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PERSPECTIVE

Resveratrol and Resveratrol Analogues—Structure—Activity Relationship

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ABSTRACT Resveratrol (3,4′,5-trihydroxy-*trans*-stilbene) is a compound found in wine and is held responsible for a number of beneficial effects of red wine. Besides the prevention of heart disease and significant anti-inflammatory effects, resveratrol might inhibit tumor cell growth and even play a role in the aging process. We here describe the structure-activity relationship of resveratrol and analogues of resveratrol regarding the free radical scavenging and antitumor effects of this exciting natural compound. In addition, we have synthesized a number of analogues of resveratrol with the aim to further improve the beneficial effects of resveratrol. Our studies were based on the analysis of structural properties, which were responsible for the most important effects of this compound. Striking *in vivo* effects can be observed with hexahydroxystilbene (M8), the most effective synthetic analogue of resveratrol. We could show that M8 inhibits tumor as well as metastasis growth of human melanoma in two different animal models, alone and in combination with dacarbacine.

KEY WORDS apoptosis · gallic acid · resveratrol · ribonucleotide reductase · stilbene analogues

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INTRODUCTION

Resveratrol was identified as one ingredient of red wine, which could cause the so-called "French paradox" (1). The incidence of heart infarction is 40% lower in France than in other comparable countries. An examination of the French diet reveals that it cannot be the cause of this health advantage. As wine consumption, in particular the consumption of red wine, is very popular in France, potentially beneficial ingredients of wine were investigated to explain this phenomenon.

In 1987, Richard reports about a French paradox regarding coronary risk factors and the incidence of heart disease; the incidence of ischemic heart diseases is much lower in France than in the USA or the rest of Europe, even after adjusting for risk factors. The authors speculate that the relatively high alcohol consumption might play a role in this effect (1).

As a result, a search for active ingredients in wine began. As the key candidate for causing beneficial effects, resveratrol was identified. Resveratrol is a stilbene derivative (3,4′,5-trihydroxy-*trans*-stilbene, Fig. 1) which is present in wine, particularly red wine (2). The compound is synthesized in the skin of the grapes to defeat fungal infections and is present in both white and red grapes (2). However, due to the production process, concentrations found in red wines are far higher than in white wines. In addition to resveratrol, other polyphenolic compounds, such as gallic acid, or metabolites of resveratrol are ingredients of wine, but even ethanol itself might play an important role in causing beneficial effects of wine. However, resveratrol was identified to be the most likely single ingredient of wine to cause beneficial effects, such as prevention of blood vessel disease or prevention of the development of malignancies (3–6). It might well be that various flavonoids together with other compounds exert their positive effects.

