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Review

Regulation of signal transduction cascades by Pterostilbenes in different cancers: Is it a death knell for oncogenic pathways

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Abstract: Interdisciplinary research has revolutionized the field of medicine and we have witnessed exponential increase in the high-impact research in past few decades. However, the road to this burgeoning research field is obstacle-ridden because of intratumor heterogeneity, loss of apoptosis and dysregulation of spatio-temporally controlled signaling pathways. Ground-breaking findings obtained through genetic, genomic and proteomic studies have considerably improved our concepts related to the complexity of protein network and excitingly, discovery of miRNAs has added another layer of intricacy to quantitatively regulated gene networks. In this review, we chronicle the milestone achievements and discuss how Pterostilbenes effectively regulated different cellular pathways. We have provided detailed mechanistic insights related to regulation of JAK-STAT signaling, Notch pathway, Wnt mediated intracellular signaling by pterostilbene. Underlying mechanisms about regulation of PI3K/AKT and MAPK pathways by pterostilbene in different cancers. Regulation of Metastasis-associated protein 1 (MTA1) proteins and Human telomerase reverse transcriptase (hTERT) in cancer cells by pterostilbene. Pterostilbene has also been reported to modulate the expression of various oncogenic and tumor suppressor microRNAs in cancer cells. Better and sharper comprehension of the concepts associated with the modes of action of pterostilbene in different cancers will be useful in identification of cancers which can be efficiently targeted by pterostilbene.

Key words: Pterostilbene; Cancer; Signaling; Apoptosis; MicroRNA; TRAIL.

Introduction

Pterostilbene or 3,5-dimethoxy-4′-hydroxystilbene is a phytoalexin and non-flavonoid polyphenol chemical having structural resemblance with resveratrol (3,5,4′-trihydroxystilbene) (1). Lipid soluble nature of Pterostilbene makes it an ideal candidate for evaluation of its efficacy against wide ranging diseases. Pterostilbene exists in cis and trans forms, but trans isomer is most abundantly existing form. Pterostilbene was isolated from heartwood of red sandalwood (*Pterocarpus santalinus*) (2) and later identified in grapevines. Chemical studies have shown many features which make pterostilbene a characteristically unique chemical to overshadow resveratrol in wide ranging pharmacological properties and health promoting effects. Pterostilbene has higher membrane permeability because of its physicochemical properties which include, lipophilicity (cLogP = 4.1) (3), fewer hydrogen bond donors, 4 rotatable bonds and lower polar surface area (38.7°A2). In this review we have attempted to set spotlight on recent advancements in our understanding of the biological activities, molecular effects, and bioavailability of pterostilbene and summarize its potential for the prevention and treatment of different cancers.

We will provide an overview about the cell signaling pathways targeted by pterostilbene in different cancers. We have comprehensively reviewed different signal transduction cascades which are spatio-temporally deregulated in different cancers and how theses pathways are effectively regulated by pterostilbene.

JAK-STAT pathway

Stimulation of MDA-MB-231 cells with leptin at different concentrations (4, 40, and 80 ng/mL) at 48 hours induced an increase in proliferation (4). Pre-treatment with 4, 40, and 80 ng/mL of leptin in combination with 75 µmol/L pterostilbene significantly inhibited leptin-stimulated proliferation of breast cancer cells. Treatment with 25, 50, and 75 µmol/L of pterostilbene markedly reduced constitutive phosphorylation of STAT3 in MDA-MB-231 cells (4). Pterostilbene dose- and time-dependently decreased constitutive STAT3

phosphorylation at 24- and 48-h time points in both PANC-1 and MIA PaCa-2 cells (4). In another study, phosphorylated JAK2 and STAT3 were investigated by western blot analysis in pterostilbene-treated osteosarcoma cells for 24 hours (5). It was found that pterostilbene reduced phosphorylation of these proteins in osteosarcoma cells. Pterostilbene in combination with AG490 (JAK2/STAT3 inhibitor) further inhibited the viability of osteosarcoma cells (5). In the upcoming section we set spotlight on the Notch pathway and how this cascade can be targeted to improve cancer therapy.

