

## Detection and Quantitation of Resveratrol in Tomato Fruit (*Lycopersicon esculentum* Mill.)

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Resveratrol is a stilbene phytoalexin well-known for its presence in grape, wine, and peanut. As a result of its antioxidant and chemopreventative properties, it has gained much attention as a functional food ingredient. A gas chromatography–mass spectrometry method for the detection of resveratrol, its 3-glucopyranoside piceid, and the *cis* isomers of both compounds has been developed and used to quantitate the levels of these compounds in the skin of commercially available tomato fruit (*Lycopersicon esculentum* Mill.). The resveratrol concentration remains relatively stable during fruit maturation, reaching a maximum concentration in the skin of  $18.4 \pm 1.6 \mu\text{g/g}$  dry weight at 4 weeks postbreaker. No stilbenes were detected in the flesh of tomato fruit.

**KEYWORDS:** Resveratrol; piceid; *Lycopersicon*; tomato; metabolic profiling

### INTRODUCTION

The plant-derived stilbene resveratrol has long been known as a phytoalexin, which is produced in response to infection and stress in grapes and a limited number of other plant species (1). It has become one of the more thoroughly studied phytochemicals in the past 10 years because of numerous reports of its *in vitro* and *in vivo* effects relevant to cardiovascular disease (2), breast cancer (3), colorectal cancer (4), prostate cancer (5), inflammation, and aging (6). Much of the epidemiological and clinical evidence for disease prevention associated with resveratrol comes from studies on the consumption of red wine, grapes, and grape juice (7). While these commodities have been reported as the primary dietary sources of resveratrol, several other sources have also been identified (8), including peanuts and the Japanese traditional herbal remedy, Itadori tea (from the root of *Polygonum cuspidatum*), which may be the richest source of resveratrol known (9).

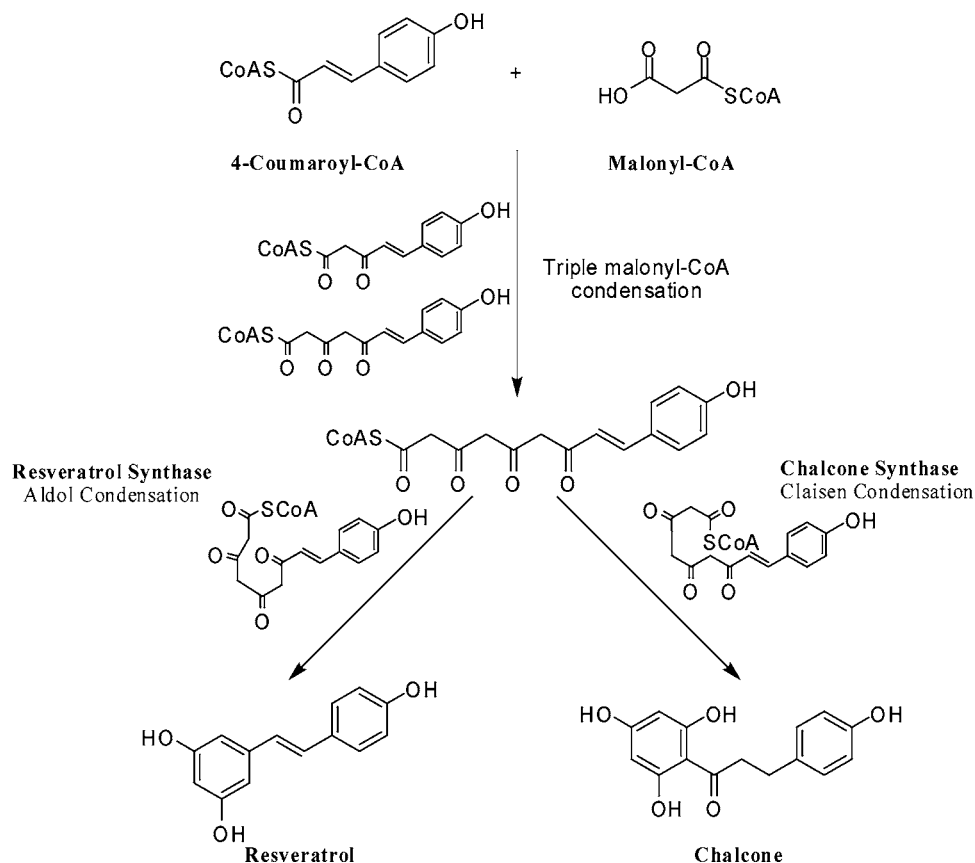
Resveratrol was first recognized as an important phytonutrient in 1996, when it was reported to possess cancer prevention properties based on *in vitro* assay results (10). It was around this time that it was also recognized as potentially being one of the phytonutrients responsible for the French Paradox: the observation that wine consumption by the French may be responsible for the relatively low incidence of heart disease in this population despite eating an otherwise relatively unhealthy diet from a cardiovascular health perspective (11). Resveratrol is found primarily in the grape skin, which is consistent with the observation that resveratrol is important in cardiovascular protection because red wine and grape juice have been demonstrated to have a greater protective effect than white wine

