



Resveratrol and derivatives for the prevention and treatment of cancer

Simone Fulda

Institute for Experimental Cancer Research in Pediatrics, Goethe-University, D-60528 Frankfurt, Germany

Resveratrol, a naturally derived stilbene that exists in various foods and beverages, has attracted increasing attention over the past decade because of its multiple beneficial properties, including chemopreventive and antitumor activities. There are several other natural derivatives of resveratrol that are structurally similar to resveratrol and are also present in food. In addition, a series of resveratrol analogs have been synthesized by the addition of defined functional groups to increase the potency and/or enhance the activity of specific properties of resveratrol. Such resveratrol derivatives might provide promising tools as cancer chemopreventive agents, as well as cancer therapeutics in the prevention and treatment of cancer. This review provides an overview of key derivatives of resveratrol as cancer therapeutics.

Introduction

Resveratrol (3,4',5-trihydroxystilbene) is a polyphenolic natural product [1,2]. It harbors a stilbene structure and belongs to the group of phytoalexins that become activated under stress conditions of plants. These compounds exist in foods and beverages (e.g. in grapes and red wine) and are widely consumed. Resveratrol is also classified as a phytoestrogen because of its ability to interact with estrogen receptors. In addition, its stilbene is related to the synthetic estrogen diethylstilbestrol.

Resveratrol exerts various biological activities that are beneficial to human health, including chemopreventive, anti-inflammatory, antioxidant, antiproliferative, proapoptotic, cardioprotective and anticancer properties [1,2]. Accordingly, resveratrol can be exploited in the control of atherosclerosis, heart disease, arthritis, autoimmune disorders or cancer. More recently, resveratrol has been identified as a sirtuin-activating compound [3,4]. Sirtuins are a conserved family of NAD⁺-dependent deacetylases (class III histone deacetylases) [5]. Like SIRT1, small-molecule activators of sirtuins including resveratrol extend lifespan in yeast and higher organisms [6,7].

Structure–activity studies have revealed crucial elements of the parental components that are required for specific effects. To give one example, the 4-hydroxy group in the *trans* conformation on

the 4- and 4'-positions of the stilbenic backbone has been identified as crucial for the antiproliferative effect of resveratrol [8]. These structure–activity studies also provide the basis for the development of novel resveratrol analogs with more potent antitumor activity or other properties by selective modification of the stilbene scaffold of resveratrol. In addition, there are various naturally occurring stilbene-like compounds that are related to resveratrol. A better understanding of the specific activities of distinct components of resveratrol and its derivatives is expected to open new avenues for drug discovery. This review gives an overview of key resveratrol derivatives with chemopreventive or antitumor properties.

Methoxylated derivatives of resveratrol

Analysis of structure–activity relationships revealed that the substitution of hydroxyl groups of resveratrol to methoxy groups substantially potentiated Resveratrol's cytotoxic activity [9]. Therefore, a series of methoxylated analogs of resveratrol were prepared with the aim of increasing the antitumor activity of resveratrol (Table 1). In addition to the substitution with methoxy groups at certain positions, the *cis* form of the stilbene backbone in general showed increased cytotoxic activity over the corresponding *trans* isomers [9–11]. The only exception is resveratrol itself, which exhibits higher activity as *trans* isomer [9–11]. Furthermore, a 3,5-dimethoxy motif was found to be important for conferring

E-mail address: simone.fulda@kgu.de.

TABLE 1

Resveratrol derivatives

Derivatives	Refs
Methoxylated resveratrol derivatives	
Pterostilbene	[13–22,24–31]
Trimethoxystilbene	[8,32–38,44]
Tetramethoxystilbene	[9,39–45,60]
Pentamethoxystilbene	[46–48]
<i>N</i> -Hydroxy- <i>N'</i> -(trimethoxyphenyl)-trimethoxy-benzamidine	[49,50]
Hydroxylated resveratrol derivatives	
Hydroxystilbene	[8,51]
Dihydroxystilbene	[52,53,55]
Tetrahydroxystilbene	[44,56,60]
Pentahydroxystilbene	[70]
Hexahydroxystilbene	[39,44,57–62]
Other resveratrol derivatives	
Resveratrol triacetate	[65]
Gloriosols A–C	[68]
Mitochondria-targeted resveratrol derivatives	[71]
Digalloylresveratrol	[66]
Bridged stilbenes	[69]
Fluorinated stilbenes	[64]

the proapoptotic activity to stilbene derivatives. Accordingly, the *cis*-3,5-dimethoxy derivatives of resveratrol (i.e. 3,5,3'-trihydroxy-4'-methoxy-*trans*-stilbene and its 3'-amino derivative) displayed apoptotic activity at nanomolar concentrations in HL-60 promyelocytic leukemia cells [10]. In addition, these methylated derivatives of resveratrol were active toward resistant HL-60 cells with a multi-drug resistant phenotype [10].

Pterostilbene (3,5-di-methoxy-4'-hydroxystilbene)

Besides resveratrol, several other stilbenes, which are structurally similar to resveratrol, occur naturally in food. Pterostilbene (Fig. 1a), for example, is a dimethylated analog of resveratrol, which is present in – for example – blueberries and has been studied most extensively [12]. The substitution of hydroxy with methoxy groups increases the lipophilicity of pterostilbene over resveratrol, resulting in better bioavailability [13]. These differences in pharmacokinetics might account for the higher biological activity of pterostilbene over the parental compound resveratrol.

Regulation of cell-cycle, proliferation and apoptosis by pterostilbene

Pterostilbene has been reported to exert various pharmacological effects including anticancer, antiproliferative, proapoptotic, antioxidant, anti-inflammatory, anti-invasive and antimetastatic functions [12]. In a variety of human cancer cell lines – including pancreatic, breast, lung, gastric cancer, melanoma and leukemia – pterostilbene decreases cell viability [14–21]. In breast cancer cell lines, pterostilbene induced apoptosis in a caspase-dependent manner [15]. In this model, loss of mitochondrial membrane potential and production of superoxide anion might contribute to activation of effector caspase-3 and -7 [15]. Similarly, caspase-dependent apoptosis upon treatment with pterostilbene was associated with the production of reactive oxygen species, loss of mitochondrial membrane potential, cytochrome *c* release, a shift in the balance of pro- and antiapoptotic Bcl-2 proteins, and activation of caspases in the human gastric carcinoma cell line AGS [18].

Moreover, pterostilbene and 3,5-hydroxypterostilbene, the natural 3,5-dimethoxy analogs of piceatannol, proved to be effective even in resistant hematological malignancies, including cases that were nonresponsive to imatinib [19]. Both compounds were able to induce apoptosis in Fas-ligand-resistant lymphoma cell lines and in multi-drug-resistant leukemia cell lines, including a Bcr-Abl-expressing cell line (K562-ADR) that is refractory to imatinib mesylate [19]. Of note, pterostilbene-induced apoptosis could not be inhibited by the pancaspase-inhibitor zVAD.fmk, pointing to a caspase-independent pathway [19]. In comparison, 3'-hydroxypterostilbene triggered apoptosis via the intrinsic apoptotic pathway [19]. In contrast to apoptosis induction in malignant cells, neither pterostilbene nor 3'-hydroxypterostilbene exerted any cytotoxicity against normal hemopoietic stem cells, thus pointing to some tumor selectivity [19].

