|   | Prevention of Cancer |   | Melanoma |   | Leukemia |   | Stomach Cancer |   | Colorectal Cancer |   | Liver Cancer |   | Breast Cancer |   | Lung Cancer |   | Endometrial Cancer |   | Prostate Cancer |   | Pancreatic Cancer |   | Bladder Cancer |   | Osteosarcoma |   | Oral Cancer |   | Glioma |   | Cancer Stem Cells |   | Antibacterial |   | Activator of SIRT1 |   | Activator of NRF2 |   |
|---|----------------------|---|----------|---|----------|---|-------------|---|----------------|---|--------------|---|-------------|---|------------|---|----------------|---|--------------|---|---------------|---|-------------|---|
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Prevention of Cancer


Cancer chemopreventive and antioxidant activities of pterostilbene, a naturally occurring analogue of resveratrol.

Rimando AM¹, Cuendet M, Desmarchelier C, Mehta RG, Pezzuto JM, Duke SO.

Author information

Abstract

Pterostilbene, a natural methoxylated analogue of resveratrol, was evaluated for antioxidative potential. The peroxyl-radical scavenging activity of pterostilbene was the same as that of resveratrol, having total reactive antioxidant potentials of 237 +/- 58 and 253 +/- 53 microM, respectively. Both compounds were found to be more effective than Trolox as free radical scavengers. Using a plant system, pterostilbene also was shown to be as effective as resveratrol in inhibiting electrolyte leakage caused by herbicide-induced oxidative damage, and both compounds had the same activity as alpha-tocopherol. Pterostilbene showed moderate inhibition (IC50 = 19.8 microM) of cyclooxygenase (COX)-1, and was weakly active (IC50 = 83.9 microM) against COX-2, whereas resveratrol strongly inhibited both isoforms of the enzyme with IC50 values of approximately 1 microM. Using a mouse mammary organ culture model, carcinogen-induced preneoplastic lesions were, similarly to resveratrol, significantly inhibited by pterostilbene (ED50 = 4.8 microM), suggesting antioxidant activity plays an important role in this process.

PMID: 12033810


Pterostilbene, an active constituent of blueberries, suppresses aberrant crypt foci formation in the azoxymethane-induced colon carcinogenesis model in rats.

Suh N¹, Paul S, Hao X, Simi B, Xiao H, Rimando AM, Reddy BS.

Author information
Abstract

PURPOSE:
Epidemiologic studies have linked the consumption of fruits and vegetables to reduced risk of several types of cancer. Laboratory animal model studies have provided evidence that stilbenes, phenolic compounds present in grapes and blueberries, play a role in inhibiting the risk of certain cancers. Pterostilbene, a naturally occurring stilbene from blueberries, was tested for its preventive activity against colon carcinogenesis.

EXPERIMENTAL DESIGN:
Experiments were designed to study the inhibitory effect of pterostilbene against the formation of azoxymethane-induced colonic aberrant crypt foci (ACF) preneoplastic lesions in male F344 rats. Beginning at 7 weeks of age, rats were treated with azoxymethane (15 mg/kg body weight s.c., once weekly for 2 weeks). One day after the second azoxymethane treatment, rats were fed experimental diets containing 0 or 40 ppm of pterostilbene. At 8 weeks after the second azoxymethane treatment, all rats were sacrificed, and colons were evaluated for ACF formation and for inhibition of inducible nitric oxide synthase (iNOS) and proliferating cell nuclear antigen. Effects on mucin MUC2 were also determined.

RESULTS:
Administration of pterostilbene for 8 weeks significantly suppressed azoxymethane-induced formation of ACF (57% inhibition, P < 0.001) and multiple clusters of aberrant crypts (29% inhibition, P < 0.01). Importantly, dietary pterostilbene also suppressed azoxymethane-induced colonic cell proliferation and iNOS expression. Inhibition of iNOS expression by pterostilbene was confirmed in cultured human colon cancer cells.

CONCLUSIONS:
The results of the present study suggest that pterostilbene, a compound present in blueberries, is of great interest for the prevention of colon cancer.

PMID: 17200374

Dietary intake of pterostilbene, a constituent of blueberries, inhibits the beta-catenin/p65 downstream signaling pathway and colon carcinogenesis in rats.

Stilbenes are phytochemicals present in grapes, berries, peanuts and red wine. A widely studied stilbene, resveratrol (trans-3,5,4'-trihydroxystilbene), has been shown to exert antioxidant, anti-inflammatory, chemopreventive and antiaging effects in a number of biological systems. We reported earlier that pterostilbene (trans-3,5-dimethoxy-4'-hydroxystilbene), a structurally related stilbene found in blueberries, was effective in reducing the incidence and multiplicity of aberrant crypt foci formation in the colon of rats injected with azoxymethane (AOM). Our present study was to identify the chemopreventive potential of pterostilbene with colonic tumor formation as an end point and further to evaluate the mechanistic action of pterostilbene during colon carcinogenesis. F344 rats were given two AOM injections subcutaneously when they were 7 and 8 weeks old and continuously fed the control or 40 p.p.m. pterostilbene diet for 45 weeks. Overall analyses indicated that pterostilbene reduced colon tumor multiplicity of non-invasive adenocarcinomas, lowered proliferating cell nuclear antigen and downregulated the expression of beta-catenin and cyclin D1. Pterostilbene decreased mucosal levels of the proinflammatory cytokines, tumor necrosis factor-alpha, interleukin (IL)-1beta and IL-4. Colon tumors from pterostilbene-fed animals showed reduced expression of inflammatory markers as well as nuclear staining for phospho-p65, a key molecule in the nuclear factor-kappaB pathway. In HT-29 cells, pterostilbene reduced the protein levels of beta-catenin, cyclin D1 and c-MYC, altered the cellular localization of beta-catenin and inhibited the phosphorylation of p65. Our data with pterostilbene in suppressing colon tumorigenesis, cell proliferation as well as key inflammatory markers in vivo and in vitro suggest the potential use of pterostilbene for colon cancer prevention.