and white grape juice, which are produced by removing the grape skin (12). In support of the hypothesis that resveratrol has protective effects against cardiovascular disease are reports of the platelet aggregation inhibition activity of resveratrol (13) and its strong antioxidant potential.

More recently, resveratrol has also been reported to repress expression of the SIR2 gene, which codes for a histone deacetylase, responsible for programming cellular lifetime. Repression of SIR2 *in vivo* leads to an extended lifespan in *C. elegans* and mice (14). While all of these reports add up to a series of very compelling theories about the importance of resveratrol in human health ranging from cardiovascular disease prevention, to cancer prevention, to delaying aging, there have been no clinical studies conducted with resveratrol alone to determine its independent effect on any of these diseases, their biomarkers, or other disease endpoints. Nonetheless, the magnitude of the circumstantial data that is being compiled results in a very compelling argument for the importance of resveratrol in human health and disease prevention.

Tomato is known to be an abundant source of carotenoids, flavonoids, and other antioxidant phytonutrients. Most notably, lycopene has been associated with the prevention of prostate cancer, and lutein has been associated with the prevention of age-related macular degeneration. Our interests in improving the phytonutrient content of tomato by breeding and/or transgenesis has motivated further analysis of the natural phytonutrient content of tomato fruit (*Lycopersicon esculentum* Mill.). The observation that most flavonoids accumulate in the skin of tomato (15, 16) and that flavonoids and resveratrol are derived from the common biosynthetic precursor, 4-coumaroyl-CoA (Figure 1), led us to carefully search for resveratrol in tomato skin. Here, we report the detection and quantitation of resveratrol, its 3-glucopyranoside piceid, and the *cis* isomers of these

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**Figure 1.** Biosynthetic pathway to resveratrol and its derivatives diverge from the flavonoid pathway after the third malonyl-CoA condensation. Cyclization of the polyketide intermediate catalyzed by resveratrol synthase yields the initial and biologically active stilbene, resveratrol.

compounds in tomato skin. This appears to be the first report of resveratrol in nontransgenic tomato or any plant within the family Solanaceae.

## MATERIALS AND METHODS

**Cultivation of *L. esculentum* Mill.** Seeds of MicroTom tomato (*L. esculentum* Mill.) obtained from Tomato Growers Supply Company (Fort Myers, FL) were germinated on half-strength Murashige-Skoog media (Sigma-Aldrich, St. Louis, MO) supplied with 15 g/L sucrose. Plants were propagated on the media for 2–3 weeks, transferred to soil, and grown for 2 months in an environmentally controlled greenhouse (16:8 h light/dark cycle, 24–25 °C) with 300–400  $\mu$ E illumination. After the fruit were set, plants were monitored for the breaking point. Once the fruit turned orange, they were tagged and the maturation time to the ripening stage was measured on the basis of visual observations. The first sample of the time course was collected 2.5 weeks postbreaker. Fruit was then collected every 0.5 weeks up to 4.5 weeks.