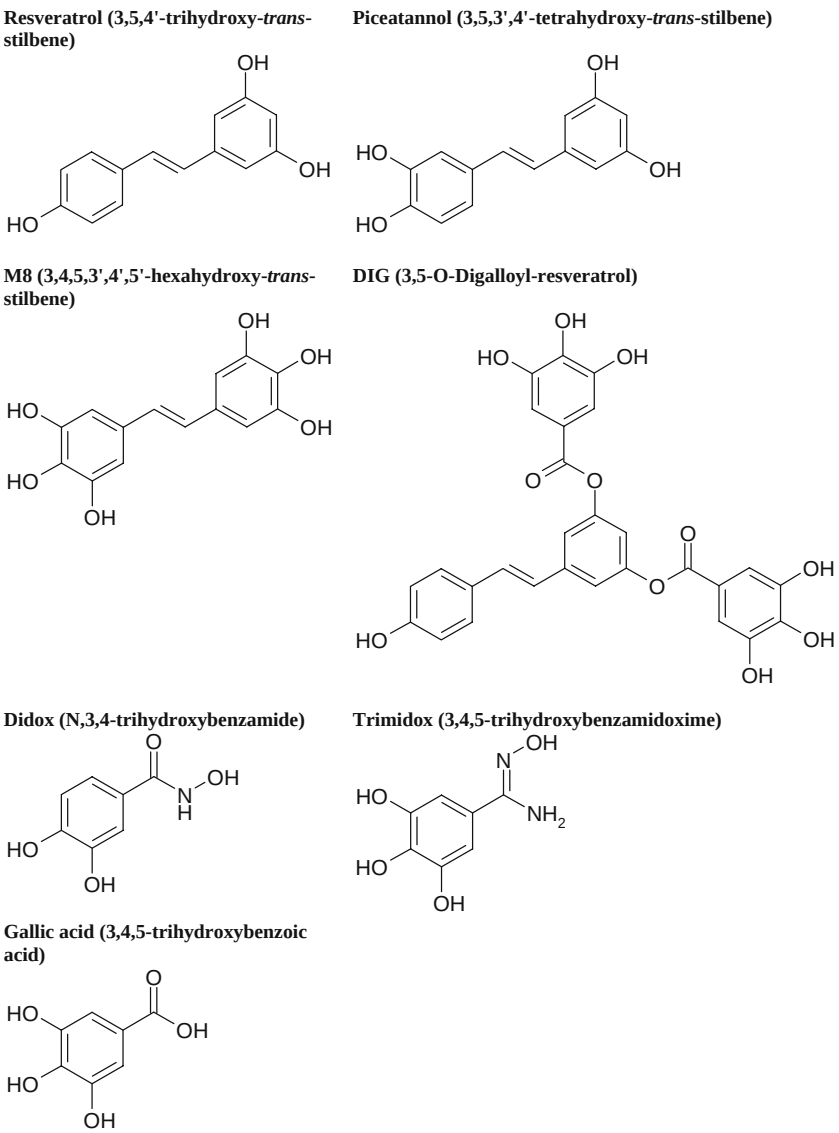

Fig. 1 Structural formula and nomenclature of resveratrol and its analogues.

METABOLISM OF RESVERATROL

Potter and coworkers first described the conversion of resveratrol to piceatannol, a monohydroxylated resveratrol by the cytochrome p450 enzyme CYP1B1 (7). Piceatannol itself is an active anticancer compound also present in wine, however in far lower concentrations than resveratrol. The authors also speculate that further polyhydroxylated resveratrol metabolites might be formed and exert their activity. Their findings and our previous experience with other polyhydroxylated phenolic compounds, such as benzohydroxamic acid derivatives, prompted us to investigate the structure-activity relationship of phenolic compounds, such as stilbenes, with different number and positioning of hydroxyl groups.

Resveratrol is also converted to 3-O-beta-D-, 4′-O-beta-D-glucuronide conjugates or 3-O-sulfates. Sulfates were the predominant metabolites in Caco-2 human colon carcinoma cells; however, its formation could be inhibited by resveratrol itself (8). Sulfotransferase 1A1 (SULT 1A1) expression is responsible for the conversion of resveratrol to 3-O-sulfates; high activity reduced the anticancer activity of resveratrol in human breast cancer cells, indicating that, depending on the metabolism of resveratrol, either active metabolites, such as piceatannol, or less active intermediates, such as sulfates, can be formed (9).

MECHANISMS OF ACTION OF RESVERATROL

Frankel *et al.* showed in 1993 that resveratrol can inhibit the oxidization of LDL cholesterol, thus eventually reducing the risk of coronary artery disease (4). In addition, resveratrol was known to inhibit arachidonate metabolism

in leukocytes and to inhibit platelet aggregation in platelet-rich plasma (6,10). The free radical scavenging capacity of resveratrol and other polyphenols might also contribute to the beneficial effects of this compound (11).