Notch pathway

Notch signaling pathway is reportedly involved in cancer development and progression. Data obtained through use of western blot and immunofluorescence assays clearly suggested that Pterostilbene increased the Notch intracellular domain (NICD) levels in A549 cells (6). Increase in the NICD levels markedly enhanced Notch1 signaling as evidenced by an increase in the activity of a downstream target, Hes1. Pterostilbene was noted to increase the expression of Hes1. NICD was produced by proteolytic processing of Notch1 receptor by the gamma secretase complex. Mechanistically, this multi-protein complex was formed by assembly of four subunits (Presenilin-1, presenilin enhancer 2 (Pen-2), Nicastrin and anterior pharynx-defective 1 (Aph-1)) (6). Pterostilbene induced expression of NICD at least partially by increasing the activity of gamma secretase complex. The treatment of A549 cells with Pterostilbene induced the expression of Nicastrin and Presenilin-1. Overall the findings provided evidence that Pterostilbene mediated activation of Notch1 pathway in lung adenocarcinoma cells that consequently resulted in the survival of cancer cells. Therefore use of Notch signaling pathway inhibitors sensitized lung adenocarcinoma cells to Pterostilbene treatment (6). Future studies must converge on effects of pterostilbene on Notch pathway in different other cancer cell lines to see whether or not pterostilbene inhibited Notch pathway to exert its anticancer effects.

Pterostilbene epigenetically inhibited Mastermind-like-2 protein (MAML2) in breast cancer cells which consequently reduced NOTCH signaling activity. MAML2 depletion with siRNA in cancer cells also inhibited Notch pathway (7). Following section is focused on Wnt pathway and how this cascade can be targeted to improve cancer therapy.

Wnt pathway

Pterostilbene was given for 6 or 23 weeks to the mice, intraperitoneally injected with azoxymethane (8). Pterostilbene effectively inhibited azoxymethane mediated formation of adenomas, aberrant crypt foci and promoted transcriptional repression of COX-2 and iNOS mRNA and protein levels in mouse colon stimulated by azoxymethane. Pterostilbene induced apoptosis in mouse colon. Furthermore, pterostilbene administration for 23 weeks significantly repressed azoxymethane -mediated GSK3β phosphorylation and Wnt/β-catenin transduction cascade (8).

Fluorinated N,N-dialkylaminostilbenes reduced nuclear β-catenin levels in treated cells as compared to the cells treated with Dimethyl sulfoxide (DMSO) (9). Significantly higher levels of nuclear β-catenin were still observed in the nuclear extracts of treated cells. Data clearly suggested that modified compound inhibited Wnt pathway through mechanisms other than β-catenin regulation and localization. There was a significant reduction in protein levels of pygopus2 and TCF4 in colorectal cancer cells. Fluorinated N,N-dialkylaminostilbenes markedly reduced tumor growth in mice subcutaneously injected with cancer cells (9).

GSK3β was de-phosphorylated in pterostilbene-treated cancer cells. Growth rate increased considerably in β-catenin mutant expressing cancer cells (10). Data clearly suggested that β-catenin mutant partially rescued the growth-inhibitory effects exerted by pterostilbene (10).

In the next section we will summarize about PI3K/AKT and MAPK pathways and how these pathways can be pharmacologically targeted to improve cancer therapy.

Regulation of PI3K/AKT and MAPK pathways by pterostilbenes

Pterostilbene was found to be effective against different breast cancer (BCa) cell lines and it efficiently arrested BCa cells at the G0/G1 phase (11). More importantly, pterostilbene was a notable apoptosis-inducer in MDA-MB-468 cells. Pterostilbene mediated stronger and sustained activation of extracellular signal-regulated kinase (ERK) ½. Pterostilbene was noted to exert inhibitory effects on phosphorylation of PKB/AKT and mammalian target of rapamycin (mTOR), followed by subsequent BAX upregulation (11).

