Structure-activity relationship of *trans*-resveratrol and its analogues*

Minireview

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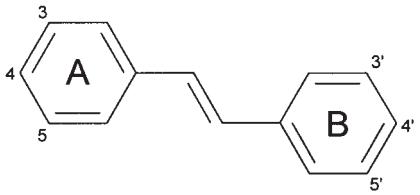
Cancer is one of the main causes of death in both men and women, claiming over 6 million people each year worldwide. Chemoprevention in combination with anti-cancer treatment is therefore important to reduce morbidity and mortality. Stilbene-based compounds have over the years attracted attention of many researchers due to their wide ranging biological activities. One of the most relevant and extensively studied stilbenes is *trans*-resveratrol, a phytoalexin present in grapes and other foods. One of the most striking biological activities of *trans*-resveratrol soundly investigated during recent years has been its cancer-chemopreventive potential. It has been found that the biological activity of *trans*-resveratrol and its analogues depends significantly on the structural determinants, which are (i) number and position of hydroxyl groups, (ii) intramolecular hydrogen bonding, (iii) stereoisomery and (iv) double bond. The observation that *trans*-stilbene compounds having 4'-hydroxy group, double bond and bearing *ortho*-diphenoxyl or *para*-diphenoxyl functionalities possess remarkably higher chemopreventive activity than *trans*-resveratrol gives us useful information for further chemopreventive drug design.

Key words: trans-resveratrol, piceatannol, structure-activity relationship, chemopreventive activity, antioxidant activity

In recent years, the development of more effective and safer agents has been intensively required for chemoprevention of human cancer, and natural products from plants have been expected to play an important role in creating new and better chemopreventive agents. There is a growing interest in biological properties of natural products as the means to identify novel small compounds that could have potential in clinical medicine [31, 32].

trans-Resveratrol (3,4',5-trihydroxy-*trans*-stilbene; t-RES) is a polyphenolic compound accounting to the stilbene class (Fig. 1). It has been found in high concentrations in a wide variety of plants, including grapes, peanuts, berries, pines and traditional oriental medicine plants [4]. Thus, relatively high concentrations of this compound are present in grape juice and, especially, in red wine [1, 16]. In plants t-RES is synthesized in response to stress conditions such as trauma, exposure to ozone and fungal infection, and thus it can be considered to be a phytoalexin, a class of antibiotics of plant origin [39, 40]. Other abiotic elicitors, such as ultraviolet rays and heavy metals, can trigger t-RES production [1]. t-RES has been reported to be a phytoestrogen due to its structural



Compounds	3	4	5	3'	4'	5'
trans-resveratrol	OH		OH		OH	
piceatannol	OH		OH	OH	OH	
pterostilbene	OCH_3		OCH_3		OH	
3'-hydroxypterostilbene	OCH_3		OCH_3	OH	OH	

Figure 1. Chemical structures of *trans*-resveratrol, piceatannol, pterostilbene and 3'-hydroxypterostilbene

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similarity to the estrogenic agent diethylstilbestrol [24]. In recent years, it has been shown to exhibit estrogenic activity in mammals [3,18]. t-RES has been reported to have both anti-carcinogenic and cardioprotective activities, which could be attributed to its antioxidant and anti-coagulant properties [13, 42]. Besides these effects, t-RES has been reported to be effective in inhibiting platelet aggregation and lipid peroxidation, altering eicosanoid synthesis, modulating lipoprotein metabolism [8, 23, 33], and exhibiting vasorelaxing and anti-inflammatory activities [16, 40]. In different rodent species as well as in humans, t-RES is well absorbed, distributed to various organs, and metabolized to *trans*-resveratrol-3-O-glucuronide and *trans*-resveratrol-3-O-sulfate [19, 44, 47].

The anti-cancer activity of t-RES was first revealed by its ability to reduce incidence of carcinogen-induced development of cancers in experimental animals [10, 22]. It has since been demonstrated that it possesses chemopreventive and cytostatic properties via the inhibition of tumor initiation, promotion and progression [22]. It causes cell arrest in the S and G_2 phases of the cell cycle [36] and is capable of inducing differentiation and apoptosis in a multitude of tumor cell lines, such as human leukemic, colonic, breast, prostate and esophageal cells via CD95-dependent or independent mechanisms or through activation of caspase 3 or cleavage of poly(ADP-ribose) polymerase [9, 17, 27, 35, 38, 48]. It has also been demonstrated that t-RES inhibits the ribonucleotide reductase catalyzing the rate limiting step of *de novo* DNA synthesis [14]. t-RES also demonstrates non-selective cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) inhibition [28].