It could be demonstrated that resveratrol also has cancer chemopreventive activity *in vitro* and in animals. Resveratrol proved to be effective in preventing the development of cancer in a skin cancer animal model (12). This effect could also be caused by the inhibitory effects of resveratrol on the enzyme ribonucleotide reductase (RR) (13). RR is the key enzyme of *de novo* DNA synthesis and is significantly up-regulated in tumor cells. It was identified as an important target of antitumor therapy. The enzyme needs a tyrosl free radical for its activity and can therefore be inhibited by free radical scavengers, such as resveratrol or other polyhydroxyphenolic compounds.

We have previously investigated a number of compounds as inhibitors of this enzyme. Benzohydroxamic acid derivatives, such as didox, amidox or trimidox, were synthesized as inhibitors of RR and proved to be effective free radical scavengers and antitumor compounds (Fig. 1, 14). They also possess a polyhydroxyphenolic moiety similar to resveratrol, indicating that this chemical entity is responsible for the free radical scavenging and anticancer effects observed for resveratrol, its metabolites and analogues.

It was also shown that RR inhibitors can cause erythroid differentiation and can be used for the treatment of sickle cell anemia. Rodrigue *et al.* used the human erythroleukaemic K562 cell line as an *in vitro* model and showed that 50 µmol/l of resveratrol induced a higher haemoglobin production in K562 cells than 500 µmol/l of hydroxyurea, which is a known RR inhibitor used for the treatment of sickle cell anemia (15). This erythroid differentiation was linked to inhibition of cell proliferation and associated with an increased expression of p21 mRNA and protein. Resveratrol and hydroxyurea also induced fetal haemoglobin synthesis in cultured erythroid progenitors of sickle cell patients.

Many other beneficial effects of resveratrol were described, such as direct effects on blood vessels or on the oestrogen receptor (16). Protection from ischemia reperfusion injury or inhibition of cyclooxygenases might contribute to the cardioprotective as well as the antitumor effects of polyhydroxyphenolic compounds, such as resveratrol (17).

Sinclair and coworkers even showed, first in yeast, that resveratrol mimics calorie restriction by stimulating sirtuin Sir2 and increasing DNA stability. They could extend the lifespan of yeast by 70% (18). They showed later that resveratrol can reverse the adverse effects of a high calorie diet in animals (19). Shortened lifespan could be normalized, which was the consequence of protective and beneficial effects on numerous biochemical pathways. The authors speculate that resveratrol or other small molecules mimicking calorie restriction might be options to treat obesity-related disorders. In order to find even more effective sirtuin activators, stilbene derivatives with modifications at the 4′ position of the B ring were synthesized. These compounds had lower toxicity and better sirtuin-activating effects than the natural compound (20).

However, concentrations of resveratrol found after oral administration to animals or humans were rather low, indicating that other ingredients of wine might be important besides of resveratrol itself (21). Metabolites, like polyhydroxylated resveratrol metabolites or sulfated metabolites, might significantly contribute to the effects seen with this compound. However, the question whether therapeutic doses could be achieved after oral administration of resveratrol has to be addressed. Solubility studies revealed that even better aqueous solubility did not improve oral bioavailability (22). However, liposomal encapsulation could significantly increase the bioavailability of resveratrol and caused reduced prostate cancer incidence in animals (23). Taken together, optimized bioavailability and administration of resveratrol in the ideal dose could be used in humans. Resveratrol conjugate metabolites, which can be found after oral administration in higher concentrations in the serum, might also be responsible for the chemopreventive effects of resveratrol (24).

STRUCTURE-ACTIVITY RELATIONSHIP

We have synthesized and tested a number of resveratrol derivatives. First, we increased the number of hydroxyl groups on the phenol rings of the stilbene structure. All hydroxystilbene analogues proved to inhibit the growth of human tumor cell lines. In an extensive study, the free radical scavenging capacities of hydroxystilbenes were then studied (25,26).

Radical scavenging experiments showed that 3,3′,4′,5-tetrahydroxy-*trans*-stilbene, 3,4,4′,5-tetrahydroxy-*trans*-stilbene and 3,3′,4,4′,5,5′-hexahydroxy-*trans*-stilbene showed a more than 6,600-fold higher antiradical activity than resveratrol (25,26). Furthermore, in HL-60 leukemic cells, hydroxystilbenes with ortho-hydroxyl groups exhibited a more than three-fold higher cytostatic activity compared to hydroxystilbenes with other substitution patterns.