Consistent with the role of pterostilbene in the regulation of apoptosis, gene expression profiling studies using the model yeast *Saccharomyces cerevisiae* revealed that pterostilbene upregulated genes involved in mitochondrial functions [22]. These studies also showed downregulation of genes involved in lipid and methionine metabolism by pterostilbene, in line with its hypolipidemic properties [22].

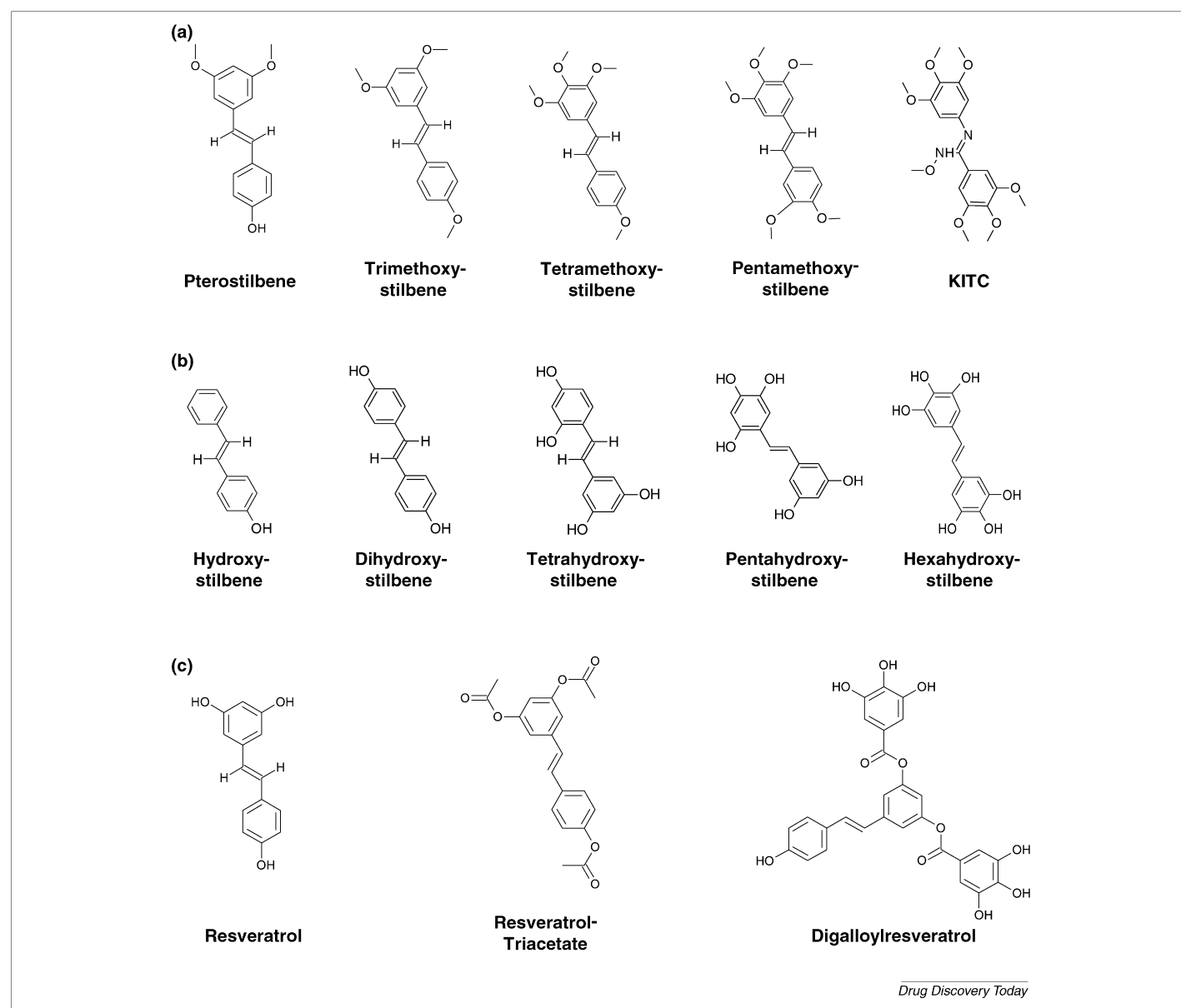
Furthermore, pterostilbene inhibited cell proliferation and cell-cycle progression in a concentration- and time-dependent manner. To this end, pterostilbene blocks cell-cycle progression at the G1 phase, accompanied by an increase in p53, p21, p27 and p16 proteins and a concomitant decrease in cyclin A, cyclin E and cyclin-dependent kinase (Cdk)2, Cdk4 and Cdk6 [18].

Antioxidative, anti-inflammatory and chemopreventive activities of pterostilbene

Evaluation of the antioxidative and chemopreventive potential of pterostilbene revealed that pterostilbene displayed peroxyl-radical scavenging activity similar to resveratrol, whereas it was less potent than resveratrol in inhibiting both isoforms of cyclooxygenase, or COX (i.e. COX-1 and COX-2) [23]. In a mouse mammary organ culture model, the chemopreventive potential of pterostilbene to prevent carcinogen-induced preneoplastic lesions turned out to be comparable to that of resveratrol [23].

When pterostilbene and resveratrol were compared for their chemopreventive properties in a multistage mouse skin carcinogenesis model using 12-O-tetradecanoylphorbol-13-acetate (TPA) as tumor promoter; however, pterostilbene was either equally or considerably more potent than resveratrol in suppressing the TPA-induced activation of NF- κ B and activator protein-1 (AP-1) and the upregulation of COX-2 and iNOS in the mouse epidermis [24]. This higher biological activity of pterostilbene might be related to its better bioavailability because the substitution of hydroxy with methoxy groups increases the lipophilicity of pterostilbene [24].

Assessment of the chemopreventive potential of pterostilbene in a colon carcinogenesis model in rats based on azoxymethane injection revealed that the administration of pterostilbene markedly suppressed azoxymethane-induced formation of aberrant crypt foci and azoxymethane-induced proliferation of colonic cells and iNOS expression [25]. In the same model, long-term continuous dietary intake of pterostilbene for 45 weeks resulted in suppression of colon tumorigenesis, which was accompanied by reduced cell proliferation and downregulation of inflammatory

**FIGURE 1**

Structure of selected resveratrol derivatives. **(a)** Methoxylated derivatives of resveratrol. **(b)** Hydroxylated derivatives of resveratrol. **(c)** Resveratrol and miscellaneous derivatives.

markers [26]. *In vivo*, animals that were fed with pterostilbene showed decreased colon tumor multiplicity, downregulation of proliferating cell nuclear antigen expression and decreased expression of components of the Wnt pathway, which is deregulated by mutations in the majority of colorectal cancers [26]. In addition, nuclear levels of phospho-p65 (a marker of NF- κ B activity) were reduced, accompanied by suppression of pro-inflammatory cytokines (i.e. TNF- α , IL-1 β and IL-4) [26]. Similarly, pterostilbene reduced expression of β -catenin, cyclin D1 and c-MYC and inhibited the phosphorylation of p65 *in vitro* in the human colon carcinoma cell line HT-29 [26].

