Potential Cancer-Chemopreventive Activities of Wine Stilbenoids and Flavans Extracted From Grape (*Vitis vinifera*) Cell Cultures

**Pierre Waffo-Téguo, Michael E. Hawthorne, Muriel Cuendet, Jean-Michel Mérillon, A. Douglas Kinghorn, John M. Pezzuto, and Rajendra G. Mehta**

**Abstract:** Moderate consumption of wine is associated with a reduced risk of cancer. Grape plant cell cultures were used to purify 12 phenols: the stilbenoids trans-astringin, trans-piceid (2), trans-resveratrol, trans-resveratrolol, trans-resveratrol, trans-resveratrolinil, cis-resveratrol, cis-piceid, and cis-resveratrol; the flavans (+)-catechin, (-)-epicatechin, and epicatechin 3-O-gallate; and the flavon dimer procyandin B2 3'-O-gallate. These compounds were evaluated for potential to inhibit cyclooxygenases and preneoplastic lesion formation in carcinogen-treated mouse mammary glands in organ culture. At 10 µg/ml, trans-astringin and trans-piceatannol inhibited development of 7,12-dimethylbenz[a]anthracene-induced preneoplastic lesions in mouse mammary glands with 68.8% and 76.9% inhibition, respectively, compared with untreated glands. The latter compound was the most potent of the 12 compounds tested in this assay, with the exception of trans-resveratrol (87.5% inhibition). In the cyclooxygenase (COX)-1 assay, trans isomers of the stilbenoids appear to be more active than cis isomers: trans-resveratrol [50% inhibitory concentration (IC50) = 14.9 µM, 96%] vs. cis-resveratrol (IC50 = 55.4 µM). In the COX-2 assay, among the compounds tested, only trans- and cis-resveratrol exhibited significant inhibitory activity (IC50 = 32.2 and 50.2 µM, respectively). This is the first report showing the potential cancer-chemopreventive activity of trans-astringin, a plant stilbenoid recently found in wine. Trans-Astringin and its aglycone trans-piceatannol were active in the mouse mammary gland organ culture assay but did not exhibit activity in COX-1 and COX-2 assays. Trans-Resveratrol was active in all three of the bioassays used in this investigation. These findings suggest that trans-astringin and trans-piceatannol may function as potential cancer-chemopreventive agents by a mechanism different from that of trans-resveratrol.

**Introduction**

Recent studies have demonstrated the role of dietary factors in causing as well as preventing major diseases, such as cancer and cardiovascular disease (1). Numerous epidemiological studies have shown the protective effect of fruits and vegetables against these diseases (2,3). Investigations carried out in Europe and North America have examined specifically the association between alcoholic beverage consumption and causes of mortality and suggest that regular and moderate red wine consumption can have health benefits, contributing in particular to a decrease in the risk of cardiovascular disease (4–6). Some studies have shown that wine, unlike other alcoholic beverages, does not increase the risk of cancer (7–9), while other studies have indicated that wine, also unlike other alcoholic beverages, significantly reduces the risk of cancer (10,11).

For about the last 100 years, the grapevine *Vitis vinifera* L. (Vitaceae), the agricultural source of wine, has been the subject of chemical studies; numerous compounds belonging to different chemical classes have been isolated from this species. Unlike other alcoholic beverages, red wine contains phenolic compounds in high concentration, up to ~3 g/l (12). Among the components that have been identified, several flavonoids and stilbenoids are the most interesting from a pharmacological point of view (13). Hydroxystilbenes have been found in a number of plant species, but grapes and related products are probably the most important foods containing these substances (14,15). *trans*-Resveratrol (*trans*-3,5,4'-trihydroxystilbene), a phytoalexin that is biosynthesized in the grapevine in response to fungal infection (16,17), has been proposed as one of the components in red wine that may be beneficial to human cardiovascular health. These studies include prevention of low-density lipoprotein...
oxidation (18) and in vitro platelet aggregation (19). This could explain the reduction of atherogenesis.