Ortho-hydroxystilbenes formed ortho-semiquinones, which were identified by electron spin resonance (ESR) spectroscopy. These intermediates underwent redox-cycling and formed cytotoxic oxygen radicals (25). On the other hand, hydroxystilbenes with one or two resorcinol groups did not show additional oxygen consumption or semiquinone formation.

These findings suggest that ortho-hydroxystilbenes are more effective than other hydroxyl-substituted resveratrol derivatives. An increased number of hydroxyl groups on the ring-structure showed better cytotoxic and free radical scavenging capacities (25,26).

Investigating the effects of resveratrol and its derivatives on cyclooxygenases (COX), we could verify that resveratrol is a non-selective COX inhibitor. As COX 1 inhibition is responsible for side effects of anti-inflammatory drugs, and only COX 2 inhibition causes pain relief and the anti-inflammatory effects, we tested whether any of the resveratrol analogues showed selective effects. A series of methoxylated and hydroxylated resveratrol derivatives were synthesized and tested (25,26). Hydroxylated, but not methoxylated, resveratrol derivatives showed a high rate of COX inhibition. The most potent resveratrol compounds were piceatannol and hexahydroxystilbene; they displayed COX enzyme inhibitory effects at very low concentrations and were highly selective COX 2 inhibitors. Methoxylated resveratrol analogues did not show any COX inhibition. Docking studies on both COX 1 and COX 2 protein structures revealed that binding to a certain area of the enzyme is responsible for COX inhibition of hydroxystilbenes. It is important to note that concentrations required to inhibit COX enzymes are at least one order of magnitude lower than the concentrations needed to inhibit tumor cell growth (25,26). However, hydroxylated resveratrol analogues, although more effective, retain the free radical scavenging capacity and RR as well as COX enzyme inhibitory effects of resveratrol itself (25,26).

Hydroxylated resveratrol analogues represent a promising class of highly selective COX 2 inhibitors. The effectiveness of OH-resveratrol analogues was also shown by Thakkar and coworkers, who synthesized a number of analogues and identified 3,3′,5,5′-tetrahydroxy-*trans*-stilbene, 3,3′,5-trihydroxy-*trans*-stilbene, and 3,4,4′-trihydroxy-*trans*-stilbene as the most potent compounds in the series of OH-stilbenes (27).

Rüweler and coworkers also synthesized a number of polyhydroxy-substituted resveratrol analogues and investigated their effects in human glioma tumor cells (28). The compounds showed cytotoxic effects and were identified as free radical scavengers. However, only resveratrol and piceatannol inhibited cellular radical generation at lower than cytotoxic concentrations.

Lee *et al.* investigated the resveratrol analogue 3,5,3′,4′,5′-pentahydroxy-*trans*-stilbene, which inhibits cell transformation (29). The hydroxyl group at the meta position of the B ring is crucial for MEK/ERK inhibition and was identified as one of the mechanisms responsible for the activity of 3,5,3′,4′,5′-pentahydroxy-*trans*-stilbene (29).

IDENTIFICATION OF HEXAHYDROXYSTILBENE (M8) AS LEAD COMPOUND

We identified hexahydroxystilbene (M8) to be the most effective resveratrol analogue and therefore further investigated the effects of M8 in various tumor cell lines, such as leukemia, melanoma, breast cancer or colon tumor cell lines. M8 displayed the lowest IC50 concentrations for tumor cell cytotoxicity and was the most effective free radical scavenger of all resveratrol analogues which were tested (25,26).

The compound turned out to be the most effective inhibitor of deoxynucleosidetriphosphate formation (dATP and dTTP) by inhibition of RR, thus causing significant antitumor effects. As mentioned above, we could demonstrate the selective inhibition of cyclooxygenase 2 activity and synergistic effects with other antitumor compounds such as Ara-C (30).

