

## Comparison of Resveratrol Contents in Medicinal Plants

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**ABSTRACT** : Secondary phenolic metabolites play an important role in plant defense mechanisms, and increasing evidence indicates that many phenolic compounds are important in human health. To date, few studies have investigated the impact of various medicinal plants on levels of secondary plant metabolites. To address this issue, 82 species of Korean medicinal plants were screened to determine their resveratrol contents. Among 82 medicinal plants, 5 species such as *Gardenia jasmonoides*, *Phlomis umbrosa*, *Rheum palmatum* L., *Polygala tenuifolia*, *Rubus chingii* HU contained relatively high concentrations of resveratrol (179.75~42.71 µg/g). But, 40 species including *Adenophora triphylla* var. *japonica* HARA were only observed low concentrations or trace of resveratrol, and 20 species including *Alpinia officinarum* HANCE did not contain a resveratrol.

**Key words** : medicinal plants, resveratrol, secondary phenolic metabolites

### INTRODUCTION

Resveratrol (trans-3,5,4'-trihydroxystilbene) is found in plants such as mulberries, grapes, and peanuts (Sobolev & Cole, 1999; Zhu *et al.*, 2000). Resveratrol and hydroxylated stilbenes are accumulated in plants in response to attacks by pathogens such as *Plasmopora viticola* or *Botrytis cinerea* (fungal infections), the causal agents against downy mildew and grey mould or abiotics stresses such as UV light, mechanical injury, and aluminium chloride (Adrian *et al.*, 2000). Irradiation of plant tissues with UV light has some important effects on phenolic metabolism. UV-B light irradiation seems to be associated with an increase in the enzymes responsible for flavonoid biosynthesis, as these compounds can act as UV screens preventing the UV-induced damage in the genetic material of plant cells (Dong *et al.*, 1995;

Cantos *et al.*, 2000). Stilbene synthase (STS) is plant-specific polyketide synthase which plays a pivotal role in the biosynthesis of stilbenes containing resveratrol (Schroder, 1999). The stilbene convert p-coumaroyl-CoA to the major product, resveratrol. The phenolic compound resveratrol (3,5,4'-trihydroxystilbene) is a non-flavonoid phytoalexin produced by plants in response to fungal infection or stress (Langcake, 1981). They occur in widely unrelated plant families and in some cases, only a few species of a large family are able to synthesize these substances. STSs are rare in higher plants and occur in distantly related species such as peanut (*Arachis hypogaea* L.) (Schppner & Kindl, 1984), grapevine (*Vitis vinifera* L.) (Sparvoli *et al.*, 1994), pines (*Pinus sylvestris* L., *Pinus strobus* L.) (Schanz *et al.*, 1992; Raiber *et al.*, 1995), and rhubarb (*Rheum palmatum* L.) (Kashiwada *et al.*, 1988).

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Received April 6, 2004 / Accepted April 19, 2004.

Increasing interest in monitoring the presence of resveratrol in plants was caused by so called the "French paradox". It has been found that in some parts of France, the death rate caused by coronary artery diseases was respectively low in spite of high consumption of fats. The consumption of wine was one of the dietary factors, which might partially explain the low mortality caused by atherosclerosis (Renauld & De Lorgeril, 1992). The wide range of biological effects exhibited by resveratrol are thought to be due to its powerful antioxidant properties (Belguendouz *et al.*, 1997) and its ability to interact with redox sensitive cell signalling pathways (Bertelli, 1998). The ability of resveratrol to scavenge reactive oxygen species (ROS) *in vitro* has been well documented. For example, resveratrol was observed to prevent oxidative DNA damage induced in the kidney by  $\text{KBrO}_3$  (Cadenas & Barja, 1999) and act as a potent scavenger of peroxy radicals in an isolated rat heart ischaemia reperfusion model (Ray *et al.*, 1999). Recently, the cancer chemopreventive activity (Palomino *et al.*, 2000) of resveratrol has been reported to be related to its ability to trigger apoptosis (Carbo *et al.*, 1999; Huang *et al.*, 1999) and a mechanism of programmed cell death which has been linked to ROS and lipid peroxides (Hale *et al.*, 1996). In contrast, resveratrol has been shown to prevent apoptosis in K562 cells via the direct inhibition of arachidonate-metabolising enzymes such as lipoxygenase and cyclooxygenase (Maccarrone *et al.*, 1999). *Cis*- and *trans*-resveratrol and their corresponding resveratrol glucoside present in plant have been linked to this effect by virtue of their *in vitro* inhibitory activities on the oxidation of human low-density lipoproteins (Frankel *et al.*, 1995), antiplatelet properties (Bertelli *et al.*, 1995) and eicosanoid synthesis (Pace-Asciak *et al.*, 1995). On the other hand, as a medicinal natural product, resveratrol is known to be a cancer chemopreventive agent (Jang *et al.*, 1997) as well as an agonist for the estrogen receptor (Gehm *et al.*, 1997) and as a phytochemical, human health benefits are revealed as its association with reduced cardiovascular disease has been demonstrated (Fremont, 2000). However, there is very little information on the impact of