Because chronic inflammation is implicated in several pathologic conditions in humans, including cancers of the colon, it has been discussed whether the anti-inflammatory property of pterostilbene contributes to its chemopreventive activity in colon

cancer. Recently, the p38 mitogen-activated protein kinase (p38 MAPK) cascade has been identified as a central signal transduction pathway for mediating the anti-inflammatory action of pterostilbene in colon cancer cells [27]. Pterostilbene reduced the cytokine-induced expression of iNOS and COX-2 and downregulated mRNA levels of pro-inflammatory cytokines, such as TNF- α , IL-1 β and IL-6, in HT-29 colon cancer cells [27]. Of note, pterostilbene showed a higher anti-inflammatory activity than resveratrol [27], which might be explained by structural differences. Accordingly, pterostilbene comprises two methoxy groups and one hydroxyl group, resulting in a better cellular uptake because of improved lipophilicity compared to resveratrol, which harbors trihydroxy groups. In that study, pterostilbene also reduced cell proliferation, which was associated with downregulation of c-Myc and cyclin D1 expression, and induced apoptosis, as evident from increased

levels of cleaved poly(ADP-ribose) polymerase [27]. Together, these studies underscore the potential use of pterostilbene for the prevention of colon cancer.

Anti-invasive and antimetastatic activities of pterostilbene

Among its diverse pharmacologic activities, pterostilbene has also been reported to exert anti-invasive and antimetastatic functions. In a model of invasive breast carcinoma caused by overexpression of human epidermal growth factor receptor (HER)2, pterostilbene reverted the aggressive and highly invasive phenotype [28]. Using heregulin-beta1 (HRG- β 1), a ligand for HER3, to stimulate HER2 signaling, the authors demonstrated that pterostilbene suppressed HRG- β 1-mediated cell growth, motility and cell invasion of MCF7 breast carcinoma cells [28]. Signal transduction studies showed that this anti-invasive activity of pterostilbene involved suppression of HRG- β 1-driven matrix metalloproteinase-9 (MMP-9) expression and phosphorylation of Akt and p38 MAPK [28]. These properties probably contribute to the cancer chemopreventive activity of pterostilbene.

Also in hepatocellular carcinoma, pterostilbene has been reported to function as an anti-invasive and antimetastatic agent [29]. Here, pterostilbene considerably suppressed TPA-induced invasion and migration of human HepG2 hepatoma cells *in vitro* [29]. Importantly, systemic administration of pterostilbene markedly reduced the number of lung metastases in an *in vivo* metastasis model of hepatocellular carcinoma [29]. Mechanistic studies revealed that pterostilbene blocked the TPA-stimulated activation of ERK1/2, p38 MAPK, JNK1/2, PI3K/Akt and PI3K/PKC and inhibited the TPA-triggered activation of NF- κ B and AP-1 and the subsequent increase in MMP-9 expression and enzyme activity and the expression of VEGF, EGF and EGFR [29].

In breast and prostate cancer cell lines, the anti-invasive and antimetastatic activity of pterostilbene has been linked to suppression of MMP-9 and alpha-methylacyl-CoA racemase, two very well known invasion and metastasis inducers [30,31].

Trimethoxystilbene

In several studies, *trans*-3,4',5-trimethoxystilbene (Fig. 1a) turned out to be the most potent proapoptotic analog of resveratrol [11,32,33]. In lung carcinoma cell lines, *trans*-3,4',5-trimethoxystilbene induced apoptosis via reduction of mitochondrial membrane potential, an increased Bax/Bcl-2 ratio, activation of caspase-9 and -3 and subsequent cleavage of poly(ADP-ribose) polymerase [34]. By contrast, Stivala *et al.* reported that resveratrol exerts stronger antioxidant effects than *trans*-3,4',5-trimethoxystilbene [8].

Concerning its antiangiogenic activity, *trans*-3,4',5-trimethoxystilbene proved to be considerably more potent in inhibiting angiogenesis than resveratrol [35]. In general, two major mechanisms are involved in the regulation of neovascularization in neoplasia: first, blockade of neovascularization by antiangiogenic compounds, and second, immature vessel disruption by vascular-targeting agents. In a zebrafish model, *trans*-3,4',5-trimethoxystilbene caused intersegmental vessel regression, which was associated with downregulation of VEGFR2 mRNA expression and G2/M cell-cycle arrest (i.e. in endothelial cells of zebrafish embryos) [35]. Belleri *et al.* [36] reported that the antiangiogenic

and vascular-targeting activity of 3,4',5-trimethoxystilbene was up to 100 times more potent than the parent compound resveratrol, as determined by endothelial cell proliferation, sprouting, collagen gel invasion and morphogenesis. 3,4',5-Trimethoxystilbene also acted as a vascular-targeting agent by causing microtubule disassembling and tubulin depolymerization [36]. In addition, 3,4',5-trimethoxystilbene interfered with the microtubule organization center and with endothelial cell migration [36]. *In vivo*, 3,4',5-trimethoxystilbene caused rapid stasis of blood flow and regression of intersegmental vessels in the trunk of zebrafish embryos [36]. It also inhibited blood vessel growth and caused the disappearance of pre-existing blood vessels in the area vasculosa of the chick embryo [36]. Thus, resveratrol derivatives exhibit both antiangiogenic and vessel-disrupting properties.

Moreover, 3,4',5-trimethoxy-*trans*-stilbene inhibits invasion of lung carcinoma cells by suppressing phosphorylation of JNK and p38 [37]. In addition, 3,4',5-trimethoxy-*trans*-stilbene reduced nuclear levels of two transcription factors that have been implicated to promote invasion (i.e. NF- κ B and AP-1), which, in turn, resulted in downregulation of MMP-2 expression [37]. Both 3,4',5-trimethoxy-*trans*-stilbene and resveratrol inhibited the migratory and invasive properties of HepG2 and Hep3B hepatocellular carcinoma cells upon exposure to phorbol 12-myristate 13-acetate [38]. This anti-invasive effect was accompanied by a decrease in MMP-9 and MMP-2 activity, whereas TIMP-1 and TIMP-2 protein expression increased [38].

Tetramethoxy-*trans*-stilbene

In addition to 3,4',5-trimethoxystilbene, 3,4,5,4'-tetramethoxy-*trans*-stilbene (Fig. 1a) turned out to be much more potent than resveratrol in inhibiting the growth of cancer cell lines, such as colon, prostate, hepatocellular and ovarian cancer cells [39–42]. This was accompanied by cell-cycle arrest at G2/M-phase [39]. In addition, 3,4,5,4'-tetramethoxy-*trans*-stilbene induced apoptosis, which was associated with characteristic DNA laddering, p53 accumulation, an increase in Bax protein level and an elevated Bax/Bcl-2 mRNA ratio, perinuclear clustering of mitochondria, and caspase activation [41]. By contrast, 3,4,5,4'-tetramethoxy-*trans*-stilbene had little effect on proliferation or apoptosis of normal cells, indicating that 3,4,5,4'-tetramethoxy-*trans*-stilbene selectively affects transformed compared to nontransformed cells [41].