**Fruit Sample Preparation.** Tomato or grape fruit (three whole fruit per data point) were washed with warm water to remove possible pesticide residues and also to prepare the skin for peeling. A scalpel was used to initiate a tear in the peel, and then the remaining skin was separated from the flesh and immediately immersed in liquid nitrogen. The fruit skin was stored at  $-80$  °C and then lyophilized (Virtis FreezeMobile, Gardiner, NY) for 3 days to remove the water in preparation for extraction.

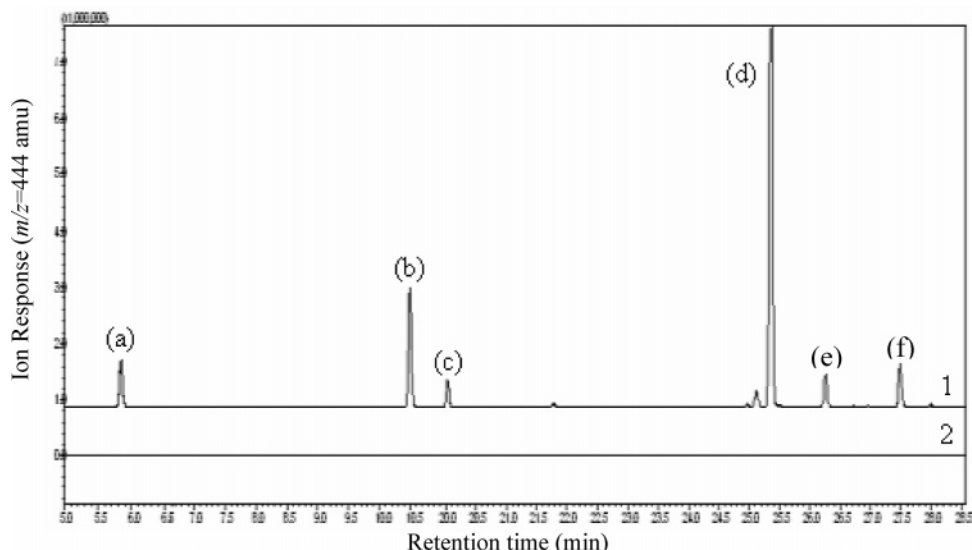
**Extraction of Resveratrol from Fruit Skin.** Lyophilized tomato or grape skin (30 mg) was crushed to a fine powder and extracted with ethyl acetate (1.25 mL) in a cryotube (Axygen, Union City, CA) at 70 °C for 30 min with shaking. The extract was centrifuged using a benchtop model (Eppendorf NA, Westbury, NY) at 14 000 rpm for 4 min to separate the plant material from the ethyl acetate. The ethyl acetate extract (1.0 mL) was transferred to a gas chromatography–mass spectrometry (GC–MS) sample vial, and the solvent was removed

by centrifugal evaporation under reduced pressure (Savant SpeedVac, Thermo Electron, San Jose, CA).

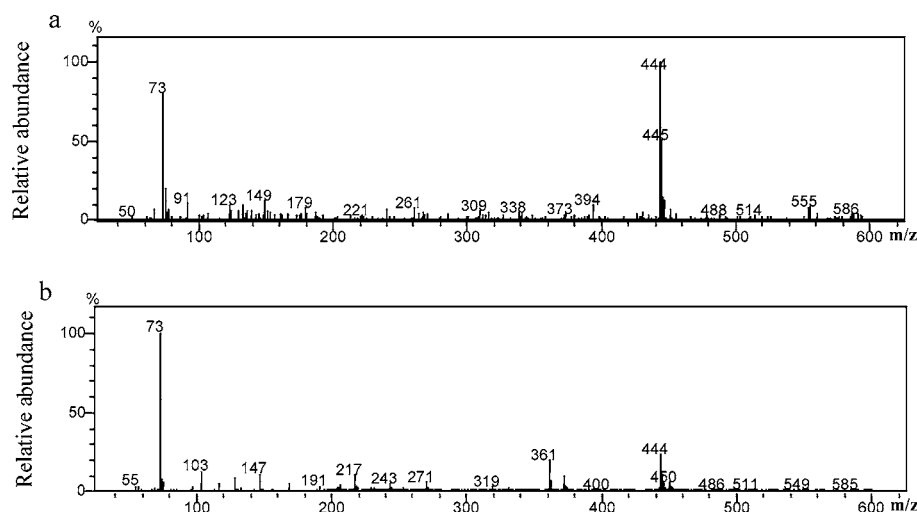
**Derivatization and GC–MS Analysis of Fruit-Skin Extracts.** Dried extracts were resuspended in pyridine (80  $\mu$ L) and shaken at room temperature for 90 min. *N*-Methyl-*N*-(trimethylsilyl)trifluoroacetamide (MSTFA, Sigma-Aldrich, 120  $\mu$ L) was added, and the samples were incubated at 37 °C for 30 min to derivatize the extract for GC–MS analysis.