When cancer is considered in particular, Clifford et al. (20) found that a diet with red wine solids rich in phenols delays the onset of tumors in transgenic mice. Several reports indicate that trans-resveratrol inhibits the proliferation of tumor cells (21,22) and also protein tyrosine kinase activities (23). Recently, Jang et al. (24–26) established the cancer-chemopreventive potential of trans-resveratrol in various assays reflective of the three major stages of carcinogenesis. Thus anti-initiation activity was indicated by its antioxidant and antimitogenic effects, inhibition of carcinogen bioactivation, and induction of phase II drug-metabolizing enzymes. Anti-promotion activity was shown by its anti-inflammatory and induction of phase II drug-metabolizing enzymes. Anti-progression activity was suggested by its induction of human promyelocytic leukemia cell differentiation. In addition, trans-resveratrol inhibited carcinogenesis in a mouse mammary organ culture model and tumorigenesis in a mouse skin cancer model (24). It was also shown that flavans from grape seeds afford significant protection against tumor promotion in a mouse skin tumorigenesis model (27). Conversely, wine phenols have been shown to have agonistic properties for estrogen-α (28,29). These results indicate that additional work is needed to clarify the role of wine phenols in carcinogenesis and cancer progression.

In the present investigation, which was directed toward the search for new cancer-chemopreventive agents in wine, we have evaluated selected phenols from grape cell cultures for their potential to inhibit cyclooxygenase activity and 7,12-dimethylbenz[a]anthracene (DMBA)-induced preneoplastic lesions with mouse mammary glands in organ culture. We have further analyzed structure-activity relationships of these compounds in these assays.

Materials and Methods

Cell Culture

Cell cultures of Vitis vinifera (L.) cv. Gamay Freaux var. Teinturier were established in 1978 from pulp fragments of young fruits and provided by C. Ambid (ENSA, Toulouse, France). Suspension cultures of V. vinifera were maintained as previously described (30). Experiments were carried out by inoculating a 7-day-old cell suspension into an induction medium at a 1:8 (vol/vol) ratio for one transfer (31).

Isolation and Purification of Phenolic Compounds

Frozen cells were extracted with acetone-water as previously described (30,32). The aqueous mixture was partitioned with ethyl acetate. The ethyl acetate extract was chromatographed over a cationic-exchange resin (Dowex 50X4-400, Sigma Chemical, St. Louis, MO) and eluted with methanol-water. Crude phenols were eluted with 50% methanol in water. For further fractionation, the crude phenols were purified by passage over Sephadex LH-20 (Sigma Chemical) into two main fractions. Fraction 1 (trans-astringin, trans-piceid, trans-resveratrololoside, trans-resveratrol, cis-resveratrololoside, cis-piceid, (+)-catechin, and (−)-epicatechin) was eluted by a gradient of methanol in water (20–30%). These compounds were purified and characterized by high-performance liquid chromatography (HPLC) as previously described (33). Fraction 2, eluted by 50% methanol in water, was purified on Toyopearl HW-40S gel (Supelco, Bellefonte, PA), and epicatechin 3-O-gallate and procyanidin B2 3-O-gallate were obtained in pure form by semipreparative HPLC (ODS-AQ, 5 µm, 120 Å, C18 reversed-phase column, 250 × 20 mm ID; YMC, Wilmington, NC), with a guard column, eluted by a gradient system (Solvent A: water adjusted to pH 2.4 with trifluoroacetic acid; Solvent B: 20% Solvent A with 80% acetonitrile). The elution program at 8 ml/min was as follows: 30% Solvent B to 100% Solvent B in 40 min. Epicatechin 3-O-gallate and procyanidin B2 3-O-gallate were identified by comparison of their nuclear magnetic resonance data with those reported previously (34,35). cis-Resveratrol and trans-piceatannol were obtained by enzymatic hydrolysis of cis-piceid and trans-astringin, respectively, using β-glucosidase (EC 3.2.1.21; Sigma Chemical).

Oxygen Consumption Assay

Cyclooxygenase-1 activity was measured by monitoring oxygen consumption at 37°C using an oxygen sensor (model 5300, Yellow Springs Instruments, Yellow Springs, OH) that features a micro-oxygen probe (model 5357, Yellow Springs Instruments) (36). Reaction mixtures (total volume 600 µl) were composed of assay buffer (0.1 M sodium phosphate, pH 7.4, 1 mM phenol) containing 0.01 mM hemin, 10 µl of dimethyl sulfoxide (DMSO) or test sample (4 mg/ml in DMSO), and microsomes (0.2 mg of protein) derived from sheep seminal vesicles as a crude source of cyclooxygenase-1 (37). The enzyme reaction was started by addition of 0.36 mM arachidonic acid. The initial reaction rate was measured, and inhibitory activity was obtained by comparing the rate of oxygen consumption in the presence of test sample with that observed with solvent (DMSO) only.