Analysis of *cis*-isomers of various *trans*-stilbene derivatives to explore structure–activity relationship revealed that the *cis* isoform of 3,4,5,4'-tetramethoxystilbene (i.e. 3,4,5,4'-tetramethoxy-*cis*-stilbene) was approximately ten times more potent than the *trans* isoform to suppress the growth of human WI38VA virally transformed fibroblasts [43]. 3,4,5,4'-Tetramethoxy-*cis*-stilbene rapidly caused perinuclear mitochondrial clustering accompanied by membrane permeability transition, release of cytochrome *c* into the cytosol and DNA fragmentation similar to the *trans* isoform, indicating that both isomers might share a common mechanism of action [43]. Functional studies using isogenic colorectal carcinoma cells proficient or deficient in p53 demonstrated that the mitochondrial clustering and cell death occurred in a p53-independent manner [43].

Pharmacokinetic studies in mice revealed that higher levels of 3,4,5,4'-tetramethoxy-*trans*-stilbene compared to resveratrol were

achieved in the gastrointestinal tract [40]. However, comparison of the ability of 3,4,5,4'-tetramethoxy-*trans*-stilbene and resveratrol to prevent adenoma development in the Apc(Min+) mouse showed similar efficacy of both compounds [40].

Similarly, 3,3',4,5'-tetramethoxy-*trans*-stilbene was found in another study to be a potent inducer of apoptosis and to cause cell-cycle arrest at G0/G1 phase [44]. Side-by-side comparison showed that 3,3',4,5'-tetramethoxy-*trans*-stilbene displayed an intermediate activity to inhibit growth and to induce apoptosis between resveratrol and 3,5,4'-trimethoxy-*trans*-stilbene, which exhibited lower and higher potency, respectively, compared to 3,3',4,5'-tetramethoxy-*trans*-stilbene [44].

In addition, 3,5,2',4'-tetramethoxy-*trans*-stilbene was reported to exhibit a much higher cytotoxicity than resveratrol against colon and non-small cell lung carcinoma cells, and this cytotoxicity was associated with the induction of apoptotic DNA fragmentation [9,45].

Pentamethoxystilbene

3,5,3',4',5'-Pentamethoxystilbene (Fig. 1a), a synthetically methoxylated analog of resveratrol, has been reported to exert more potent inhibition of cell growth than resveratrol and other methoxylated derivatives in the human breast carcinoma cell line MCF7 [46]. 3,5,3',4',5'-Pentamethoxystilbene triggers G1 cell-cycle arrest, which was associated with suppression of G1 cell-cycle regulatory proteins [46]. Accordingly, expression levels of cyclins (i.e. cyclin D1, D3 and E) and cyclin-dependent kinases (i.e. CDK2, 4 and 6) decreased and CDK4 kinase activity was inhibited [46]. Vice versa, expression of CDK inhibitors such as p15, p16, p21 and p27, increased [46]. All these changes in G1 cell-cycle regulatory proteins are in line with inhibition of G1/S transition by 3,5,3',4',5'-pentamethoxystilbene [46]. In addition, 3,5,3',4',5'-pentamethoxystilbene reduced the phosphorylation and, thus, activation of several kinases that promote cell-cycle progression such as Akt, mitogen-activated protein kinase (ERK1/2) and focal adhesion kinase [46]. By comparison, phosphorylation of p38 MAPK increased upon exposure to 3,5,3',4',5'-pentamethoxystilbene, consistent with the role of p38 MAPK in the regulation of apoptosis [46].

2,3',4,4',5'-Pentamethoxy-*trans*-stilbene was reported to be a potent and selective inhibitor of human cytochrome P-450 1A1 [47]. This activity is considered to contribute to its chemopreventive activity because cytochrome P-450 1A1 is one of the most important enzymes involved in tumor initiation. In addition, 2,3',4,4',5'-pentamethoxy-*trans*-stilbene displayed a more potent *in vitro* antimutagenic effect on colon cancer cells than its parental compounds [48]. 2,3',4,4',5'-Pentamethoxy-*trans*-stilbene caused polymerization of microtubules and G(2)/M mitotic arrest, which resulted in caspase-dependent apoptosis [48]. In addition, 2,3',4,4',5'-pentamethoxy-*trans*-stilbene inhibited tumor growth *in vivo* in a colon cancer xenograft model [48].

N-Hydroxy-N'-(3,4,5-trimethoxyphenyl)-3,4,5-trimethoxybenzamide

N-Hydroxy-N'-(3,4,5-trimethoxyphenyl)-3,4,5-trimethoxybenzamide (KITC) (Fig. 1a) is another polymethoxylated resveratrol analog that exerted considerable antitumor activity, for example against HL-60 human promyelocytic leukemia cells and pancreatic

cancer cells [49,50]. In the promyelocytic leukemia cell line HL-60, KITC caused a dose-dependent induction of apoptosis, and no substantial alterations in the cell-cycle distribution were found [50]. In addition, KITC inhibited the activity of ribonucleotide reductase, a key enzyme of *de novo* DNA synthesis, resulting in the depletion of the intracellular pool of ribonucleotides [50]. In addition, KITC acted in concert with anticancer agents that interfere with DNA synthesis (e.g. the antimetabolite cytosine arabinoside that mimics the structure of metabolic pyrimidines) [50]. Furthermore, KITC arrested pancreatic cancer cells in the G0/G1 phase and induced dose-dependent apoptosis [49]. KITC also markedly reduced ribonucleotide reductase activity, as determined by *in situ* measurement of enzyme activity [49]. Like promyelocytic leukemia cells, KITC synergistically cooperated to inhibit clonogenic growth in combination with cytotoxic drugs that interfere with DNA synthesis (e.g. the pyrimidine analog gemcitabine) [49].

Hydroxylated resveratrol analogs

Structure-activity studies suggested that the 4-hydroxy group in the *trans* conformation on 4- and 4'-positions of the stilbenic backbone was essential for the antiproliferative effect of resveratrol [8,51].

Dihydroxystilbenes

To increase the growth inhibitory potential of resveratrol, the resveratrol analog 4,4'-dihydroxy-*trans*-stilbene (Fig. 1b), which contains two OH in 4' and 4-positions, was synthesized (Table 1). 4,4'-Dihydroxy-*trans*-stilbene inhibited clonogenicity of fibroblasts considerably more than resveratrol [52]. Studies into the underlying mechanism revealed that 4,4'-dihydroxy-*trans*-stilbene induced a G1-phase arrest, which was associated with increased levels of p21 and p53 protein [52]. In comparison, resveratrol blocked the G1/S-phase transition and triggered the phosphorylation of Chk, an S-phase checkpoint protein [52]. Furthermore, several dihydroxystilbene analogs of resveratrol (i.e. 2,3-, 3,4- and 4,4'-dihydroxystilbene) suppressed tumor growth and inhibited tumor-induced neovascularization by interfering with VEGF-induced endothelial cell migration and angiogenesis in colon carcinoma [53].