various species have on the production of secondary phenolic metabolites such as resveratrol in medicinal plants.

HPLC techniques have become the dominant and very frequently used method of resveratrol determination. LC methods with gradient elution and UV or fluorimetric detection have been reported for the determination of resveratrol in biological samples, especially in grape berries and wines. Recently, resveratrol has been assayed by the direct injection without purification and pre-concentration steps. LC with electrochemical detection has been shown to be selective and sensitive enough for the determination of resveratrol and other phenolic compounds in natural sources (Zhu *et al.*, 2000; Melzoch *et al.*, 2000).

Resveratrol is found in a limited number of unrelated species, such as peanut and grapevine. Resveratrol in vines is produced in leaves and berries. It has recently been observed that resveratrol is synthesized non-inducibly in peanut tissue and a relatively large amount of resveratrol is found in uninfected peanut seeds. Their contents dependents variously on different species of medicinal plants, therefore it should be performed quantitative analysis of resveratrol in various plants.

The aim of this reserach was selecting plants having high resveratrol contents with medicinal plants these might develop to chemicals related to antioxidants, as well as become most popular substance at many industrial materials by monitoring the presence of resveratrol in plants and concluded that resveratrol could be useful as a phytoalexin for plant health, as well as a phytochemical for human health.

## MATERIALS AND METHODS

A survey of polyketide compounds, especially resveratrol, using high performance liquid chromatography was performed in 82 species of traditional medicinal plants. The amount of resveratrol in leaf, fruit, flower, seed, root, stem, tuber, and bulb, part of use for therapeutical in medicinal plant were determined.

Mature fruits, leaves, and the other organs were collected and fresh samples were stored frozen in sealed clear polyethylene plastic bags (168×150 mm,

**Table 1.** HPLC conditions for analysing phenol compounds.

Column	YMC AM303 (4.6 × 250 mm)		
	Gradient		
	Solvent A	Solvent B	
Mobile phase	98% H <sub>2</sub> O + 2% glacial acetic acid in 0.018 M ammonium acetate	70% solvent A + 30% organic solvent (82% MeOH, 16% n-butanol and 2% 0.018 M ammonium acetate)	
Flow rate	1.0 ml · min <sup>-1</sup>		
Detector (UV)	SPD-10A spectrophotometer, 280 nm		
Injection volume	20 µl		
	Time (min.)	Solvent A (%)	Solvent B (%)
Time program	0.0	90	10
	1.0	90	10
	21.0	75	25
	36.0	55	45
	56.0	0	100
	82.0	90	10
	92.0	90	10

Glad-Lock zipper sandwich bags, First Brands Corp., Danbury, CT) at  $-80^{\circ}\text{C}$  until they were used. Collected samples were freeze dried at  $-80^{\circ}\text{C}$  in brown paper bags for at least 24 hr and dried samples were ground into a fine powder (40-mesh) by mill. Samples (approximately 2 g) were extracted with 12 ml of 0.1N aqueous HCl:acetonitrile (1:5, v/v) mixture at room temperature for one hour. The extract were filtrated through filter paper (Whatman No. 42) and evaporated (Heidoph VV2011,  $40^{\circ}\text{C}$ ). The evaporated extract was resuspended with 10 ml of 80% MeOH and prepared for HPLC analysis. The standard chemical (trans-3,5,4'- trihydroxystilbene) was purchased from Sigma.