GC–MS analysis was performed on a Shimadzu QP2010 with the injection temperature of 280 °C with a 1:10 split ratio. Each sample (1  $\mu$ L) was injected onto a Varian Factor Four (Varian, Palo Alto, CA) column (VF-5MS 0.25 mm  $\times$  0.25  $\mu$ m  $\times$  30 m with a 10 m integrated guard column) with a flow rate of 1 mL/min at 162 kPa helium pressure. The column temperature was initially held at 240 °C for 3 min followed by a temperature gradient of 5 °C/min for 22 min, producing a maximum temperature of 350 °C, which was held for 5 min. The interface was set at 260 °C, and the ion source was set at 250 °C. Data were acquired in the electron impact (EI) mode at 1.10 kV with a scan range of 60–600 ( $m/z$ ) and monitored at  $m/z$  444 amu for resveratrol and piceid.

**Preparation of Standards and Calibration Curve.** *trans*-Resveratrol and its 3-glucopyranoside piceid were purchased from Chromadex (Santa Ana, CA). A stock solution (0.1 mg/mL) was prepared and used to produce a seven-point 1:2 serial dilution (50, 25, 12, 6.2, 3.1, 1.6, and 0.78  $\mu$ g/mL) of each metabolite in ethyl acetate. The solvent was removed from the standards, and each standard was derivatized according to the procedure described above (except that 50  $\mu$ L of pyridine was used to resuspend the sample and 50  $\mu$ L of MSTFA was used for the derivitization reaction). Standards were analyzed by GC–MS using the method described above to produce a standard curve ranging from 50 to 0.78  $\mu$ g/mL for each compound. Robustness of the method was validated by calculating the standard error of each point in the calibration curve run on different days during the time-course study (Figure S1 in the Supporting Information). The lowest limit of quantitation (LLOQ, at a signal-to-noise ratio of 5) was 130 pg on the



**Figure 2.** Single-ion chromatogram ( $m/z$  444 amu) of tomato-skin extract (top trace 1) and tomato flesh (bottom trace 2) from commercially purchased MicroTom tomato. Identified peaks confirmed by standards are as follows: *cis*-resveratrol (a), *trans*-resveratrol (b), *cis*-piceid (c), and *trans*-piceid (d). Additional peaks (e and f) were not fully characterized, but initial identification based on mass spectra indicate that these may be resveratrol glycoside-related (Figure S2 in the Supporting Information).



**Figure 3.** EI mass spectra of resveratrol (a) and piceid (b) in tomato skin.

column, which was equivalent to 9 ng/g in fruit skin using the methodology described above.