Tumor-associated extracellular matrix, including fibronectin (FN) and collagen is characterized by the polymerization of fibrillar components on tumor cell surfaces both in suspended and adherent forms (12). During polymerization of FN, disulfide-bonded FN dimer undergoes polymerization into mature polymeric FN (polyFN) through self-assembly that is mediated by other covalent bonds. polyFN is morphologically formed on surfaces of suspended tumor cells as randomly distributed puncta. Assembly of PolyFN on suspended LLC cells was necessary for pulmonary metastases of circulating tumor cells and polyFN depletion on suspended tumor cells may be useful to strategically target metastases. polyFN was important for endothelial DPP IV binding and metastatic spread of suspended LLC cells. Pterostilbene potently depleted suspended tumor cells of polyFN by interfering with FN transportation across cell membrane (12). Pterostilbene inhibited the binding of a soluble DPP IV peptide possessing FN-binding ability to polyFN. Pterostilbene -treatment significantly increased p-AKT levels and simultaneously reduced phosphorylated ERK levels in suspended LLC cells in a dose-dependent manner. Surprisingly, no change was noted in the phosphorylation statuses of p38 and JNK. Data clearly suggested that Pterostilbene -activated PI3K/AKT pathway inhibited phosphorylation of ERK to impair the assembly of polyFN on suspended LLCs (12).

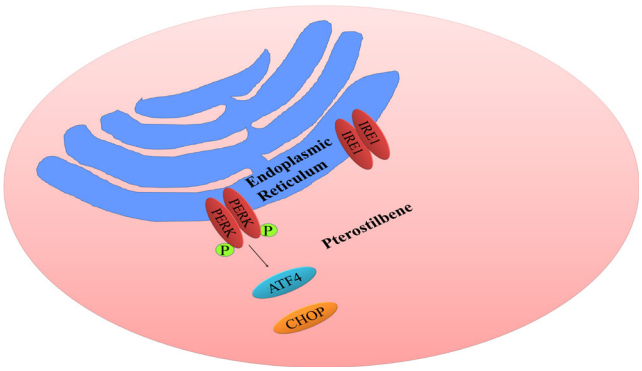

Figure 1. Pterostilbene mediated increase in ER stress associated signaling. Pterostilbene p-PERK, ATF4, CHOP and IRE1.

Regulation of MTA proteins

Metastasis-associated protein 1 (MTA1) alongwith the HDAC1 and HDAC2 played important role in post-translational modification of different proteins particularly p53 (13). Pterostilbene dose-dependently downregulated MTA1 mRNA in SMMC7721 cells and elevated both total and acetylated levels of p53 (13).

There was a marked reduction in tumor growth at week 5 post-transplantation in mice xenografted with MTA1 silenced Du145 cells (14). Furthermore, tumor inhibitory response in MTA1-knockdown tumors treated with resveratrol or pterostilbene became highly significant (resveratrol ($p=0.001$) and pterostilbene ($p=0.0004$). MTA1shRNA tumors treated with resveratrol or pterostilbene did not develop any kidney metastasis or smaller lesions in any kidney. Findings revealed that inhibition of metastasis in response to MTA1-targeted agents and MTA1 inhibition clearly suggested that MTA1 contributed to local invasion, dissemination and metastases (14).

It has recently been persuasively revealed that Phosphatase and tensin homolog (PTEN) loss and MTA1 upregulation worked with effective synergy and significantly promoted prostate cancer development and progression (15). $Pten^{f/f}$ mice treated with pterostilbene exhibited a significant and an age-dependent increase in cleaved caspase-3 what was suggestive of prolonged treatment benefits. Pterostilbene supplementations or daily injections of pterostilbene in $Pten^{+/f}$ and $Pten^{f/f}$ immune-competent mice considerably downregulated MTA1 levels and exerted inhibitory effects on MTA1 tumor-promoting signaling proteins (15).

Regulation of human telomerase reverse transcriptase (hTERT)

Pterostilbene time- and dose-dependently inhibited cellular proliferation of MCF-7 and MDA-MB-231 breast cancer cells (16). Pterostilbene dose-dependently arrested MCF-7 and MDA-231 cells in G1 and G2/M phase. Pterostilbene downregulated Human telomerase reverse transcriptase (hTERT) in breast cancer cells. Pterostilbene dose-dependently reduced activity levels of telomerase with remarkable reductions noted at 7.5 and 10 µM (16).