HPLC Analysis of Cyclooxygenase Metabolites

Cyclooxygenase-2 activity was determined by measuring arachidonic acid metabolite production (25,36,38). The test mixture contained cyclooxygenase-2 (0.45 µg of protein from microsomal membranes of insect cells transfected with recombinant human cyclooxygenase-2 cDNA), 1 mM reduced glutathione, 1 mM epinephrine-hydrogen tartrate, and 0.05 mM sodium-EDTA in 0.1 M Tris buffer (pH 8.0). The reaction was started by addition of 2.5 µM [3H]arachidonic acid (0.25 µCi; American Radiolabeled Chemicals, St.
Louis, MO) and incubated for 30 min at 37°C. Then 5 µl of 10% formic acid were added to stop the reaction. Samples were extracted with 1 vol of ethyl acetate and briefly centrifuged. The ethyl acetate layer was dried under N₂ and dissolved in 100 µl of acetonitrile for separation on HPLC (10 µl were injected on a 5-µm Novapak C₁₈ column, 150 × 3.9 mm ID; Waters Associates, Milford, MA) and eluted using the following conditions: acetonitrile-water (1% 0.1 N phosphoric acid) 3:7 to 6:4 in 18 min and 6:4 to 9:1 in 5 min and, finally, 100% water (1% 0.1 N phosphoric acid) for 9 min (flow 1 ml/min). The separated arachidonic acid metabolites were monitored with a radioactivity detector, and the peaks were identified by cochromatography with nonlabeled reference compounds [prostaglandin (PG) E₂ and 15S-hydroxyeicosatetraenoic acid (Sigma Chemical) and PGD₂, PGF₂α, and 12S-hydroxyeicosatetraenoic acid (Cayman Chemical, Ann Arbor, MI)]. The inhibition rate of cyclooxygenase-2 was assessed by determining inhibition of PG formation against the control.

Mouse Mammary Organ Culture Assay

The inhibition of lesion formation in mouse mammary organ culture was performed as previously described (39). BALB/c female mice (4 wk old; Charles River, Wilmington, MA) were pretreated for 9 days with 1 µg of estradiol and 1 mg of progesterone. On the 10th day, the mice were sacrificed and the second thoracic mammary glands were dissected on silk and transferred to 60-mm culture dishes containing 5 ml of Waymouth’s 752/1 MB medium supplemented with 100 U of streptomycin and penicillin and 35 µg/ml glutamine. The glands were incubated for 10 days (37°C, 95% O₂-5% CO₂) in the presence of growth-promoting hormones (5 µg of insulin, 5 µg of prolactin, 1 μg of aldosterone, and 1 μg of hydrocortisone per milliliter of medium). Glands were exposed to 2 µg/ml DMBA between 72 and 96 h. After exposure, the glands were rinsed and transferred to new dishes with fresh medium. The fully differentiated glands were then permitted to regress by withdrawal of all hormones except insulin for 14 additional days. Test compounds were present in the medium during Days 1–10 of culture (10 µg/ml); mammary glands were scored for incidence of lesions (40). To compare the efficacy of trans-resveratrol with that of trans-astringin, mammary glands (15/treatment) were incubated with increasing concentrations of test agent. The chemopreventive agents were tested at 1–10 µg/ml. The glands were scored for the presence or absence of alveolar lesions. Results were subjected to χ² analysis to determine statistical significance.

Results

The chemical structures of the wine phenols [stilbenoids and flavans (Table 1)] isolated and characterized from grape cell culture suspensions are shown in Fig. 1. The primary objectives of this study were to investigate the in vitro activity of wine phenols in cyclooxygenase-1 and -2 inhibitory assays and to evaluate their effects in a mouse mammary organ culture system.

Table 1. Effects of Phenols From Grape Cell Cultures on Inhibition of COX-1 and COX-2 and on Incidence of DMBA-Induced Lesions in a BALB/c Mouse Mammary Gland Culture