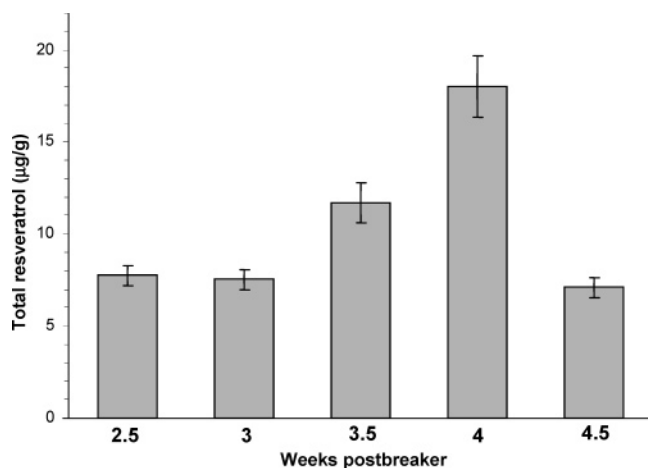
## RESULTS

**Detection of Resveratrol in *L. esculentum* Mill.** Initial qualitative GC–MS analysis of the tomato skin and flesh of MicroTom tomato (*L. esculentum* Mill.) obtained from a local grocer resulted in the detection of resveratrol in the skin (Figure 2). The absence of resveratrol in the flesh may be the result of an inadequate supply of the biosynthetic precursor 4-coumaroyl-CoA and is consistent with the previous observation that flavonoids are not produced in the flesh (15, 16).

In addition to *trans*-resveratrol, its 3-glucopyranoside piceid and the *cis* isomers of both compounds were also detected in tomato skin. The identity of the *trans* isomers were confirmed by a comparison of the retention time and mass spectra to those of the corresponding standards (Figure 3). As a result of the stable structure of resveratrol, the only diagnostic mass spectra peaks were those associated with the free trimethylsilyl (TMS) group ( $m/z$  73 amu) and the fully derivatized tri-TMS-resveratrol ( $m/z$  444 amu). In the case of piceid, a mass spectrum similar

to tri-TMS-resveratrol was observed with the addition of a fragment mass associated with penta-TMS-glucopyranoside ( $m/z$  361 amu). The *cis* isomers of resveratrol and piceid were also detected at slightly shorter retention times than their corresponding *trans* isomers, and these peaks were identified by a comparison of their mass spectra to those of the corresponding *trans* isomers.

**Resveratrol Accumulation during Fruit Maturation.** MicroTom tomato was grown from a seed in the greenhouse, and fruit were collected during a 2.5 week time period while fruit were maturing. The skin of tomato fruits was analyzed through developmental stages to determine the rate of accumulation of resveratrol and related compounds. *cis*-/*trans*-Resveratrol and *cis*-/*trans*-piceid were measured separately and combined to calculate the total resveratrol content. The time course started after the breaker stage, which is when the tomato fruit turns orange. Fruit collection was started 2.5 weeks postbreaker, and subsequent samples were collected every 0.5 weeks until the fruits were ripened at 4.5 weeks postbreaker (Figure 4). Total resveratrol accumulated slowly after the breaker stage and increased slightly after 3.5 weeks to a maximum at 4 weeks.



**Figure 4.** Quantitation of the total resveratrol content in MicroTom tomato (*L. esculentum* Mill.) skin during fruit maturation from 2.5 to 4.5 weeks after the break period.

**Table 1.** Comparative Quantitative Analysis of *cis/trans*-Resveratrol and *cis/trans*-Piceid in the Skin of Commercial Tomato Varieties, MicroTom Tomato Investigated in This Study (Data from Time Course 4.0 Weeks Postbreaker), and Commercial Seedless Red Table Grape<sup>a</sup>

source	<i>cis</i> -resveratrol	<i>trans</i> -resveratrol	<i>cis</i> -piceid	<i>trans</i> -piceid	total resveratrol
MicroTom	2.71	15.30	0.26	0.10	18.4
Beafsteak	ND	ND	ND	ND	ND
UglyRipe	ND	0.38	ND	ND	0.38
Heirloom	0.11	1.75	ND	ND	1.86
PlumTom	ND	0.34	ND	ND	0.34
Grape	20	2680	30	50	2780

<sup>a</sup> Commercial varieties were obtained from local markets. All values are in µg/g. ND = not detected (<9 ng/g).

Quantitation of the total resveratrol content using calibration curves created from the pure standards (Figure S1 in the Supporting Information) revealed that the maximum accumulation of total resveratrol reached  $18.4 \pm 1.6$  µg/g of dried tomato skin at 4 weeks postbreaker. Resveratrol accumulation abruptly dropped off at 4.5 weeks, which may be due to its further metabolism as the fruit over-ripened.