Telomerase inhibition promoted DNA damage response, activation of the intra-S-phase checkpoint, senescence and replication fork stalling (17). There are direct pieces of evidence which shed light on DNA damage induced signaling pathway in cells following hTERT inhibition using a comet assay. Significantly enhanced DNA strand breaks were noted in pterostilbene-treated H460 cells. Overexpression of hTERT rescued pterostilbene-induced DNA damage and senescence in hTERT-overexpressing H460 cells (17). Therefore, pterostilbene may be considered a good weapon against lung cancer through the induction of senescence via hTERT downregulation.

Following section is strictly focused on endoplasmic reticulum stress and different pathways which are ″switched on″ in cancer cells after treatment with pterostilbene.

Endoplasmic reticulum stress

Pterostilbene dose-dependently enhanced the expression of p-PERK, ATF4, CHOP and IRE1 in both NSCLC cell lines (shown in figure 1) (18). Pterostilbene concentration-dependently triggered accumulation of autophagy-related protein LC3BII protein in NSCLC cells. Pterostilbene (50 mg/kg) or Thapsigargin, an ER stress inducer (1 mg/kg) upregulated ER stress signaling molecules (CHOP and p-PERK) in mice xenografted with cancer cells (18).

Pterostilbene induced an increase in GRP78 and CHOP in HeLa cells. Thapsigargin enhanced Pterostilbene-mediated ER stress and nuclear factor erythroid 2-related factor-2 (Nrf2) phosphorylation levels (19). However, N-acetyl-l-cysteine (NAC) reduced Pterostilbene-modulated ER stress which consequently resulted in decrease in the levels of PERK and Nrf2 phosphorylation (19).

After an overview of the ER stress pathway, we focus our attention on the available data related to oncogenic and tumor suppressor microRNAs and how different miRNAs are controlled by pterostilbene.

Regulation of MicroRNAs by pterostilbene

Binding of BCL-G/BCL2L14 to p53 binding sites have previously been reported to contribute significantly to p53-induced apoptotic cell death. BCL-G/BCL2L14 also binds to Bcl-X(L) (anti-apoptotic protein) via its BH3 domain (shown in figure 2) (20). miR-663b directly targeted BCL2L14 and repressed apoptosis. Expectedly,

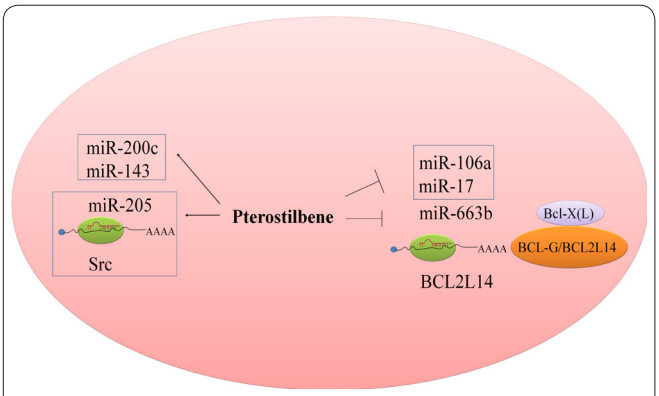

Figure 2. Pterostilbene mediated regulation of oncogenic and tumor suppressor microRNAs. Pterostilbene upregulated miR-200c, miR-143 and miR-205. Pterostilbene downregulated miR-17, miR-106a and miR-663b.

there was a dramatic increase in proliferation rates of Ishikawa and HTB-111 cells transfected with siRNA-BCL2L14 and miR-663b mimics. miR-663b was found to be downregulated but its target BCL2L14 increased significantly in pterostilbene treated endometrial cancer cells (20).

miR-205, a tumor suppressor miRNA directly targeted Src in breast cancer cells (21). miR-205 overexpression dramatically suppressed mRNA expression of Src in MDA-MB-231 (42%) and Hs578t (38%) cells. miR-205 was found to be upregulated in pterostilbene-treated Hs578t and MDA-MB-231 cells. Pterostilbene also significantly reduced Src mRNA expression in breast cancer cells (shown in figure 2) (21). It was suggested that pterostilbene upregulated miR-205 to negatively regulate Src in breast cancer cells.