In addition, M8 was investigated in two different melanoma animal models. Wacheck and coworkers demonstrated the effective *in vivo* antitumor effects of M8 as a single compound and in combination with dacarbacine (31). Three out of six animals, which were treated with a combination of M8 and dacarbacine, were tumor-free after treatment, due to synergistic action of the two anticancer compounds used in this animal model. As a result, M8 was studied in a melanoma metastasis model by the group of Kunstfeld, demonstrating excellent *in vitro* and *in vivo* activity. M8 inhibited cell migration in matrigel assays. In a melanoma scid mouse model, they showed that M8 significantly impaired tumor growth and prevented the metastatic spread of melanoma cells to distant lymphnodes (32).

OTHER SELECTED POLYHYDROXYPHENOLIC COMPOUNDS

Piceatannol

As mentioned, monohydroxylated resveratrol, piceatannol, can be found in low concentrations in wine and is being formed from resveratrol *in vivo*. The compound has better antitumor effects than resveratrol itself and is an excellent selective cyclooxygenase 2 inhibitor. It was also identified as an inhibitor of protein-tyrosine kinase activity. It inhibited the activities of p40 and p56 protein tyrosine kinases, but not cAMP-dependent protein kinase in thymocyte cells or cell membranes (27,33,34). Piceatannol was also identified as an inhibitor of NF-kappaB. Ashikawa showed that hydroxyl groups of stilbenes are critical to suppress NF-kappaB activation, which was induced by various inflammatory agents (34).

Wieder and coworkers showed that piceatannol, like resveratrol, could induce apoptosis in burkitt-like BJAB

lymphoma cells by activation of caspase-3 and mitochondrial permeability transition (35). Our group identified piceatannol as an inhibitor of RR and showed that a combination of piceatannol, like resveratrol, with Ara-C exhibits synergistic cytotoxic effects in human HL-60 leukemia cells by increasing the concentration of Ara-CTP, the active metabolite of Ara-C (36–39). Therefore, piceatannol might be further investigated as a potential drug for treatment of leukemia.

Beneficial effects attributed to red wine can at least in part be caused by piceatannol as well.

Gallic Acid

Gallic acid (GA) is also present in wine and various other natural products, like green tea, apple peels, strawberries, pineapples, bananas and lemons. It was demonstrated that gallic acid has antiproliferative effects in cancer cells and acts as an excellent free radical scavenger.

GA inhibited RR activity and caused a significant imbalance of deoxynucleosidetriphosphate (dNTP) pool sizes in HL-60 human promyelocytic leukemia cells. Moreover, GA induced dose-dependent apoptosis in HL-60 cells and attenuated progression from G0/G1 to the S phase of the cell cycle. We further determined IC50 values of 3.5 and 4.4 nM for the inhibition of cyclooxygenases 1 and 2, respectively. When cells were simultaneously treated with GA and trimidox, another inhibitor of RR, highly synergistic growth-inhibitory effects could be observed (40). GA inhibited dATP and dGTP pools in HL-60 cells, whereas trimidox caused a decrease of dCTP levels; the molecular mechanisms of both RR inhibitors were different. Therefore, both compounds could cause synergistic effects in this cell line; however, these results indicate that inhibition of RR is not solely caused by the polyhydroxyphenolic moiety.

SYNTHESIS AND TESTING OF DIGALLOYLRESVERATROL

Digalloylresveratrol (DIG) is a new synthetic ester of the naturally occurring polyhydroxyphenolic substances gallic acid and resveratrol, which both exert anticancer activity in a number of tumor cell lines. DIG inhibited human colon cancer cells as well as human leukemia cells with IC50s in the low micromolar range. The compound could also be identified as an effective inhibitor of RR and inducer of apoptosis. DIG inhibited the transition from S to G2/M phase of the cell cycle. However, in contrast to resveratrol or gallic acid, DIG did not inhibit COX activities (41).