**Resveratrol Accumulation in Other Tomato and Grape Varieties.** Analyses of several other tomato varieties purchased from local produce vendors (referred to as “Beefsteak”, “UglyRipe”, “Heirloom”, and “PlumTom”) revealed the presence of *trans*-resveratrol in the skin of all varieties except “Beefsteak” (Table 1). *cis*-Resveratrol was also detected in the “Heirloom” variety. The MicroTom variety of tomato possessed the highest levels of all of the tomatoes investigated (18.4 µg/g total resveratrol at 4 weeks postbreaker), although this was significantly less than red seedless table grape skin obtained from a local grocer (2.78 mg/g).

## DISCUSSION

The detection of resveratrol in tomato skin reported here is in contrast to the common belief that resveratrol is produced only in grape and a very limited number of other edible species (7, 8). In fact, metabolic engineering of tomato using the grapevine stilbene synthase gene has been reported to produce resveratrol in *L. esculentum* Mill. (17, 18). In these reports, nontransgenic fruit were not reported to contain resveratrol. This apparent inconsistency may be explained because of differences in the cultivars studies or by the fact that these previous studies

analyzed whole fruit rather than dissecting skin from flesh of the fruit. Because we did not detect resveratrol in tomato fruit flesh, using whole fruit may have diluted the resveratrol content below the UV detection method used in this report (18). This detection method may also be less sensitive than the MS method described herein. A third explanation could be that environmental and genetic factors lead to differences in resveratrol content in different varieties of *L. esculentum*.

Subsequent analyses of several tomato varieties obtained from local produce vendors revealed that resveratrol content varied by several orders of magnitude between tomato varieties (Table 1). Concentrations of total resveratrol in tomato skin ranged from 18.4 µg/g in the MicroTom variety, which was the focus of this study, to below the LLOQ of the GC–MS method (<9 ng/g) for the Beefsteak variety. For comparative purposes, the skin of seedless red table grapes was also analyzed for resveratrol content using the GC–MS method. A commercial table variety obtained from a local grocer contained 2.78 mg/g total resveratrol (Table 1). This value is significantly higher than previously reported in the skin of wine-making varieties (19). This difference may be due to differences in the grape varieties investigated and in the extraction methods employed.

The highest level of total resveratrol determined in MicroTom tomato skin (18.4 µg/g) is 2 orders of magnitude below those determined in the skin of seedless red grapes (2.78 mg/g), suggesting that this tomato variety is unlikely to contribute adequate amounts of resveratrol in a normal diet to recognize the health benefits associated with this phytonutrient. Further investigation of other fresh and processing tomato varieties and tomato products is needed to determine their resveratrol content and understand whether they contribute a significant amount of resveratrol in a normal diet.

Identification of resveratrol in tomato skin provokes the idea that resveratrol may be present in the skin of other fruits (e.g., plums, cherries, etc.). Several reports have shown that transgenic plants overexpressing the resveratrol synthase gene confer resistance to UV irradiation (20) and pathogens (21). If the primary role of resveratrol in plants is to serve a defensive purpose, it would be sensible for the skin of the fruit to contain this metabolite as a first line of defense against certain external stresses.

At this time, the exact biosynthetic origin of resveratrol produced in tomato skin is unclear. Resveratrol may be produced by the established biosynthetic pathway (Figure 1) starting with 4-coumaroyl-CoA via a yet to be identified resveratrol synthase in *L. esculentum*. The *L. esculentum* genome has been the subject of several public sequencing initiatives, including the NSF-funded Tomato Genomics Project based at Cornell University and the International Solanaceae Genomics Project (22). Blast searches of the *L. esculentum* public sequences available at this time using *Vitis vinifera* (grape) resveratrol synthase as the query sequence failed to identify an obvious candidate for a resveratrol synthase in *L. esculentum*, but the similarity in sequence and structure of resveratrol and chalcone synthases makes it difficult to draw definitive conclusions (23). A second hypothesis for the origin of resveratrol in tomato is that it is produced as a byproduct of a promiscuous chalcone synthase, which accommodates the alternate substrate binding, which has been demonstrated as the difference between stilbene and chalcone synthases (24).