Introduction of miR-205 mimics in GBM8401 cells induced an increase in miR-205 level that consequently reduced expression of GRP78, c-Myc, vimentin and β-catenin (22). Moreover, immunofluorescence analyses revealed that treatment of GBM8401 cells with either miR-205 mimics or pterostilbene resulted in suppression of GRP78 and c-Myc. More importantly, combinatorial treatment of GBM8401 cells with miR-205 mimics and pterostilbene exerted significantly higher anticancer effects (22).

It has previously been convincingly revealed that levels of tumor suppressor miRNAs (miR-200c and miR-143) (shown in figure 2) and Argonaute-2 were considerably higher in MDA-MB-231-luc-D3H2LN cells treated with pterostilbene (23).

Pterostilbene markedly inhibited miR-106a, miR-106b, miR-17 and miR-20a in PTEN expressing 22Rv1 and DU145 prostate cancer cells (24). DU145-Luc cells that stably overexpressed miRNA-17/106a were used to study pterostilbene mediated molecular effects. Stable overexpression of miRNA-17/106a markedly downregulated protein and mRNA levels of PTEN. Moreover, Pterostilbene impressively suppressed ectopically expressed oncogenic miRNAs that consequently resulted in rescue of PTEN. DU145-Luc EV and miR-17/106a overexpressing cells were implanted into flanks (right) of mice. Pterostilbene induced regression of tumor in mice xenografted with miR-17/106a overexpressing cancer cells. Pterostilbene downregulated miR-106a and miR-17 effectively in mice inoculated with miR-17/106a overexpressing cancer cells (24).

It has been well established that different sub-populations of activated macrophages are present within tumor micro-environment (25). Pterostilbene concentration- dependently reduced percentage of TAM-co-cultured MDA-MB-321 CD44+/CD24− cells. MCF7 cells (lower metastatic potential) had approximately two-fold higher miRNA-448 as compared to M2 TAM-co-cultured counter-parts. Relatively lower miRNA-448 was noted in MDA-MB-231 cells (highly metastatic cells). Pterostilbene induced an increase in miRNA-448 in M2 TAM-co-cultured MCF7 cells. Furthermore, 2.5-fold increase in miR-488 was calculated in pterostilbene-treated M2 TAM-co-cultured MDA-MB-231 cells (25).

TRAIL mediated intracellular signaling has gained overwhelming attention and many TRAIL-based therapeutics and death receptor targeting antibodies have entered into various phases of clinical trials. It is one of the hottest topics in molecular oncology but unfortunately we do not see sufficient experimental evidence related to pterostilbene mediated regulation of death receptors in TRAIL-resistant cancer cells and whether or not pterostilbene holds potential as a powerful TRAIL sensitizer in different cancers. However, we have recently seen that certain hints point towards role of pterostilbene as a TRAIL sensitizer. Following section exclusively summarizes the findings of that report.

Regulation of TRAIL mediated signaling in cancer cells

It has recently been convincingly demonstrated that pterostilbene triggered upregulation of death receptors (DR4 and DR5) (shown in figure 3) and markedly reduced decoy receptors (DcR1 and DcR2) in cancer cells (26). Pterostilbene was noted to inhibit anti-apoptotic proteins c-FLIPS/L, Survivin, X-linked inhibitor of apoptotic protein (XIAP), Bcl-2 and Bcl-XL. Pterostilbene modulated proteolytic processing of bid protein and enhanced the expression of pro-apoptotic proteins particularly, Bax. Furthermore, pterostilbene considerably enhanced DR4 and DR5 through the reactive oxygen species (ROS)-induced activation of p38MAPK and ERK 1/2. Pterostilbene was also an inducer of ER stress and C/EBP-homologous protein (CHOP)-mediated upregulation of DR4 and DR5 (26).

Pharmacokinetic studies

Pterostilbene is structurally different from resveratrol and contains one hydroxyl group and two methoxy groups while resveratrol has three hydroxyl groups. These 2 methoxy groups make pterostilbene more lipophilic, which consequently results in an increase in oral absorption and a higher cellular uptake. Pterostilbene had a higher half-life (105 minutes) and orally higher bioavailability (80%).