Structure-activity relationship of t-RES

In order to establish the influence of the spatial position of the hydroxyl groups on the radical-scavenging effect of t-RES, STOJANOVIC et al [42] compared the activity of t-RES with activities of its analogues 4-hydroxy-*trans*-stilbene and 3,5-dihydroxy-*trans*-stilbene. All three stilbenes efficiently suppressed formation of the lipid hydroperoxides, but t-RES and 4-hydroxy-*trans*-stilbene were found to be more reactive than 3,5-dihydroxy-*trans*-stilbene. The fact, that t-RES and 4-hydroxy-*trans*-stilbene show almost the same antioxidant effect, indicates that the radical-scavenging activity of t-RES depends on the position of the hydroxyl groups. Therefore, for t-RES it can be concluded that its *para*-hydroxyl group dominates in the radical-scavenging efficiency whereas its *meta*-hydroxyl groups show only minor reactivity. Using the pulse radiolysis, reactions of t-RES and its analogues with trichloromethylperoxyl radicals (CCl3OO.) were studied. Spectral and kinetic properties of the transients showed great similarity between t-RES and 4-hydroxy-*trans*-stilbene which seems to confirm that *para*-hydroxyl group of t-RES scavenges free radicals more effectively than its *meta*-hydroxyl groups.

FANG et al [12] studied the antioxidant effect of t-RES and its analogues, which are 4-hydroxy-*trans*-stilbene, 3,5-dihydroxy-*trans*-stilbene, 4,4'-dihydroxy-*trans*-stilbene, 3,4-dihydroxy-*trans*-stilbene, 3,4,5-trihydroxy-*trans*-stilbene and 3,4,4'-trihydroxy-*trans*-stilbene, against the peroxidation of linoleic acid in sodium dodecyl sulfate and cetyltrimethyl ammonium bromide micelles. They found that the antioxidant activity of t-RES analogues depends significantly on the position of the hydroxyl groups. Molecules with *ortho*-dihydroxyl and/or *para*-hydroxyl functionalities possessed highest antioxidative activity. This can be understood because the *ortho*-hydroxyl phenoxyl radical, the oxidation intermediate for more active species (3,4-dihydroxy-*trans*-stilbene, 3,4,5-trihydroxy-*trans*-stilbene and 3,4,4'-trihydroxy-*trans*-stilbene), is more stable due to the intramolecular hydrogen bonding interaction, as evidenced from both experiments [15] and theoretical calculations [46]. In addition, it should be easier to further oxidize the *ortho*-hydroxyl phenoxyl radical and/or *ortho*-semiquinone radical anion to form the final *ortho*-quinone. The 4'-hydroxy group also enhanced the activity, since the 4'-hydroxy group can stabilize the semiquinone radical-anion intermediate by resonance through the *trans* double bond. Therefore, the antioxidative activity of 3,4,4'-trihydroxy-*trans*-stilbene is so high [12]. Later, CAI et al [5] studied the same structure/activity relationship in biological systems. They investigated the antioxidative effect of t-RES and related *trans*-stilbene analogues, that were 3,4-dihydroxy-*trans*-stilbene, 4,4'-dihydroxy-*trans*-stilbene, 4-hydroxy-*trans*-stilbene, and 3,5-dihydroxy-*trans*-stilbene, on free radical-induced peroxidation of rat liver microsomes. They found, that t-RES and its analogues, especially 3,4-dihydroxy-*trans*-stilbene, are good antioxidants for both peroxyl radical- and hydroxyl radical-initiated peroxidation of rat liver microsomes. The antioxidant mechanism may involve trapping the initiating peroxyl radicals and/or hydroxyl radicals and reducing α-tocopheroxyl radical (TO°) to regenerate the endogenous α-tocopherol.