Resveratrol is classified as a phytoestrogen because of its ability to bind to estrogen receptors. Structure-activity relationships studies of resveratrol and its analogs in estrogen-sensitive breast carcinoma cells revealed that even little changes in the structure of resveratrol derivatives resulted in distinct binding properties to estrogen receptor alpha. 3,4'-Dihydroxystilbene, 4,4'-dihydroxystilbene, 4-hydroxystilbene and resveratrol bond to estrogen receptor alpha with decreasing activities, whereas 3,5-dihydroxystilbene did not display any binding activity [54]. These different binding properties to estrogen receptor alpha directly translated into differential biological responses of these resveratrol analogs (i.e. growth stimulation in estrogen-sensitive breast cancer cells) [54]. Furthermore, 4,4'-dihydroxy-*trans*-stilbene was reported to exhibit higher antioxidant and cytotoxic activity than resveratrol against HL-60 promyelocytic leukemia cells [55].

Tetrahydroxystilbene

Preferential inhibition of cell growth and induction of apoptosis were also reported for 3,4,5,4'-tetrahydroxy-*trans*-stilbene (Fig. 1b)

in transformed versus nontransformed human cells [56]. By contrast, resveratrol did not exhibit these cancer-cell-selective properties [56]. 3,4,5,4'-Tetrahydroxy-*trans*-stilbene-triggered apoptosis was accompanied by p53 accumulation, upregulation of GADD45 and Bax genes, and suppression of Bcl-2 and Cox-2 [56].

Hexahydroxystilbene

In line with the concept that the introduction of additional hydroxyl groups into the stilbene structure increased the biological activity of resveratrol, 3,3',4,4',5,5'-hexahydroxystilbene (Fig. 1b) showed higher antitumor activity than resveratrol (i.e. better growth inhibition and more potent induction of apoptosis in several human cancer cell lines, e.g. HL-60 promyelocytic leukemia cells and PC-3 and LNCaP prostate carcinoma cells) [39,57]. Treatment with 3,3',4,4',5,5'-hexahydroxystilbene inhibited activation of the transcription factor NF- κ B and caused cell-cycle arrest at S- or G2/M-phases [39,57–59]. In addition, the antiproliferative activity of 3,3',4,4',5,5'-hexahydroxy-*trans*-stilbene has been linked to its effect on the intracellular pool of deoxyribonucleoside triphosphates. To this end, 3,3',4,4',5,5'-hexahydroxystilbene was reported to cause a dysbalance of intracellular deoxyribonucleoside triphosphates, similar to the inhibition of ribonucleotide reductase, one of the key enzymes in DNA synthesis, with profound suppression of the dATP pool and an increase in the dCTP and dTTP pools [44]. In human breast cancer cells, 3,3',4,4',5,5'-hexahydroxystilbene-mediated cytotoxicity was associated with the inhibition of cell proliferation and clonogenic survival and induction of apoptosis [44,60]. Molecular studies demonstrated that 3,3',4,4',5,5'-hexahydroxystilbene triggered p53 accumulation, loss of mitochondrial potential and caspase activation [44,60]. In addition, treatment with 3,3',4,4',5,5'-hexahydroxystilbene resulted in changes in intracellular redox profiles with downregulation of mitochondrial superoxide dismutase and loss of reduced glutathione [44,60]. Moreover, 3,3',4,4',5,5'-hexahydroxystilbene markedly suppressed tumor growth in a metastatic melanoma mouse model *in vivo* and also reduced the metastatic spread of melanoma cells *in vivo* [61].

Hydroxylated resveratrol analogs represent a novel class of highly selective COX-2 inhibitors and promising candidates for *in vivo* studies. Docking studies on both COX-1 and COX-2 protein structures revealed that hydroxylated resveratrol analogs (i.e. 3,3',4,4',5,5'-hexahydroxy-*trans*-stilbene and 3,3',4,4',5-tetra-*trans*-hydroxystilbene) are able to bind to the binding sites of the enzymes [44,60]. Of note, this binding of 3,3',4,4',5-tetra-*trans*-hydroxystilbene and 3,3',4,4',5,5'-hexahydroxy-*trans*-stilbene to COX-1 and COX-2 enzymes occurred with a selectivity index, which was in part higher than celecoxib, an established selective COX-2 inhibitor [44,60]. In contrast to hydroxylated analogs of resveratrol, methoxylated derivatives turned out to be poor COX-2 inhibitors with no specificity for COX-2 [44,60].

Furthermore, the presence of *ortho*-dihydroxy structures was reported to increase the antioxidant activities of resveratrol derivatives and to enhance their protective effects against oxidative DNA damage caused by oxygen radicals [62,63]. For example, 3,3',4,4',5,5'-hexahydroxystilbene, 3,3',4,4',5-tetrahydroxystilbene and 3,4,4',5-tetrahydroxystilbene displayed higher antioxidant properties than resveratrol and prevented the incidence of DNA

single-strand breaks upon exposure to hydrogen peroxide in leukemia cell lines [62,63].

Fluorinated resveratrol derivatives

Several fluorinated resveratrol derivatives showed a potency equal to resveratrol, and the fluorinated analog (E)-3,5-difluoro-40-acetoxystilbene displayed an even greater anticancer activity than the parent compound resveratrol [64] (Table 1). In combination studies with the conventional chemotherapeutic drug epirubicin, (E)-3,5-di(trifluoroacetyl-amino)-40-fluorostilbene showed the greatest synergy and the greatest antiproliferative effect [64].

Acetylated resveratrol derivatives

Acetylated derivatives of resveratrol were synthesized to increase cellular uptake. Indeed, resveratrol triacetate displayed a better cellular uptake, although cytostatic and cytotoxic activities of the parental molecule were retained [65] (Table 1). Accordingly, resveratrol triacetate (Fig. 1c) proved to be as efficient as *trans*-resveratrol in inducing cell-cycle arrest at S-phase and enhances 5-fluorouracil-mediated inhibition of proliferation [65].

Digalloylresveratrol

Digalloylresveratrol (Fig. 1c, Table 1), a new synthetic ester of the naturally occurring polyhydroxyphenolic compounds gallic acid and resveratrol, induced apoptosis and inhibited the transition from S to G2/M-phase of the cell-cycle [66]. Simultaneous treatment with digalloylresveratrol and 5-FU cooperated to inhibit the growth of colon cancer cells [66].

Resveratrol methylethers

The chemopreventive action of resveratrol has also been linked to its stilbene backbone, which is responsible for the inhibition of cytochromes P-450 (CYP) family 1 enzymes [67]. Compared to the parental compound, resveratrol methylethers seemed to be specific and potent inhibitors of CYP family 1, which play a crucial part in the activation of procarcinogens. Analysis of a series of 4-thiomethyl-*trans*-stilbene derivatives differing in the number and position of additional methoxy groups instead of hydroxyl groups revealed that 2-methoxy-4'-thiomethyl-*trans*-stilbene and 3-methoxy-4'-thiomethyl-*trans*-stilbene exhibited the most potent and selective inhibitory effect on CYP isozyme activities (i.e. of CYP1A1 and CYP1B1) [67].