Regardless of which of the two above hypotheses hold true or whether a third as yet undetermined hypothesis explains the origins of resveratrol in tomato, it is clear that differences in reports of resveratrol in tomato varieties are due to changes in



the rate of synthesis or degradation of the molecule resulting from differences in pathway genes and gene expression. If a resveratrol synthase does exist in tomato and the differences in reports of resveratrol in tomato is simply due to differences in gene expression in different varieties, the possibility exists to utilize marker-assisted breeding or metabolic engineering to create tomato varieties with higher levels of resveratrol. The most direct transgenic approach would be to place the endogenous gene under the control of a stronger, fruit-specific promoter. In this way, it may be possible to create tomato varieties with high levels of resveratrol, which could be used fresh, processed to tomato sauce, ketchup, and other products that would provide the beneficial health effects of resveratrol in our diet to help prevent disease and enhance the health of consumers.

#### ACKNOWLEDGMENT

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**Supporting Information Available:** Calibration curve of total resveratrol standards (*cis*-, *trans*-resveratrol and *cis*-, *trans*-piceid) ranging from 50–0.78  $\mu\text{g/mL}$  (Figure S1) and EI mass spectra of peaks e and f from Figure 2 (Figure S2). This material is available free of charge via the Internet at <http://pubs.acs.org>.