STIVALA et al [41] have investigated whether antioxidant and anti-proliferative activities of t-RES are dependent on (i) the stereoisomery, (ii) the position of the different phenolic hydroxyl groups, and (iii) the stilbenic double bond of the molecule. For this purpose, the *cis*-form was obtained by UV irradiation of t-RES; three different derivatives were synthesized in which the hydroxylic functions were selectively protected by methyl groups: 3,5-dihydroxy-4'-methoxy-*trans*-stilbene, 3,5-dimethoxy-4'-hydroxy-*trans*-stilbene, and 3,4',5-trimethoxy-*trans*-stilbene; and the α,β-dihydroxo-3,4',5-trihydroxystilbene was obtained by reduction of the stilbenic double bond. The antioxidant activity of these compounds was evaluated by measuring the inhibition of citronellal thermo-oxidation, or the reduction of 2,2-diphenyl-1-picrylhydrazyl radical. In addition, the protection against lipid peroxidation was determined in rat microsomes, and in human primary cell cultures. The anti-proliferative activity was evaluated by a clonogenic assay, and by analysis of

cell cycle progression and DNA synthesis. The results showed that (i) 4'-hydroxy group in *trans*-conformation (hydroxystyryl moiety) is not the sole determinant for antioxidant properties, while it is absolutely required for anti-proliferative activity. (ii) There is a direct correlation, from a structural point of view, between the anti-proliferative effect and the ability to inhibit DNA pol α and β. Thus, a mechanism underlying the inhibition of cell cycle progression is the interaction between the 4'-hydroxystyryl moiety of t-RES and DNA polymerases.

MATSUOKA et al [25] reported that t-RES is negative in the bacterial reverse mutation assay but in high concentrations induces micronuclei and sister chromatid exchanges *in vitro* (10–87 μmol/l; 48 h treatment). Later, they synthesized six analogues of t-RES differing in number and position of hydroxyl groups, and they investigated structure-activity relationship in chromosomal aberration, micronucleus and sister chromatid exchange tests in a Chinese hamster cell line. Of the six t-RES analogues, only 3,4'-dihydroxy-*trans*-stilbene and 4-hydroxy-*trans*-stilbene were clearly positive in a concentration-dependent manner in all the cytogenetic studies performed. Both were equal to, or stronger than t-RES in genotoxicity. The 4'-hydroxy-*trans*-stilbene had the simplest chemical structure and was the most genotoxic. The other analogues did not have a 4'-hydroxy group. Their results suggest, that the 4'-hydroxy group is essential to the genotoxicity of stilbenes [26].

OHGUCHI et al [30] studied the inhibitory effect on tyrosinase activity of stilbene derivatives, which are t-RES oligomers ranging from monomer to tetramer (t-RES, dihydroresveratrol, (-)-ε-viniferin, (+)-α-viniferin, vaticanol, (-)-hopeaphenol), isolated from Dipterocarcaceae plants. The structure-activity relationship obtained in this study suggest that the double bond in the parent stilbene skeleton is necessary for the tyrosinase inhibitory activity, and also that the whole molecular size is important for the inhibition. The inhibitory potency of the t-RES oligomers was strongly reduced by increasing polymerization.

From the experimental crystal structure and ab initio calculations on t-RES and its derivatives, structural features of mechanistic importance were described. The molecular structure reveals relative coplanarity of the *trans*-stilbene skeleton, and the molecular packing in the solid state showed an extensive hydrogen bond network that elucidates the flip-flop motion of the three hydroxyl groups that alternately form break hydrogen bonds with each of the neighboring phenolic oxygens. The dynamic behavior provoked by the alternation of hydrogen bond formation and breaking can result in the ready mobility of up to three hydrogen atoms per t-RES molecule that can be transferred to reactive oxidants that are rich in electron density. In addition, theoretical studies confirm the planarity of t-RES as well as for half of the molecule of a condensation dimeric derivative of t-RES, *trans*-σ-viniferin. Furthermore, these studies show the *para*-4'-hydroxy group to be more acidic compared to the other two *meta*-hydroxyl groups. These features correlate with the biological activity of t-RES as an antioxidant and support earlier studies showing hydrogen atom transfer to be the dominant mechanism by which phenolic antioxidants intercept free radicals [7].