Our studies indicate that molecules with more phenolic moieties and an increased number of OH-groups on these rings show better anticancer activities. This might be caused by different effects, such as free radical scavenging capacities, thus inhibiting key enzymes of DNA synthesis and causing programmed cell death of tumor cells. On the other hand, anti-inflammatory effects, such as inhibition of COX enzymes, might contribute to the cancer preventive effects of polyhydroxyphenols.

OTHER RESVERATROL ANALOGUES

Cushman and coworkers synthesized a number of methoxy-substituted *cis*-stilbenes, structurally similar to combretastatins (42). These compounds proved to be cytotoxic in five cell lines and to be active as inhibitors of tubulin polymerization. However, in contrast to hydroxy-substituted resveratrol analogues, free radical scavenging capacity could not be observed for this group of compounds.

2,4-dimethoxyresveratrol was synthesized by Jeong *et al.*, who show that this compound overcomes resistance conferred by Bcl-2 in human U937 leukemia cells (43).

Fluorinated derivatives of resveratrol with hydroxyl groups replaced by amino groups were synthesized by Moran *et al.* (44). They investigated the biological activities of these compounds in different cell lines and identified a number of active analogues. Aromatic hydroxylation of two hydroxylated methoxystilbenes led to two new compounds, which were evaluated as anti-angiogenic agents (44).

Shang *et al.*, who synthesized a number of resveratrol dimers speculate that the hydroxyl group at the 4-position is much easier to be oxidized than other hydroxyl groups and that a dioxane-like dimer is formed via an o-quinone intermediate (45).

Weng *et al.* investigated resveratrol and its analogues in lung cancer cells and come to the conclusion that resveratrol, dibenzoylmethane and their analogues might be good candidates for chemoprevention of lung cancer (46).

A series of trans-N-phosphoryl amino acid-modified resveratrol analogues were synthesized by Liu *et al.* (47). The compounds induced apoptosis and caused cytotoxic effects in various cell lines investigated. Kang and coworkers synthesized a 78-membered library of resveratrol analogues (48). The library contains inhibitors against COX 1, COX 2 or the transcription factor NF-kappaB. An extensive study of the structure-activity relationship of these exciting compounds is warranted.

Heynekamp and coworkers screened 75 compounds in order to identify substituted trans-stilbenes that are more active than resveratrol (49). They found that compounds that were strong inhibitors of the activation of NFkappaB generally did not exhibit antioxidant activity.

Many of the active compounds also inhibited COX 2 activity.

Simoni and coworkers also synthesized stilbenes, related to resveratrol. They identified as most potent compound 3,4′,5-trimethoxy-*trans*-stilbene, which caused apoptosis at low concentrations (50). This compound also impressed by causing a decrease of cells in all phases of cell cycle (G0-G1, S, and G2-M) and a proportional increase of apoptotic cells.

Induction of programmed cell death was the effect common for resveratrol and most of its active analogues; however, the concentrations required for activity differed from compound to compound (25,26).

CONCLUSION

Resveratrol is a trihydroxy stilbene with a number of beneficial effects. At least in part, the compound was responsible for the cardioprotective effects of wine. It is not clear whether resveratrol itself or intermediates or metabolites exhibit *in vivo* effects. However, due to the broad spectrum of beneficial effects seen with this compound, during the past years, research has focused on the investigation of biochemical effects caused by resveratrol. Resveratrol is active against inflammation, blood vessel disease and malignant transformation, making it almost a magic bullet. Nevertheless, it is not clear whether it can be used as a drug to prevent or treat diseases in humans. Numerous analogues were recently synthesized with the aim to further improve the effects seen with resveratrol. We summarized many of these studies in order to give an overview of the present knowledge. Some of the synthetic resveratrol analogues have a promising activity-spectrum and might therefore be further investigated.

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