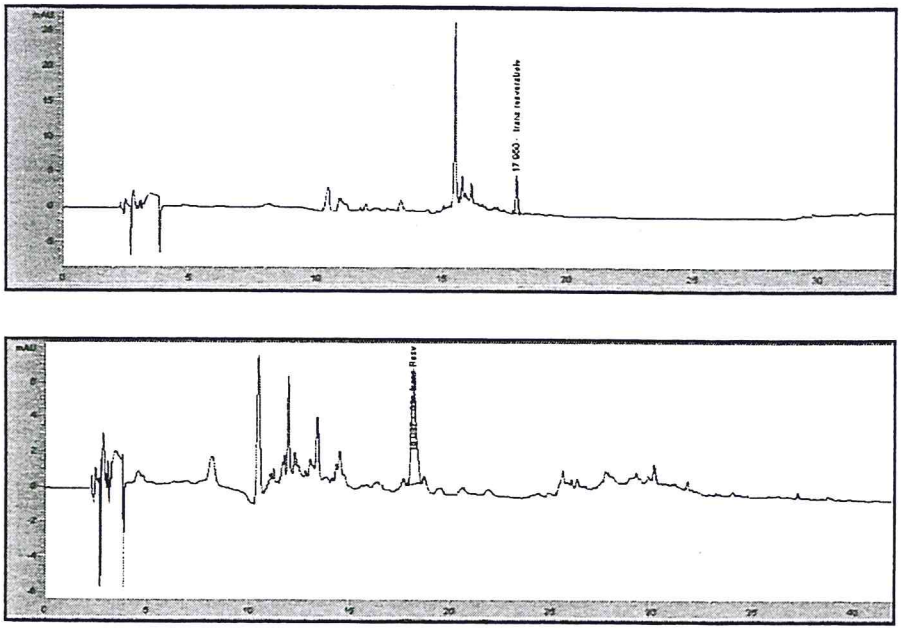

Figure 3. Chromatograph of *trans*-resveratrol and *trans*-piceid in pistachio samples.

Detection of stilbenes in propolis samples

We detected high concentration of 3'-hpt and flavonoids in Italian propolis, for 3'-hpt ranged from 0.1 ± 0.04 to 2.2 ± 0.12 mg/Kg, for total flavonoids ranged from 1.39 ± 0.08 to 98.80 ± 0.28 mg/Kg, but quercetin were not detected. For each one stilbene and flavonoid, it was reported the minimum and maximum values in **Table 6**. Indeed, among Italian propolis samples analyzed, it was highlight the high amount of 3'-hpt only in a sample coming from Sicily (2.2 ± 0.12 mg/Kg). We observed a high amount of pterostilbene and 3'-hpt in Japan propolis of 5.06 ± 0.02 mg/Kg and 9.46 ± 0.11 mg/Kg, respectively. The concentration of these compounds along that of flavonoids was showed in **Table 7**. High amount of total flavonoids was been emphasise in Japan propolis (of 153.12 ± 0.50 mg/Kg), due in particular at the high concentrations of chrysin and pinocembrin, but galangin was not detected.

Table 6. Concentration of pterostilbene, 3'htp and flavonoids in Italian propolis samples.

Compounds	Minimum Value (mg/Kg) ± S.D.	Maximum Value (mg/Kg) ± S.D.
Pterostilbene	0.38 ± 0.01	1.20 ± 0.01
3'hpt	2.22 ± 0.04	0.08 ± 0.02
Apigenin	0.10 ± 0.01	2.20 ± 0.12
Kaempferol	0.57 ± 0.03	1.35 ± 0.08
Naringenin	0.03 ± 0,01	0.40 ± 0.05
Chrysin	1.18 ± 0.11	42.16 ± 0.15
Pinocembrin	0.21 ± 0.01	16.24 ± 0,20
Galangin	36.60 ± 0.10	37.70 ± 0.04

Table 7. Concentration of pterostilbene, 3'htp and flavonoids in Japan propolis sample. (n.d.: not detected).

Compounds	Concentration (mg/Kg) ± S.D.
Pterostilbene	9.46 ± 0.11
3'hpt	5.06 ± 0.02
Quercetin	1.37 ± 0.12
Apigenin	1.36 ± 0.08
Kaempferol	n.d.
Naringenin	2.10 ± 0.04
Chrysin	56.30 ± 0.72
Pinocembrin	92.01 ± 0.14
Galangin	n.d.

Discussion

In this work we investigated about the content of some stilbenes endowed with healthy effects on some natural products. We observed that all samples of Sicilian grape analysed contained *trans*-resveratrol, *trans*-piceid and, of interest, free piceatannol, which is a stilbene compound no frequently observed in grapes compared to resveratrol. Little amount of pterostilbene and 3'-hpt were observed in two samples of grapes (Nero d'Avola).

Also sicilian pistachio nuts contain *trans*-resveratrol and its glucoside but not piceatannol, pterostilbene and 3'-hpt. Recently, Tokuşoğlu *et al.* have reported the presence of *trans*-resveratrol in Turkey peanuts and pistachio varieties (26). However, in Tokuşoğlu's study, *trans*-piceid was no detected. *trans*-piceid is a form of resveratrol

important for human health because it is converted in a free form (*trans*-resveratrol) by human small intestine and liver β-glucosidase activity after ingestion (27).

The most important data of our work was the detection of high amount of pterostilbene, 3'-hpt and a very hight amount of flavonoids in different variety of propolis. In particular the values shown a hight amount of chrysin, pinocembrin and galangin three important flavonoid compounds for their anticancer action. 3'hpt is a stibene compound previously detected only in a plant growing in China (*Sphaerophysa salsula*). Recently, we observed that 3'-hpt is able to kill - through apoptosis activation - different leukemia cells including cell lines resistant to conventional anticancer agents (16). Our data suggest that propolis may be a natural substance useful for the prevention or for the treatment of different types of leukemia, especially leukemia variety resistant toward conventional chemotherapeutic agents.

Acknowledgements

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