Higher hydroxylated analogues of t-RES

In contrast to the detailed knowledge of t-RES activities in biological systems much less is known about the effects of higher hydroxylated stilbens. t-RES undergoes cytochrome P450 catalyzed hydroxylation to piceatannol (3,3',4',5-tetrahydroxy-*trans*-stilbene; PCA; Fig. 1) and to two other unidentified mono- and dihydroxy-t-RES analogues. It demonstrates that a natural dietary cancer preventative agent can be converted to a compound with known chemopreventive and anticancer activity by an enzyme CYP1B1, which is overexpressed in a wide variety of human tumors. Importantly, this result gives insight into the functional role of the cytochrome P450 enzyme CYP1B1 and provides evidence for the concept that CYP1B1 in tumors may be functioning as a growth suppressor enzyme [34]. As t-RES, PCA displays cytotoxic activity in acute leukemia and lymphoma cells and anti-proliferative activity in colorectal cancer cell lines [45].

PCA differs from t-RES by possessing an additional hydroxyl group and it is more water-soluble than t-RES. PCA has been isolated together with t-RES from grapes and wine. Stilbene synthesis in grapes depends on different viticultural factors such as the grape variety, the environment and cultural practices. Concerning the grape variety, red berry-grapes have higher stilbene levels than white berry-grapes. With regard to climate, preliminary results suggest a positive correlation between vineyard elevation and stilbene grape concentrations. Quality-oriented cultural practices produce grapes with high levels of stilbenes [1]. Besides stilbenes, wine contains other polyphenolic compounds (flavonoids: flavonols, catechins, anthocyanins). All of these compounds exhibit interesting properties which may account in part for the so-called "French paradox," i.e. the fact that the incidence of heart infarction in Southern France is 40% lower than in the rest of Europe despite the population's high-fat diet [13].

CAI et al [6] compared the inhibiting activities of t-RES and seven other hydroxylated *trans*-stilbenes with respect to an azo compound-induced peroxidation of linolic acid *in vitro* and to induced apoptosis in cultured HL-60 and Jurkat human leukemia cells. They found that both antioxidant and apoptotic activities of the analogues containing 3,4-dihydroxyl groups namely 3,4-dihydroxy-*trans*-stilbene, 3,4,4'-trihydroxy-*trans*-stilbene and 3,4,5-trihydroxy-*trans*-stilbene were significantly higher than those of t-RES and the other analogues. These data were supported by other investigators who also found free radical scavenging activity that was several times better, along with a higher growth-inhibitory activity of PCA and 3,4,4',5-tetrahydroxy-*trans*-stilbene

compared to t-RES in tumor cells [20]. t-RES and its hydroxylated derivatives may be oxidized in an enzymatic or non-enzymatic manner via the one-electron pathway to a phenoxyl radical (ArO°) and subsequently yiels quinone or quinone-methine type prooxidant or alkylating products. Several studies showed that the quinone products from oxidation of catecholic estrogen [2] and dopamine [11] are indeed responsible for the observed apoptotic effects of these drugs on cells.

HUNG et al [21] compared antioxidative and free radical scavenging activities of t-RES and its analogues to their protective effects on ischaemia-reperfusion induced injuries of rat hearts. t-RES and PCA have been shown to be more potent inhibitors than other analogues against Cu^{2+}-induced oxidation of low-density lipoprotein (LDL). PCA was 2 to 25.5 fold more potent than t-RES in thiobarbituric acid-reactive substance and 1,1-diphenyl-2-picryl-hydrazyl (DPPH) assays. However, PCA was about 160 fold more potent than t-RES in superoxide anion scavenging. Their results showed the possible structural criteria important for the antioxidant activities of these polyphenolic compounds. Deletion of the hydroxyl group at the B-4 of t-RES reduces its antioxidant activity. In contrast, the presence of *ortho*-dihydroxy structure in ring B (PCA) enhanced its activity to inhibit LDL peroxidation and free radical trapping, especially superoxide anion. Their results showed a positive correlation between the antioxidation and cardioprotective activities among these phenolic compounds. The effects of PCA on LDL oxidation and DPPH scavenging observed here is consistent with the report by FAUCONNEAU et al [13].