Resveratrol-forming stilbene was quantified by HPLC of a model LC-10A liquid chromatography (Shimadzu Co., Kyoto, Japan) equipped with Shimadzu SPD-10A spectrophotometer operated at the wavelength of 280 nm. The separation of resveratrol-forming stilbene was performed on a J'sphere ODS-H80 fractionation column, (S-4 µm 80A, 250×10 mm) with a flow rate of 1 ml · min<sup>-1</sup>. Gradient elution was performed with solvent A consist of 2% 0.018 M aqueous ammonium acetate and solvent B comprising 70% solvent A and 30% organic solvent. Organic

solvent composed of 82% MeOH, 16% n-butanol, and 2% 0.018 M ammonium acetate. The sample was injected (10,000 ppm, 5 µl) and applied gradient elution was as follows. 0~1 min., wash of 90% solvent A; 1~21 min., linear gradient from 90 to 75% solvent A; 21~36 min., linear gradient from 75% to 55% solvent A; 36~56 min., linear gradient from 45 to 100% solvent B; 56~82 min., wash of 100% solvent B (Table 1). Identification and quantification of resveratrol were carried out by comparing the retention times and the peak areas respectively with those of resveratrol standard or by direct addition of resveratrol standard into the sample (spike test). Sample aliquots were filtered through a 0.45 µm poly (tetrafluoroethylene) filter prior to injection. All samples were run in triplicate. The linearity range of resveratrol standard was determined from 0.001 to 0.1 µg/µl ( $R^2 = 0.9997$ ).

## RESULTS AND DISCUSSION

Polyketide synthases (PKS) from bacteria, fungi, and plants produce an array of natural products (Hopwood & Sherman, 1990; Hopwood, 1997; Khosla *et al.*, 1999). Many polyketides possess pharmacological

properties and are used as antibiotics, immunosuppressants, anti-cancer agents, and anti-fungal agents (Hutchinson, 1998).

Stilbene synthase (STS) and chalcone synthase (CHS) are plant-specific polyketide synthases that play a pivotal role in the biosynthesis of stilbenes and flavonoids, respectively (Schroder, 1999). Both stilbene and chalcone synthases convert *p*-coumaroyl-CoA to the major products naringenin or resveratrol, respectively. During the past natural antioxidants have evoked the widest in human diet as protective compounds with significant biological activities and resveratrol has become one of the most popular substance. It was interesting to screen contents of resveratrol and other stilbenes from the natural sources potentially available in various plants. These interest was focused on the resveratrol contents screening in selected medicinal plants will be use for development of phytoalexin and phytochemical.

The resveratrol contents were determined in 82 medicinal plants and each medicinal plants contained resveratrol in the very different concentration. Among 82 medicinal plants, five species including *Gardenia jasmonoides*, *Phlomis umbrosa*, *Rheum palmatum*, *Polygala tenuifolia* and *Angelica dahurica* showed relatively large amount of resveratrol varied from 179.75 to 42.71  $\mu\text{g/g}$  in comparison with other 40 species. It detected only at trace amount of resveratrols. Resveratrol was not detected in 20 species (Table 2).

As part of a study of the screening of resveratrol present in medicinal plants, we founded the CHS superfamily members present in *Rheum tataricum*, or Tatar rhubarb. *Rheum* species are a rich source of polyketides including phenylbutanoids, anthraquinones, naphthalenes and stilbenes (Kashiwada *et al.*, 1988). Also, it is not yet known exactly if there is a mechanism to induce apoptosis or pseudo-apoptosis in human tumors, especially glioma using the *Gardenia jasminoides* (Wang *et al.*, 1993). As a similar species with *Polygala tenuifolia*, *Polygonum cuspidatum* has been reported to possess anti-bacterial and anti-inflammatory activity and roots of *P. cuspidatum* also contain the natural compounds, resveratrol (Kimura & Okuda, 2001). It is interesting to note that the members of the genus are also used as medicinal plants for STS activity was shown with protein extracts, although the enzyme responsible was never isolated using biochemical or molecular approaches.