<table>
<thead>
<tr>
<th>Compound</th>
<th>COX-1</th>
<th>COX-2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% Inhibition</td>
<td>IC₅₀, µM</td>
</tr>
<tr>
<td>Crude extract</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Stilbenoids</td>
<td></td>
<td></td>
</tr>
<tr>
<td>trans-Astringin (1)</td>
<td>0</td>
<td>ND</td>
</tr>
<tr>
<td>trans-Resveratrolside (2)</td>
<td>98</td>
<td>4.8</td>
</tr>
<tr>
<td>trans-Piceid (3)</td>
<td>95</td>
<td>10.6</td>
</tr>
<tr>
<td>trans-Resveratrol (4)</td>
<td>96</td>
<td>14.9</td>
</tr>
<tr>
<td>trans-Piceatanin (5)</td>
<td>0</td>
<td>ND</td>
</tr>
<tr>
<td>cis-Resveratrolside (6)</td>
<td>94</td>
<td>17.8</td>
</tr>
<tr>
<td>cis-Piceid (7)</td>
<td>32</td>
<td>ND</td>
</tr>
<tr>
<td>cis-Resveratrol (8)</td>
<td>86</td>
<td>55.4</td>
</tr>
<tr>
<td>Flavans</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(+)-Catechin (9)</td>
<td>95</td>
<td>1.4</td>
</tr>
<tr>
<td>(−)-Epicatechin (10)</td>
<td>98</td>
<td>3.2</td>
</tr>
<tr>
<td>Epicatechin 3-O-gallate (11)</td>
<td>97</td>
<td>7.5</td>
</tr>
<tr>
<td>Procyanidin B2 3'-O-gallate (12)</td>
<td>0</td>
<td>ND</td>
</tr>
</tbody>
</table>

a: Abbreviations are as follows: COX, cyclooxygenase; DMBA, 7,12-dimethylbenz[a]anthracene; MMOC, mouse mammary gland organ culture; IC₅₀, 50% inhibitory concentration; ND, not determined.
b: Numbers in parentheses coincide with compound numbers in Fig. 1.
c: Compounds were tested at 70 µg/ml; >70% inhibition was considered significant.
d: Compounds were tested at 50 µg/ml; >90% inhibition was considered significant.
e: Inhibition of DMBA-induced preneoplastic lesions with MMOC. Compounds were tested at 10 µg/ml, and results are expressed as percent inhibition. On the basis of historical controls, >60% inhibition is considered significant.
f: Crude extract of stilbenoids and flavans from grape cell cultures.
Effects of Wine Phenols on Cyclooxygenase Activity

To evaluate effects of the wine phenols against cyclooxygenase-1, an oxygen consumption assay was used. Inhibitory activity was determined by comparing the rate of oxygen consumption in the presence of wine phenols with that in the presence of solvent only. Table 1 shows that wine phenols (stilbenoids and flavans) exhibited cyclooxygenase-1 inhibition activity. As shown in Table 1, glycosylation of stilbenes increased their cyclooxygenase-1 inhibitory potency compared with the corresponding active aglycones; e.g., trans-resveratrol [50% inhibitory concentration (IC50) = 14.9 µM] was about 3 times less active than trans-resveratroloside (IC50 = 4.8 µM). Glycosylation at the C-4’ position is favorable for such enhanced activity, as may be seen by comparison of trans-resveratroloside (IC50 = 4.8 µM) with trans-piceid (IC50 = 10.6 µM). Although differences were observed in the IC50 values, all three stilbene derivatives (trans-piceid, trans-resveratroloside, and trans-resveratrol) inhibited cyclooxygenase-1 activity by >90% at 70 µg/ml. The presence of a stilbenoid catechol functionality tended to decrease or eliminate inhibitory activity [cf. trans-astringin (inactive) vs. trans-piceid (IC50 = 10.6 µM) and trans-piceatannol (inactive) vs. trans-resveratrol (IC50 = 14.9 µM)]. A trans, rather than a cis, double bond appears to be important for the mediation of potent activity in the stilbenoid class, e.g., trans-piceid (IC50 = 10.6 µM, 95% inhibition) vs. cis-piceid (inactive, 32% inhibition), trans-resveratrol (IC50 = 14.9 µM) vs. cis-resveratrol (IC50 = 55.4 µM), and trans-resveratroloside (IC50 = 4.8 µM) vs. cis-resveratroloside (IC50 = 17.8 µM). In addition to the active stilbenoids, the catechins [(+)catechin, (−)-epicatechin, and epicatechin 3-O-gallate] also exhibited >95% inhibitory activity at 70 µg/ml against cyclooxygenase-1, with IC50 = 1.4, 3.2, and 7.5 µM, respectively. The dimeric procyanidin B2 3’-O-gallate was inactive in this assay.