Open-label trial was conducted for shorter time-span in 13 healthy volunteers and activity of pterostilbene-rich extracts (*Pterocarpus marsupium*) was monitored (27). Pterostilbene was found to be safer for human use at doses upto 250 mg/day. More importantly, Pteros-

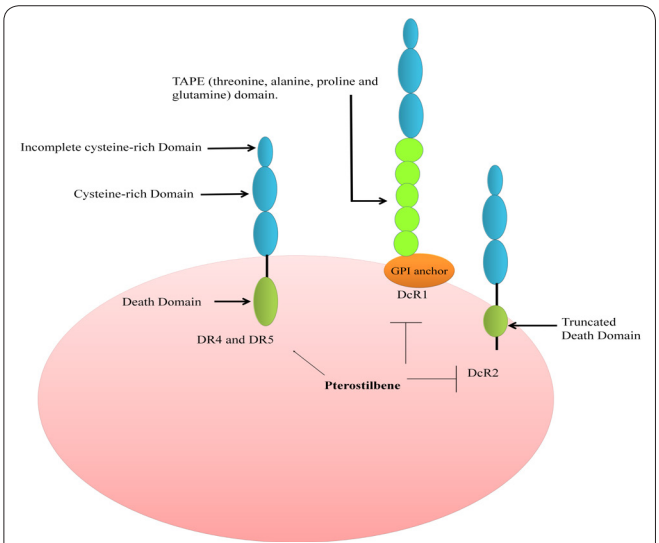

Figure 3. Pterostilbene mediated upregulation of TRAIL receptors (DR4 and DR5) and downregulation of decoy receptors.

tilbene was recorded to be well-tolerated without any adverse drug reactions at a twice a day dosing frequency (27).

Formulation of a phosphate derivative of pterostilbene was noted to be worthwhile strategy to overcome the low water solubility and for detailed analysis of tumor growth inhibitory effects in xenografted mice (28).

Pharmacokinetically, Pterostilbene was observed to be better than resveratrol. Sprague–Dawley rats were intravenously or orally administered with pterostilbene (29). Results revealed that both terminal elimination half-life (96.6 +/- 23.7 min) and clearance (37.0 +/- 2.5 mL/min/kg) were good and its absolute oral bioavailability was 12.5 +/- 4.7% (29).

Preclinical studies

Pterostilbene remarkably inhibited growth of the tumors in nude mice xenografted with MDA-MB-468 cells (11). Tumor growth inhibitory activities of pterostilbene and/or megestrol acetate (Megace) were evaluated in mice implanted subcutaneously with HEC-1A cells in the right flanks (30). Using this method, palpable tumors were typically observed following injection of endometrial cancer cells. Mice were later treated with Megace, pterostilbene and pterostilbene plus Megace via oral gavage. Tumor volume and body weights were recorded 2 times/week. Pterostilbene and Megace synergistically and significantly reduced tumor growth (both tumor weight and volume), whereas decrease in tumor growths for megestrol acetate or pterostilbene alone had been observed to be non-significant (30).

Survival rate was 100 % in pterostilbene treated mice however, in the control group survival rate was 66 % (31). For the mice treated with pterostilbene, calculated growth rate parameters were 0.026 for the 100µg/kilogram/day group, 0.0371 for 1mg/kilogram/day group and 0.0264 for 500µg/kilogram/day group. Orally administered pterostilbene markedly reduced growth of the tumor in the 100- and 500µg/kg/day groups, based on the calculated 95 % confidence interval. Perineural invasion, a hallmark feature was evident at edges of the 500µg/kg treated tumor samples in mice models of pancreatic adenocarcinoma (31).

Concluding remarks

Because of therapeutically challenging nature of cancer, efforts are being made to identify natural products having significant clinical outcome and minimum possible off-target effects. In accordance with this approach, identification of biologically and pharmacologically active molecules is necessary for a detailed analysis of its targets. Pterostilbene has emerged as an important natural product reportedly involved in inhibition of different oncogenic pathways. However, we still have insufficient information related to pterostilbene mediated regulation of TRAIL mediated signaling in different cancers. Although a recent report highlighted that pterostilbene effectively increased expression of TRAIL receptors on cancer cells. Furthermore, TGF/SMAD signaling is also involved in cancer development and progression. However, how pterostilbene modulates SMAD proteins in different cancer cell lines is insufficiently studied. There is no clue related to pterostilbene mediated modulation of Sonic hedgehog signaling pathway.

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