The resveratrol analog *trans*-resveratrol trimethylether was compared in one study to other naturally occurring resveratrol derivatives (i.e. pterostilbene, *trans*-pinostilbene and *trans*-desoxyrhapontigenin) using the androgen-responsive human prostate cancer cell line LNCaP [31]. *Trans*-resveratrol trimethylether proved to be the most active compound compared to pterostilbene, *trans*-pinostilbene and *trans*-desoxyrhapontigenin [31]. *Trans*-resveratrol trimethylether triggered cell-cycle arrest at G2/M and induced apoptosis, whereas resveratrol and the other stilbenes caused G1/S arrest [31]. The effects of *trans*-resveratrol trimethylether on cell-cycle progression were associated with upregulation of the cyclin-dependent kinase inhibitor 1A and B mRNA levels [31]. In addition, *trans*-resveratrol trimethylether, but not the other compounds, induced apoptosis [31].

Gloriosaols

Gloriosaols A–C present natural phenolic compounds that are isolated from *Yucca gloriosa* (Agavaceae) and structurally related to resveratrol [68] (Table 1). Gloriosaols demonstrated antiproliferative and proapoptotic activity against both hematological and solid tumor cell lines [68]. Among the three gloriosaols, gloriosaol C turned out to be the most active compound with a higher growth inhibitory activity than resveratrol [68]. Gloriosaol C dose-dependently triggered cell-cycle arrest at G0/G1 phase at lower concentrations and cell death (i.e. apoptosis or necrosis) at higher doses [68].

Bridged stilbene derivatives

Because resveratrol displays non-selective COX-1 and COX-2 inhibition, a series of bridged stilbene derivatives were synthesized to find more selective COX inhibitors (Table 1). Evaluation of phenyl-substituted 1,2-dihydronaphthalene derivatives and ¹H-indene derivatives to inhibit COX-1 and COX-2 enzyme activities *in vitro* showed a high rate of COX-1 inhibition and high selectivity indices [69]. Thus, phenyl-substituted 1,2-dihydronaphthalene derivatives and ¹H-indene derivatives might represent a novel class of highly selective COX-1 inhibitors. In addition, several polyhydroxylated derivatives (i.e. 3,3',4',5-tetrahydroxy-*trans*-stilbene, 3,3',4',5',5'-pentahydroxy-*trans*-stilbene and 3,3',4,4',5,5'-hexahydroxy-*trans*-stilbene) were described to act as potent and selective COX-2 inhibitors [44,60,70].

Mitochondria-targeted resveratrol derivatives

To target resveratrol to mitochondria, the subcellular compartment where its redox properties might be best exploited, resveratrol was linked to membrane-permeable lipophilic cations [71] (Table 1). The cationic charge of such derivatives is expected to drive accumulation of resveratrol into mitochondria because the mitochondrial matrix holds a negative relative charge. Coupling of resveratrol to triphenylphosphonium yielded 4-triphenylphosphoniumbutyl-4'-O-resveratrol iodide and its bis-acetylated derivative, which were found to accumulate into energized mitochondria and which exerted cytotoxic effects on fast-growing but not on slow-growing cells [71]. Thus, mitochondria-targeted

analogs of resveratrol might provide a tool to specifically interfere with cellular redox processes and mitochondrial functions.

Glycosylated resveratrol derivatives

Because plant polyphenols such as resveratrol are important components of the antioxidant and defense systems in plants and, therefore, targets of enzymic oxidation by plant oxidases, the effects of the glycosylation and methylation modification of the parent compound resveratrol have also been examined [72] (Table 1). This analysis revealed that, in particular, glycosylation at the *p*-hydroxy or *m*-hydroxy group by either glucose or methyl confers protection from enzymatic oxidation and extends its half-life in the cell [72]. Thus, glycosylation of resveratrol protects it from enzymatic oxidation, explaining why 5,4'-dihydroxystilbene-3-O-β-D-glucopyranoside, a glycosylated analog of resveratrol, is usually synthesized in nature.

Concluding remarks

Rational drug design of resveratrol derivatives opens new perspectives to selectively exploit the health beneficial properties of this natural compound for the prevention and treatment of human diseases such as cancer. A series of analogs have been generated in recent years, which exhibit increased potency and/or a range of selective activities compared to the parental compound resveratrol. In addition, such analogs might display improved pharmacokinetic properties. Currently, resveratrol is being evaluated in early clinical trials in colon cancer (<http://www.clinicaltrials.gov>). Future insights into the structure–activity relationship of resveratrol and its derivatives are expected to promote the development of this very promising class of natural compounds into cancer therapeutics and their transfer into clinical application.

Acknowledgements

This work has been partly supported by grants from the Deutsche Forschungsgemeinschaft, Deutsche Krebshilfe, Bundesministerium für Bildung und Forschung, Wilhelm-Sander-Stiftung, the Novartis Stiftung für therapeutische Forschung, the European Community (ApopTrain, APO-SYS) and IAP6/18.

References

- Gusman, J. *et al.* (2001) A reappraisal of the potential chemopreventive and chemotherapeutic properties of resveratrol. *Carcinogenesis* 22, 1111–1117
- Pervaiz, S. and Holme, A.L. (2009) Resveratrol: its biologic targets and functional activity. *Antioxid. Redox Signal.* 11, 2851–2897
- Baur, J.A. and Sinclair, D.A. (2006) Therapeutic potential of resveratrol: the *in vivo* evidence. *Nat. Rev. Drug Discov.* 5, 493–506
- Baur, J.A. *et al.* (2006) Resveratrol improves health and survival of mice on a high-calorie diet. *Nature* 444, 337–342
- Haigis, M.C. and Guarente, L.P. (2006) Mammalian sirtuins – emerging roles in physiology, aging, and calorie restriction. *Genes Dev.* 20, 2913–2921
- Howitz, K.T. *et al.* (2003) Small molecule activators of sirtuins extend *Saccharomyces cerevisiae* lifespan. *Nature* 425, 191–196
- Wood, J.G. *et al.* (2004) Sirtuin activators mimic caloric restriction and delay ageing in metazoans. *Nature* 430, 686–689
- Stivala, L.A. *et al.* (2001) Specific structural determinants are responsible for the antioxidant activity and the cell cycle effects of resveratrol. *J. Biol. Chem.* 276, 22586–22594
- Lee, S.K. *et al.* (2003) Synthesis and evaluation of cytotoxicity of stilbene analogues. *Arch. Pharm. Res.* 26, 253–257
- Roberti, M. *et al.* (2003) Synthesis and biological evaluation of resveratrol and analogues as apoptosis-inducing agents. *J. Med. Chem.* 46, 3546–3554
- Cardile, V. *et al.* (2007) Antiproliferative activity of methylated analogues of E- and Z-resveratrol. *Z. Naturforsch. [C]* 62, 189–195
- Rimando, A.M. and Suh, N. (2008) Biological/chemopreventive activity of stilbenes and their effect on colon cancer. *Planta Med.* 74, 1635–1643
- Remsberg, C.M. *et al.* (2008) Pharmacometrics of pterostilbene: preclinical pharmacokinetics and metabolism, anticancer, antiinflammatory, antioxidant and analgesic activity. *Phytother. Res.* 22, 169–179
- Mannal, P.W. *et al.* (2010) Pterostilbene inhibits pancreatic cancer *in vitro*. *J. Gastrointest. Surg.* 14, 873–879
- Alosi, J.A. *et al.* (2010) Pterostilbene inhibits breast cancer *in vitro* through mitochondrial depolarization and induction of caspase-dependent apoptosis. *J. Surg. Res.* 161, 195–201
- Schneider, J.G. *et al.* (2010) Pterostilbene inhibits lung cancer through induction of apoptosis. *J. Surg. Res.* 161, 18–22
- Schneider, J.G. *et al.* (2009) Effects of pterostilbene on melanoma alone and in synergy with inositol hexaphosphate. *Am. J. Surg.* 198, 679–684