In this result, we investigated resveratrol is found in a variety of medicinal plants. Major dietary sources include grapes, wine, peanuts and soy (Burns *et al.*, 2002). These compounds are also found in medicinal plants which has long been used in Korean and China as a traditional remedy for heart disease and stroke. For people who do not wish to consume alcohol, A large amount of stilbene containing resveratrol may be a substituent for red wine as a dietary source of resveratrol. Also, the difference of phenolic metabolite concentration between species indicates that secondary

**Table 2.** Resveratrol content in various medicinal and cereal plants.

Scientific name	Part used for therapeutic*	Resveratrol ( $\mu\text{g/g}$ )
<i>Acanthopanax gracilistylus</i> W.W. Smith	RT	2.80
<i>Achyranthes bidentata</i> Blume	RT	22.87
<i>Aconitum carmichaeli</i> Debx	RT	1.72
<i>Acorus gramineus</i> Soland	RT	9.93
<i>Adenophora triphylla</i> var. <i>japonica</i> Hara	RT	0.62
<i>Agastache rugosa</i> (Fich. et Mey) O. Ktze.	LF	1.55
<i>Alisma orientale</i> (Sam.) Juzep.	TB	16.12
<i>Alpinia officinarum</i> Hance	RT	0.00
<i>Anemarrhena asphodeloides</i> Bunge	RT	16.28
<i>Angelica dahurica</i> Benth. et Hook.	RT	34.68
<i>Angelica koreana</i> Maxim.	RT	2.37
<i>Aralia cordata</i> Thunb.	RT	1.44

Table 2. Continued.

Scientific name	Part used for therapeutical*	Resveratrol ( $\mu\text{g/g}$ )
<i>Arctium lappa</i> L.	FR	31.08
<i>Artemisia argyi</i> Levl. et Vant.	LF	11.70
<i>Artemisia capillaris</i> Thunb.	LF, ST	2.03
<i>Asparagus cochinchinensis</i> Merr	RT	0.00
<i>Astragalus membranaceus</i> Bunge	RT	1.63
<i>Atractylodes chinensis</i> (DC.) Koidz.	RT	1.38
<i>Atractylodes japonica</i> Koidz.	RT	0.00
<i>Biota orientalis</i> (L.) Endl.	SD	0.00
<i>Bupleurum chinense</i> DC.	RT	0.00
<i>Carthamus tinctorius</i> L.	FW	9.86
<i>Cassia tora</i> L.	SD	22.66
<i>Chaenomeles sinensis</i> Koehne	FR	5.34
<i>Cirsium maackii</i> var. <i>koraiense</i>	RT	0.00
<i>Cnidium officinale</i> Makino	RT	1.41
<i>Codonopsis pilosula</i> (Fr.) Nanf	RT	0.64
<i>Coix lachrymajobi</i> var. <i>mayuen</i> (Roman) Stapf	SD	0.75
<i>Crataegus pinnatifida</i> Bge.	FR	0.00
<i>Curcuma aromatica</i> Salisb	RT	1.90
<i>Curcuma zedoaria</i> (Berg.) Rosc.	RT	3.17
<i>Cyperus rotundus</i> L.	TB	5.08
<i>Dioscorea opposita</i> Thunb.	TB	0.63
<i>Dolichos lablab</i> L.	SD	0.00
<i>Ephedra sinica</i> Stapf	ST	0.00
<i>Euryale ferox</i> Salisb.	SD	0.00
<i>Foeniculum vulgare</i> Gaertner	FR	2.41
<i>Gardenia jasmonoides</i> Ellis	RT	179.75
<i>Gleditsia japonica</i> Lam	FR	5.12
<i>Glycyrrhiza uralensis</i> Fisch	RT	90.0
<i>Hordeum vulgare</i> L.	SD	0.00
<i>Imperata cylindrica</i> L.	RT	0.00
<i>Ledeouriella seseloides</i> (Hoffm.) Wolff	RT	0.70
<i>Leonurus sibiricus</i> (Lour.) S.Y.Hu	LF	27.75
<i>Lilium longiflorum</i> Thunb.	BB	0.00
<i>Liriope platyphylla</i> Wang et Tang	RT	0.00
<i>Lonicera japonica</i> Thunb.	ST	4.33
<i>Lycium chinense</i> Mill.	FR	1.79
<i>Lycium chinense</i> Mill.	RT	0.77
<i>Mentha arvensis</i> L.	LF	0.00
<i>Morus alba</i> L.	RT	1.59
<i>Nelumbo nucifera</i> Gaertn	SD	0.87
<i>Paeonia lactiflora</i> Pall	RT	1.39
<i>Paeonia suffruticosa</i> Andr.	RT	52.43
<i>Perilla frutescens</i> var. <i>acuta</i> Kudo	LF	11.65

Table 2. Continued.