The effect of wine phenols against cyclooxygenase-2 was determined by measuring [3H]arachidonic acid metabolite production. The inhibition rate of cyclooxygenase-2 was assessed by determining the inhibition of PG formation against a control. As previously documented (41), trans-resveratrol directly inhibited the activity of cyclooxygenase-2, an indolic form of cyclooxygenase (IC50 = 32.2 µM). cis-Resveratrol was also active against cyclooxygenase-2, but the potency was reduced (IC50 = 50.2 µM). All the other phenols tested were not active in this assay system (Table 1).

Mouse Mammary Organ Culture Assay

All the compounds (except trans-piceatannol) were evaluated for their potential to inhibit DMBA-induced preneoplastic lesions in mouse mammary organ culture. As noted previously (40), substances active in this model system are considered good candidates for full-term chemopreventive studies. trans-Astringin, trans-resveratrol, trans-piceatannol, (+)-catechin, and epicatechin 3-O-gallate mediated significant inhibitory activity (Table 1) and, as such, seem worthy of evaluation in experimental carcinogenesis models.

In this assay, trans double bond geometry again appears to be important for mediation of the resultant activity of the stilbenoids, as exemplified by trans-resveratrol (87.5% inhibition) vs. cis-resveratrol (inactive at the doses used). It was also observed that glycosylation decreases activity, with trans-piceid and trans-resveratroloside, the glycosidic forms of trans-resveratrol, being inactive. Likewise, trans-astringin (68.8% inhibition) was somewhat less active than its aglycone trans-piceatannol (76.9% inhibition). Only two of the four flavans tested, (+)-catechin and epicatechin 3-O-gallate, showed significant inhibition of DMBA-induced preneoplastic lesions (both 62.5%). The efficacy of trans-resveratrol and trans-astringin in this assay was compared by a dose-response study. Results showed that trans-astringin and trans-resveratrol inhibited DMBA-induced mam-
preventive agents with in vivo models. A putative mechanism by which some cancer-chemopreventive compounds may act is via inhibition of cyclooxygenase, in particular cyclooxygenase-2 (45). Of the two isozymes that lead to the formation of PGs, cyclooxygenase-1, which is constitutively expressed in most tissues, is considered to be involved in physiological cell-cell signaling, whereas cyclooxygenase-2, which is induced by specific events in a limited number of cell types, appears to be involved in inflammation and mitogenesis (46,47).

As described previously, *trans*-resveratrol inhibits DMBA-induced preneoplastic lesions in mouse mammary gland organ culture (24). Among a group of stilbenoids known to occur in red wine inclusive of *trans*-resveratrol, we have shown in this investigation that two structural criteria appear to be essential for biological activity in this assay: the presence of *trans* geometrical isomerism and the absence of glycosylation. *trans*-Piceatannol, which contains a catechol unit in ring B, exhibits substantial activity, albeit somewhat inferior to that of the potency exhibited by the C-4′ monohydroxylated *trans*-resveratrol.

The mechanism by which phenolic compounds inhibit carcinogenesis has not been established clearly. Analogous to a previous report (41), *trans*-resveratrol directly inhibited the activity of cyclooxygenase-2. These results are consistent with the fact that *cis*-resveratrol, which showed reduced activity against cyclooxygenase-2 (70% inhibition at 50 µg/ml, IC₅₀ = 50.2 µM), also showed reduced inhibition in the induction of preneoplastic lesions (53.9% vs. 87.5% for *trans*-resveratrol). Moreover, our data show that *trans*-astringin and its aglycone *trans*-piceatannol inhibit the induction of preneoplastic lesions in organ culture without any apparent activity against cyclooxygenase-2.

Stilbenoids occur naturally in species of various plant families, but grapes and wine are considered the most important dietary sources of these compounds. Four resveratrol derivatives have been detected in wine most frequently: *trans*- and *cis*-piceid and their aglycones *trans*- and *cis*-resveratrol (48–50). It was demonstrated recently that red wines from two countries (Portugal and France) have low mean concentrations of *trans* - and *cis*-resveratrol (<5 mg/l) (50), as was found previously in wine varieties in other studies (51). Levels of *trans* - and *cis*-piceid in certain wines exceeded levels of their aglycones; *trans* - and *cis*-piceid reached high concentrations: 50 and 18 mg/l, respectively (50). We have also demonstrated for the first time that *trans*-astringin was present in significant amounts in wine: most (53%) of the red wines tested contained 9–35 mg/l, whereas only 26% of the white wines contained 9–16 mg/l (50). In addition, a much higher *trans*-astringin concentration (80 mg/l) was found in a pressed young wine after a conventional red wine vinification (50).