- 18 Pan, M.H. *et al.* (2007) Pterostilbene induces apoptosis and cell cycle arrest in human gastric carcinoma cells. *J. Agric. Food Chem.* 55, 7777–7785
- 19 Tolomeo, M. *et al.* (2005) Pterostilbene and 3'-hydroxypterostilbene are effective apoptosis-inducing agents in MDR and BCR-ABL-expressing leukemia cells. *Int. J. Biochem. Cell Biol.* 37, 1709–1726
- 20 Ferrer, P. *et al.* (2007) Nitric oxide mediates natural polyphenol-induced Bcl-2 down-regulation and activation of cell death in metastatic B16 melanoma. *J. Biol. Chem.* 282, 2880–2890
- 21 Priego, S. *et al.* (2008) Natural polyphenols facilitate elimination of HT-29 colorectal cancer xenografts by chemoradiotherapy: a Bcl-2- and superoxide dismutase 2-dependent mechanism. *Mol. Cancer Ther.* 7, 3330–3342
- 22 Pan, Z. *et al.* (2008) Identification of molecular pathways affected by pterostilbene, a natural dimethylether analog of resveratrol. *BMC Med. Genomics* 1, 7
- 23 Rimando, A.M. *et al.* (2002) Cancer chemopreventive and antioxidant activities of pterostilbene, a naturally occurring analogue of resveratrol. *J. Agric. Food Chem.* 50, 3453–3457
- 24 Cichocki, M. *et al.* (2008) Pterostilbene is equally potent as resveratrol in inhibiting 12-O-tetradecanoylphorbol-13-acetate activated NF κ B, AP-1, COX-2, and iNOS in mouse epidermis. *Mol. Nutr. Food Res* 52 (Suppl. 1), S62–S70
- 25 Suh, N. *et al.* (2007) Pterostilbene, an active constituent of blueberries, suppresses aberrant crypt foci formation in the azoxymethane-induced colon carcinogenesis model in rats. *Clin. Cancer Res.* 13, 350–355
- 26 Paul, S. *et al.* (2010) Dietary intake of pterostilbene, a constituent of blueberries, inhibits the β -catenin/p65 downstream signaling pathway and colon carcinogenesis in rats. *Carcinogenesis* 31, 1272–1278
- 27 Paul, S. *et al.* (2009) Anti-inflammatory action of pterostilbene is mediated through the p38 mitogen-activated protein kinase pathway in colon cancer cells. *Cancer Prev. Res. (Phila., PA)* 2, 650–657
- 28 Pan, M.H. *et al.* (2009) Suppression of heregulin- β 1/HER2-modulated invasive and aggressive phenotype of breast carcinoma by pterostilbene via inhibition of matrix metalloproteinase-9, p38 kinase cascade and Akt activation. *Evid-Based Complement. Alternat. Med.* (Epub ahead of print)
- 29 Pan, M.H. *et al.* (2009) Pterostilbene inhibited tumor invasion via suppressing multiple signal transduction pathways in human hepatocellular carcinoma cells. *Carcinogenesis* 30, 1234–1242
- 30 Chakraborty, A. *et al.* (2010) *In vitro* evaluation of the cytotoxic, anti-proliferative and anti-oxidant properties of pterostilbene isolated from *Pterocarpus marsupium*. *Toxicol. In Vitro* 24, 1215–1228
- 31 Wang, T.T. *et al.* (2010) Differential effects of resveratrol and its naturally occurring methylether analogs on cell cycle and apoptosis in human androgen-responsive LNCaP cancer cells. *Mol. Nutr. Food Res.* 54, 335–344
- 32 Pan, M.-H. *et al.* (2008) Antitumor activity of 3,5,4'-trimethoxystilbene in COLO 205 cells and xenografts in SCID mice. *Mol. Carcinog.* 47, 184–196
- 33 Simoni, D. *et al.* (2006) Stilbene-based anticancer agents: resveratrol analogues active toward HL60 leukemic cells with a non-specific phase mechanism. *Bioorg. Med. Chem. Lett.* 16, 3245–3248
- 34 Weng, C.J. *et al.* (2009) Mechanisms of apoptotic effects induced by resveratrol, dibenzoylmethane, and their analogues on human lung carcinoma cells. *J. Agric. Food Chem.* 57, 5235–5243
- 35 Alex, D. *et al.* (2010) Resveratrol derivative, *trans*-3,5,4'-trimethoxystilbene, exerts antiangiogenic and vascular-disrupting effects in zebrafish through the downregulation of VEGFR2 and cell-cycle modulation. *J. Cell. Biochem.* 109, 339–346
- 36 Belleri, M. *et al.* (2005) Antiangiogenic and vascular-targeting activity of the microtubule-destabilizing *trans*-resveratrol derivative 3,5,4'-trimethoxystilbene. *Mol. Pharmacol.* 67, 1451–1459
- 37 Yang, Y.T. *et al.* (2009) Resveratrol analog-3,5,4'-trimethoxy-*trans*-stilbene inhibits invasion of human lung adenocarcinoma cells by suppressing the MAPK pathway and decreasing matrix metalloproteinase-2 expression. *Mol. Nutr. Food Res.* 53, 407–416
- 38 Weng, C.J. *et al.* (2010) Evaluation of anti-invasion effect of resveratrol and related methoxy analogues on human hepatocarcinoma cells. *J. Agric. Food Chem.* 58, 2886–2894
- 39 Horvath, Z. *et al.* (2007) Novel resveratrol derivatives induce apoptosis and cause cell cycle arrest in prostate cancer cell lines. *Anticancer Res.* 27, 3459–3464
- 40 Sale, S. *et al.* (2004) Pharmacokinetics in mice and growth-inhibitory properties of the putative cancer chemopreventive agent resveratrol and the synthetic analogue *trans* 3,4,5,4'-tetramethoxystilbene. *Br. J. Cancer* 90, 736–744
- 41 Gossiau, A. *et al.* (2005) A methoxy derivative of resveratrol analogue selectively induced activation of the mitochondrial apoptotic pathway in transformed fibroblasts. *Br. J. Cancer* 92, 513–521
- 42 Sale, S. *et al.* (2005) Comparison of the effects of the chemopreventive agent resveratrol and its synthetic analog *trans* 3,4,5,4'-tetramethoxystilbene (DMU-212) on adenoma development in the Apc(Min+) mouse and cyclooxygenase-2 in human-derived colon cancer cells. *Int. J. Cancer* 115, 194–201
- 43 Gossiau, A. *et al.* (2008) *Trans*- and *cis*-stilbene polyphenols induced rapid perinuclear mitochondrial clustering and p53-independent apoptosis in cancer cells but not normal cells. *Eur. J. Pharmacol.* 587, 25–34