MURIAS et al [29] studied structure-activity relationship between pro-/antioxidant properties of t-RES, PCA and five synthesized polyhydroxylated t-RES analogues. Radical scavenging experiments with O_2°- (5,5-dimethyl-1-pyrroline-N-oxide/electron spin resonance) and 2,2-diphenyl-1-picrylhydrazyl (DPPH°) revealed that 3,3',4',5-tetrahydroxy-*trans*-stilbene, PCA and 3,3',4,4',5,5'-hexahydroxy-*trans*-stilbene exerted a more than 6600-fold higher anti-radical activity than t-RES and its two other analogues. Furthermore, in HL-60 leukemic cells hydroxystilbens with *ortho*-hydroxyl groups exhibited a more than three-fold higher cytostatic activity compared to hydroxystilbenes with other substitution patterns. Oxidation of *ortho*-hydroxystilbenes in a microsomal model system resulted in the existence of *ortho*-semiquinones, which were observed by ESR spectroscopy. Further experiments revealed that these intermediates undergo redox-cycling thereby consuming additional oxygen and forming cytotoxic oxygen radicals. In contrast to compounds with other substitution patterns hydroxystilbenes with one or two resorcinol groups did not show an additional oxygen consumption or semiquinone formation. Their findings suggest that the increased cytotoxicity of *ortho*-hydroxystilbenes is related to the presence of *ortho*-semiquinones formed during metabolism or autooxidation.

Methoxylated derivatives of t-RES

ROBERTI et al [37] have synthesized and tested a library of compounds based on t-RES and have demonstrated the importance of a 3,5-dimethoxy motif in conferring pro-apoptotic activity to stilbene based compounds. Later, TOLOMEO et al [43] evaluated the ability of pterostilbene and 3'-hydroxypterostilbene (Fig. 1), natural 3,5-dimethoxy analogs of t-RES and PCA, in inducing apoptosis in sensitive and resistant leukemia cells. When tested in sensitive cells, human myeloid leukemia cell line HL-60 and human T lymphoma cell line HUT78, 3'-hydroxypterostilbene (3,5-dimethoxy analogue of PCA) was 50-97 times more potent than t-RES in inducing apoptosis, while pterostilbene appeared barely active. However, both compounds, but not t-RES and PCA, were able to induce apoptosis in the Fas-ligand resistant lymphoma cell lines, HUT78B1 and HUT78B3, and the multi drug-resistant leukemia cell lines HL-60-R and K562-ADR (a Bcr-Abl-expressing cell line resistant to imatinib mesylate). Moreover, pterostilbene and 3'-hydroxypterostilbene, when used at concentrations that elicit significant apoptotic effects in tumor cell lines, did not show any cytotoxicity in normal hemopoietic stem cells.

In order to find more selective COX-2 inhibitors a series of methoxylated and hydroxylated t-RES derivatives were synthesized and evaluated for their ability to inhibit both enzymes using *in vitro* inhibition assays for COX-1 and COX-2 by measuring prostaglandin E_2 production. Hydroxylated but not methoxylated t-RES derivatives showed a high rate of inhibition. The most potent t-RES compounds were PCA and 3,3',4,4',5,5'-hexahydroxy-*trans*-stilbene. Their selectivity index was in part higher than celecoxib, a selective COX-2 inhibitor already established on the market. Effect of structural parameters on COX-2 inhibition was evaluated by quantitative structure-activity relationship (QSAR) analysis and a high correlation was found with the topological surface area TPSA. Docking studies on both COX-1 and COX-2 protein structures also revealed that hydroxylated but not methoxylated t-RES analogues are able to bind to the binding sites of the enzymes [28].

Conclusion

It has been found that the biological activity of t-RES and its analogues depends significantly on the structural determinants, which are (i) number and position of hydroxyl groups, (ii) intramolecular hydrogen bonding, (iii) stereoisomery and (iv) double bond. The observation that *trans*-stilbene compounds having 4'-hydroxy group, double bond and bearing *ortho*-diphenoxyl or *para*-diphenoxyl functionalities possess remarkably higher chemopreventive activity than t-RES gives us useful information for further anti-cancer drug design.

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