#### LITERATURE CITED

- Langcake, P.; Pryce, R. J. The production of resveratrol by *Vitis vinifera* and other members of the Vitaceae as a response to infection and injury. *Physiol. Plant Pathol.* **1976**, *9*, 77–86.
- Bradamante, S.; Barengi, L.; Villa, A. Cardiovascular protective effects of resveratrol. *Cardiovasc. Drug Rev.* **2004**, *22*, 169–188.
- Le Corre, L.; Chalabi, N.; Delort, L.; Bignon, Y. J.; Bernard-Gallon, D. J. Resveratrol and breast cancer chemoprevention: Molecular mechanisms. *Mol. Nutr. Food Res.* **2005**, *49*, 462–471.
- Wolter, F.; Ulrich, S.; Stein, J. Molecular mechanisms of the chemopreventative effects of resveratrol and its analogs in colorectal cancer: Key role of polyamines? *J. Nutr.* **2004**, *134*, 3219–3222.
- Ratan, H. L.; Steward, W. P.; Gescher, A. J.; Mellon, J. K. Resveratrol—A prostate cancer chemopreventative agent? *Urol. Oncol.* **2002**, *7*, 223–227.
- de la Lastra, C. A.; Villegas, I. Resveratrol as an anti-inflammatory and anti-aging agent: Mechanisms and clinical implications. *Mol. Nutr. Food Res.* **2005**, *49*, 405–430.
- Cassidy, A.; Hanley, B.; Lamuela-Raventos, R. M. Isoflavones, lignans and stilbenes—Origins, metabolism and potential importance to human health. *J. Sci. Food Agric.* **2000**, *80*, 1044–1062.
- Burns, J.; Yokota, T.; Ashihara, H.; Lean, M. E. J.; Crozier, A. Plant foods and herbal sources of resveratrol. *J. Agric. Food Chem.* **2002**, *50*, 3337–3340.
- Counet, C.; Callemien, D.; Collin, S. Chocolate and cocoa: New sources of *trans*-resveratrol and *trans*-piceid. *Food Chem.* **2006**, *98*, 649–657.
- Jang, M.; Cai, L.; Udeani, G. O.; Slowing, K. V.; Thomas, C. F.; Beecher, C. W. W.; Fong, H. H. S.; Farnsworth, N. R.; Kinghorn, A. D.; Mehta, R. G.; Moon, R. C.; Pezzuto, J. M. Cancer chemopreventive activity of resveratrol, a natural product derived from grapes. *Science* **1997**, *275*, 218–220.
- Das, D. K.; Sato, M.; Ray, P. S.; Maulik, G.; Engleman, R. M.; Bertelli, A. A.; Bertelli, A. Cardioprotection of red wine: Role of polyphenolic antioxidants. *Drugs Exp. Clin. Res.* **1999**, *25*, 115–120.
- Nigdikar, S. V.; Williams, N. R.; Griffin, B. A.; Howard, A. N. Consumption of red wine polyphenols reduces the susceptibility of low-density lipoproteins to oxidation *in vivo*. *Am. J. Clin. Nutr.* **1998**, *68*, 258–265.
- Olas, B.; Wachowicz, B. Resveratrol, a phenolic antioxidant with effects on blood platelet functions. *Platelets* **2005**, *16*, 251–260.
- Howitz, K. T.; Bitterman, K. J.; Cohen, H. Y.; Lamming, D. W.; Lavu, S.; Wood, J. G.; Zipkin, R. E.; Chung, P.; Kisielewski, A.; Zhang, L.; Scherer, B.; Sinclair, D. A. Small molecule activators of sirtuins extend *Saccharomyces cerevisiae* lifespan. *Nature* **2003**, *425*, 191–196.
- Verhoeven, M. E.; Bovy, A.; Collins, G.; Robinson, S.; de Vos, C. H. R.; Colliver, S. Increasing antioxidant levels in tomatoes through modification of the flavonoids biosynthetic pathway. *J. Exp. Biol.* **2002**, *53*, 2099–2106.
- Muir, S. R.; Collins, G. J.; Robinson, S.; Hughes, S.; Bovy, A.; de Vos, C. H. R.; van Tunen, A. J.; Verhoeven, M. E. Overexpression of petunia chalcone isomerase in tomato results in fruit containing increased levels of flavonols. *Nature* **2001**, *19*, 470–474.
- Thomzik, J. E.; Stenzel, K.; Stocker, R.; Schreier, P. H.; Hain, R.; Stahl, D. J. Synthesis of a grapevine phytoalexin in transgenic tomatoes (*Lycopersicon esculentum* Mill.) conditions resistance against *Phytophthora infestans*. *Physiol. Mol. Plant Pathol.* **1997**, *51*, 265–278.
- Morelli, R.; Das, S.; Bertelli, A.; Bollini, R.; Scalzo, R. L.; Das, D. K.; Falchi, M. The introduction of the stilbene synthase gene enhances the natural antiradical activity of *Lycopersicon esculentum* Mill. *Mol. Cell. Biochem.* **2006**, *282*, 65–73.
- Sun, B.; Ribes, A. M.; Leandro, M. C.; Belchior, A. P.; Spranger, M. I. Stilbenes: Quantitative extraction from grape skins, contribution of grape solids to wine and variation during wine maturation. *Anal. Chim. Acta* **2006**, *563*, 382–390.
- Rudolf, J. R.; Resurreccion, A. V. S. Elicitation of resveratrol in peanut kernels by application of abiotic stresses. *J. Agric. Food Chem.* **2005**, *53*, 10186–10192.
- Serazetdinova, L.; Oldach, K. H.; Lorz, H. Expression of transgenic stilbene synthases in wheat causes the accumulation of unknown stilbene derivatives with antifungal activity. *J. Plant Physiol.* **2005**, *162*, 985–1002.
- About the International Tomato Sequencing Project. [http://www.sgn.cornell.edu/help/about/tomato\\_sequencing.pl](http://www.sgn.cornell.edu/help/about/tomato_sequencing.pl).
- Ferrer, J.; Jez, J. M.; Bowman, M. E.; Dixon, R. A.; Noel, J. P. Structure of chalcone synthase and the molecular basis of plant polyketide biosynthesis. *Nat. Struct. Biol.* **1999**, *6*, 775–784.
- Austin, M. B.; Bowman, M. E.; Ferrer, J. L.; Schroder, J.; Noel, J. P. An aldol switch discovered in stilbene synthases mediates cyclization specificity of type III polyketide synthases. *Chem. Biol.* **2004**, *11*, 1179–1194.

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