Flavans are abundant in grapes, in particular (+)-catechin, which is the predominant monomeric form found in California and French red wines, with most of them containing 50–200 mg/l (12,51). (+)-Epicatechin, an isomer of catechin, which is the major flavan from grape skins and seeds, is found typically at lower levels than catechin in red wines (~40–100 mg/l). Procyanidin dimers were reported at a mean total concentration of 275 mg/l in French red wines (52). Epicatechin 3-O-gallate is also a component in oligomeric and polymeric procyanidins, but the proportion of galloylated units is low (3–6% in grape skins), and these contribute significantly to wine flavan composition (53). Appreciable amounts of stilbenoids are also found in white wines (about one-third of those in red wine), but relatively low quantities of flavans are present in white and rosé wines (about one-tenth of those of red wines) (52).

In a recent study on 34,000 middle-aged French men, moderate consumption of wine, two to three glasses per day, over a long period was associated with a lowering of mortality from cancer (by 22%) and all causes (by 33%) (4). This consumption corresponds to a significant intake of stilbenes and flavans. Several of these compounds are present in wine mainly in the glycosidic form, but they may be hydrolyzed by glycosidases in the human gastrointestinal tract (54).

Figure 2. Comparative effect of *trans*-astringin and *trans*-resveratrol on carcinogen-induced development of mammary alveolar lesions. Mammary glands were incubated with growth-promoting hormones and treated with 7,12-dimethylbenza[a]anthracene (2 µg/ml) for 24 h. Groups of 15 glands were incubated with increasing concentrations of *trans*-astringin (filled circles) or *trans*-resveratrol (filled squares) during the first 10 days of culture. Mammary glands were scored for mammary lesions. Percent inhibition at each concentration is determined by comparing incidence of mammary lesions in control, respectively (Fig. 2).

Discussion

In the present investigation, we have studied the inhibitory effects of grape phenols (stilbenoids and flavans) on carcinogen-induced precancerous lesions in mouse mammary gland organ culture, which is a highly reproducible and relevant model to evaluate the efficacy of potential chemopreventive agents (42). The epithelial cells prepared from these mammary lesions form mammary adenocarcinomas in syngeneic mice. This model has permitted the selection of several promising bioactive agents, such as the naturally occurring compounds brassinin (43) and *trans*-resveratrol (44), which were then shown to be active as cancer-chemopreventive agents with in vivo models. A putative mechanism by which some cancer-chemopreventive compounds may act is via inhibition of cyclooxygenase, in particular cyclooxygenase-2 (45). Of the two isoforms that lead to the formation of PGs, cyclooxygenase-1, which is constitutively expressed in most tissues, is considered to be involved in physiological cell-cell signaling, whereas cyclooxygenase-2, which is induced by specific events in a limited number of cell types, appears to be involved in inflammation and mitogenesis (46,47).

As described previously, *trans*-resveratrol inhibits DMBA-induced preneoplastic lesions in mouse mammary gland organ culture (24). Among a group of stilbenoids known to occur in red wine inclusive of *trans*-resveratrol, we have shown in this investigation that two structural criteria appear to be essential for biological activity in this assay: the presence of *trans* geometrical isomerism and the absence of glycosylation. *trans*-Piceatannol, which contains a catechol unit in ring B, exhibits substantial activity, albeit

Vol. 40, No. 2 177
The results presented here indicate that wine stilbenoids were more potent than flavans in inhibiting the development of DMBA-induced preneoplastic lesions in a mouse mammary organ culture assay, although some flavans exhibited activity. It is conceivable that stilbenoids play a role in prevention of cancer by moderate intake of wine, as observed in epidemiological studies. Our results suggest that trans-stilbenes, a documented constituent of wine, and its aglycone trans-piceatannol are attractive new candidates for in vivo cancer-chemoprevention studies and for further elucidation of their mechanism of action.

Acknowledgments and Notes

This work was supported, in part, by National Cancer Institute Program Project Grant P01 CA-48112 (Bethesda, MD) and by the Conseil Regional d’Aquitaine France (fellowship support for P. Waffo-Teguo). Address correspondence to A. D. Kinghorn, Program for Collaborative Research in Pharmaceutical Sciences, College of Pharmacy, University of Illinois at Chicago, 833 S. Wood St. (M/C 877), Chicago, IL 60612.


References