- 44 Saiko, P. *et al.* (2008) Novel resveratrol analogs induce apoptosis and cause cell cycle arrest in HT29 human colon cancer cells: inhibition of ribonucleotide reductase activity. *Oncol. Rep.* 19, 1621–1626
- 45 Nam, K.A. *et al.* (2001) Resveratrol analog, 3,5,2',4'-tetramethoxy-*trans*-stilbene, potentiates the inhibition of cell growth and induces apoptosis in human cancer cells. *Arch. Pharm. Res.* 24, 441–445
- 46 Pan, M.H. *et al.* (2010) 3,5,3',4',5'-pentamethoxystilbene (MR-5), a synthetically methoxylated analogue of resveratrol, inhibits growth and induces G1 cell cycle arrest of human breast carcinoma MCF-7 cells. *J. Agric. Food Chem.* 58, 226–234
- 47 Lee, S.K. *et al.* (2004) Potent inhibition of recombinant human cytochrome p-450 1A1 by pentamethoxystilbene. *J. Toxicol. Environ. Health A* 67, 1987–2000
- 48 Li, H. *et al.* (2009) 2,3',4,4',5'-Pentamethoxy-*trans*-stilbene, a resveratrol derivative, is a potent inducer of apoptosis in colon cancer cells via targeting microtubules. *Biochem. Pharmacol.* 78, 1224–1232
- 49 Bernhaus, A. *et al.* (2009) Antitumor effects of KITC, a new resveratrol derivative, in AsPC-1 and BxPC-3 human pancreatic carcinoma cells. *Invest. New Drugs* 27, 393–401
- 50 Saiko, P. *et al.* (2007) N-Hydroxy-N'-(3,4,5-trimethoxyphenyl)-3,4,5-trimethoxybenzamidine, a novel resveratrol analog, inhibits ribonucleotide reductase in HL-60 human promyelocytic leukemia cells: synergistic antitumor activity with arabinofuranosylcytosine. *Int. J. Oncol.* 31, 1261–1266
- 51 Larrosa, M. *et al.* (2003) Grape polyphenol resveratrol and the related molecule 4-hydroxystilbene induce growth inhibition, apoptosis, S-phase arrest, and upregulation of cyclins A, E, and B1 in human SK-Mel-28 melanoma cells. *J. Agric. Food Chem.* 51, 4576–4584
- 52 Savio, M. *et al.* (2009) The resveratrol analogue 4,4'-dihydroxy-*trans*-stilbene inhibits cell proliferation with higher efficiency but different mechanism from resveratrol. *Int. J. Biochem. Cell Biol.* 41, 2493–2502
- 53 Kimura, Y. *et al.* (2008) Antitumor activities of synthetic and natural stilbenes through antiangiogenic action. *Cancer Sci.* 99, 2083–2096
- 54 Lappano, R. *et al.* (2009) Structure–activity relationships of resveratrol and derivatives in breast cancer cells. *Mol. Nutr. Food Res.* 53, 845–858
- 55 Fan, G.J. *et al.* (2009) 4,4'-Dihydroxy-*trans*-stilbene, a resveratrol analogue, exhibited enhanced antioxidant activity and cytotoxicity. *Bioorg. Med. Chem.* 17, 2360–2365
- 56 Lu, J. *et al.* (2001) Resveratrol analog, 3,4,5,4'-tetrahydroxystilbene, differentially induces pro-apoptotic p53/Bax gene expression and inhibits the growth of transformed cells but not their normal counterparts. *Carcinogenesis* 22, 321–328
- 57 Horvath, Z. *et al.* (2006) Cytotoxic and biochemical effects of 3,3',4,4',5,5'-hexahydroxystilbene, a novel resveratrol analog in HL-60 human promyelocytic leukemia cells. *Exp. Hematol.* 34, 1377–1384
- 58 Murias, M. *et al.* (2008) Cytotoxic activity of 3,3',4,4',5,5'-hexahydroxystilbene against breast cancer cells is mediated by induction of p53 and downregulation of mitochondrial superoxide dismutase. *Toxicol. In Vitro* 22, 1361–1370
- 59 Saiko, P. *et al.* (2006) Antitumor effects of 3,3',4,4',5,5'-hexahydroxystilbene in HL-60 human promyelocytic leukemia cells. *Nucleosides Nucleotides Nucleic Acids* 25, 1013–1017
- 60 Murias, M. *et al.* (2004) Resveratrol analogues as selective cyclooxygenase-2 inhibitors: synthesis and structure–activity relationship. *Bioorg. Med. Chem.* 12, 5571–5578
- 61 Paulitschke, V. *et al.* (2010) 3,3',4,4',5,5'-Hexahydroxystilbene impairs melanoma progression in a metastatic mouse model. *J. Invest. Dermatol.* 130, 1668–1679
- 62 Ovesna, Z. *et al.* (2006) Antioxidant activity of resveratrol, piceatannol and 3,3',4,4',5,5'-hexahydroxy-*trans*-stilbene in three leukemia cell lines. *Oncol. Rep.* 16, 617–624
- 63 Murias, M. *et al.* (2005) Antioxidant, prooxidant and cytotoxic activity of hydroxylated resveratrol analogues: structure–activity relationship. *Biochem. Pharmacol.* 69, 903–912
- 64 Moran, B.W. *et al.* (2009) Synthesis, structural characterisation and biological evaluation of fluorinated analogues of resveratrol. *Bioorg. Med. Chem.* 17, 4510–4522
- 65 Colin, D. *et al.* (2009) Effects of resveratrol analogs on cell cycle progression, cell cycle associated proteins and 5fluoro-uracil sensitivity in human derived colon cancer cells. *Int. J. Cancer* 124, 2780–2788
- 66 Bernhaus, A. *et al.* (2009) Digalloylresveratrol, a new phenolic acid derivative induces apoptosis and cell cycle arrest in human HT-29 colon cancer cells. *Cancer Lett.* 274, 299–304

- 67 Mikstacka, R. *et al.* (2008) Thiomethylstilbenes as inhibitors of CYP1A1, CYP1A2 and CYP1B1 activities. *Mol. Nutr. Food Res* 52 (Suppl. 1), S77–S83
- 68 Nigro, P. *et al.* (2007) Antiproliferative and pro-apoptotic activity of novel phenolic derivatives of resveratrol. *Life Sci.* 81, 873–883
- 69 Handler, N. *et al.* (2007) 'Bridged' stilbene derivatives as selective cyclooxygenase-1 inhibitors. *Bioorg. Med. Chem.* 15, 6109–6118
- 70 Zykova, T.A. *et al.* (2008) Resveratrol directly targets COX-2 to inhibit carcinogenesis. *Mol. Carcinog.* 47, 797–805
- 71 Biasutto, L. *et al.* (2008) Development of mitochondria-targeted derivatives of resveratrol. *Bioorg. Med. Chem. Lett.* 18, 5594–5597
- 72 Regev-Shoshani, G. *et al.* (2003) Glycosylation of resveratrol protects it from enzymic oxidation. *Biochem. J.* 374, 157–163