Scientific name	Part used for therapeutical*	Resveratrol ( $\mu\text{g/g}$ )
<i>Perilla frutescens</i> var. <i>japonica</i> (Hassk.) Hara	SD	2.42
<i>Pharbitis nil</i> Choisy	SD	33.21
<i>Phellodendron amurense</i> Rupr	ST	0.00
<i>Phlomis umbrosa</i> Turgi	RT	120.13
<i>Pinellia ternata</i> (Thunb) Breit	RT	6.42
<i>Plantago asiatica</i> L.	SD	16.30
<i>Platycodon grandiflorum</i> (Jacq.) A.DC.	RT	0.00
<i>Pleuropterus multiflorum</i> Thunb.	RT	4.30
<i>Polygala tenuifolia</i> Willd.	RT	42.71
<i>Polygonatum sibiricum</i> Redoute ex Redoute	RT	5.09
<i>Prunus mume</i> S. et Z	FR	1.44
<i>Raphanus sativus</i> L.	SD	1.25
<i>Pueraria thunbergiana</i> Bentham	RT	17.87
<i>Rehmannia glutinosa</i> (Gaertner) Liboschitz	RT	4.13
<i>Rheum palmatum</i> L.	RT	70.87
<i>Rubia akane</i> Nakai	RT	1.66
<i>Rubus chingii</i> Hu	FR	15.61
<i>Salvia miltiorrhiza</i> Bae.	RT	0.00
<i>Sanguisorba officinalis</i> L.	RT	19.21
<i>Schizonepeta tenuifolia</i> var. <i>japonica</i> Briguet	LF	0.82
<i>Scrophylaria buergeriana</i> Miq.	RT	1.26
<i>Scutellaria baicalensis</i> Georgi	RT	25.69
<i>Sinapis alba</i> L.	SD	0.00
<i>Sinocalamus beecheyanus</i>	ST	1.54
<i>Taraxacum mongolicum</i> Hand. et Mazz	LF	0.88
<i>Trichosanthes kirilowii</i> Maxim.	RT	0.00
<i>Zingiber officinale</i> Rosc.	RT	3.47
LSD.05		42.898

\* Part used for therapeutical was indicated by abbreviation (RT, roots; LF, leaves; TB, tubers; ST, stems; FR, fruits; SD, seeds; FW, flowers; BB, bulbs).

plant phenolic metabolites, such as resveratrol play critical roles in human health and may be therapeutically important. Of special interest are plant-based phenolic metabolites due to their potent wide range of pharmacologic properties including anticancer, antioxidant, and platelet aggregation inhibition activity.

To our knowledge we show for the first time a correlation between the applied various species and levels of resveratrol. Selection of medicinal plants with high biological activity might develop to chemicals related to antioxidants, as well as these become most

popular substance at many industrial materials.

## ACKNOWLEDGEMENT

This research was conducted by the financial support of the Rural Development Administration made in the BioGreen 21 project

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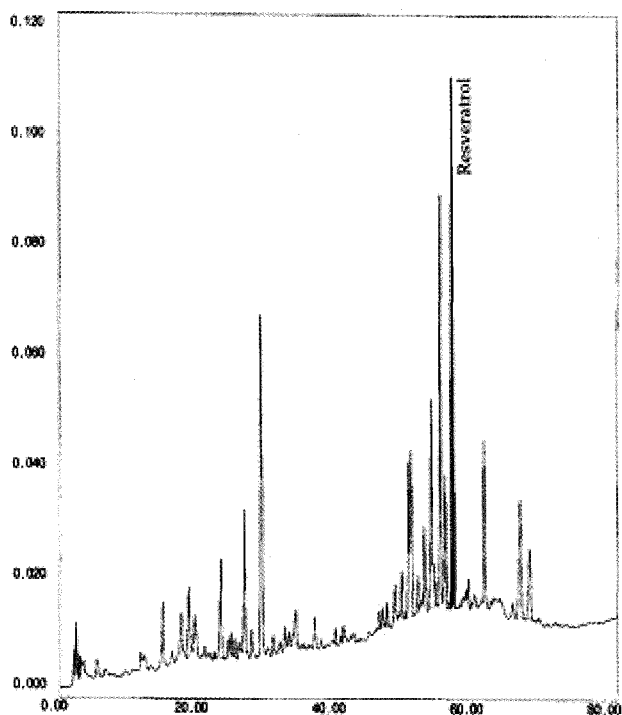


Fig. 1. HPLC profile of resveratrol in *Gardenia jasmonoides* Ellis (Detection: UV 280 nm).

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