PMID: 20061362


Pterostilbene inhibits colorectal aberrant crypt foci (ACF) and colon carcinogenesis via suppression of multiple signal transduction pathways in azoxymethane-treated mice.

Chiou YS¹, Tsai ML, Wang YJ, Cheng AC, Lai WM, Badmaev V, Ho CT, Pan MH.

Abstract

Pterostilbene (PS), a natural dimethylated analogue of resveratrol, is known to have diverse pharmacologic activities including anticancer, anti-inflammation, antioxidant, apoptosis, antiproliferation, and analgesic potential. This paper reports the inhibitory effect of dietary administration of pterostilbene against the formation of azoxymethane (AOM)-induced colonic aberrant crypt foci (ACF) preneoplastic lesions and adenomas in male ICR mice and delineates
its possible molecular mechanisms. ICR mice were given two AOM injections intraperitoneal and continuously fed a 50 or 250 ppm pterostilbene diet for 6 or 23 weeks. It was found that the dietary administration of pterostilbene effectively reduced AOM-induced formation of ACF and adenomas and inhibited the transcriptional activation of iNOS and COX-2 mRNA and proteins in mouse colon stimulated by AOM. Treatment with pterostilbene resulted in the induction of apoptosis in mouse colon. Moreover, administration of pterostilbene for 23 weeks significantly suppressed AOM-induced GSK3beta phosphorylation and Wnt/beta-catenin signaling. It was also found that pterostilbene significantly inhibited AOM-induced expression of VEGF, cyclin D1, and MMPs in mouse colon. Furthermore, pterostilbene markedly inhibited AOM-induced activation of Ras, phosphatidylinositol 3 kinase/Akt, and EGFR signaling pathways. All of these results revealed that pterostilbene is an effective antitumor agent as well as its inhibitory effect through the down-regulation of inflammatory iNOS and COX-2 gene expression and up-regulation of apoptosis in mouse colon, suggesting that pterostilbene is a novel functional agent capable of preventing inflammation-associated colon tumorigenesis.

PMID: 20681671


**Pterostilbene is more potent than resveratrol in preventing azoxymethane (AOM)-induced colon tumorigenesis via activation of the NF-E2-related factor 2 (Nrf2)-mediated antioxidant signaling pathway.**

Chiou YS, Tsai ML, Nagabhushanam K, Wang YJ, Wu CH, Ho CT, Pan MH.

**Author information**

**Abstract**

Inflammatory bowel diseases have been a risk factor of colorectal cancer (CRC). The reactive oxygen species (ROS) generated by inflammatory cells create oxidative stress and contribute to neoplastic transformation, proliferation, and even metastasis. Previously, resveratrol (RS) and pterostilbene (PS) had been reported to prevent chemical-induced colon carcinogenesis by anti-inflammatory and pro-apoptotic properties. In this study, we investigated whether RS and PS could prevent the azoxymethane (AOM)-induced colon tumorigenesis via antioxidant action and to explore possible molecular mechanisms. Male BALB/c mice were injected with AOM (5 mg/kg of body weight) with or without RS or PS, and at the end of the protocol, all of the mice were euthanized and colons were analyzed. Administrations of PS can be more effective than RS in reducing AOM-induced formation of aberrant crypt foci (ACF), lymphoid nodules (LN s), and tumors. We also find that PS is functioning more effectively than RS to reduce nuclear factor-κB (NF-κB) activation by inhibiting the phosphorylation of protein kinase C-β2 (PKC-β2) and decreasing downstream target gene expression, including inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), and aldose reductase (AR) in mouse colon stimulated by AOM.
Moreover, administration of RS and PS for 6 weeks significantly enhanced expression of antioxidant enzymes, such as heme oxygenase-1 (HO-1) and glutathione reductase (GR), via activation of NF-E2-related factor 2 (Nrf2) signaling. When the above findings are taken together, they suggest that both stilbenes block cellular inflammation and oxidative stress through induction of HO-1 and GR, thereby preventing AOM-induced colon carcinogenesis. In comparison, PS was a more potent chemopreventive agent than RS for the prevention of colon cancer. This is also the first study to demonstrate that PS is a Nrf2 inducer and AR inhibitor in the AOM-treated colon carcinogenesis model.

PMID: 21355597


**Potential chemoprevention activity of pterostilbene by enhancing the detoxifying enzymes in the HT-29 cell line.**

Harun Z¹, Ghazali AR.

**Author information**

**Abstract**

Detoxifying enzymes are present in most epithelial cells of the human gastrointestinal tract where they protect against xenobiotics which may cause cancer. Induction of examples such as glutathione S-transferase (GST) and its thiol conjugate, glutathione (GSH) as well as NAD(P)H: quinoneoxidoreductase (NQO1) facilitate the excretion of carcinogens and thus preventing colon carcinogenesis. Pterostilbene, an analogue of resveratrol, has demonstrated numerous pharmacological activities linked with chemoprevention. This study was conducted to investigate the potential of pterostilbene as a chemopreventive agent using the HT-29 colon cancer cell line to study the modulation of GST and NQO1 activities as well as the GSH level. Initially, our group, established the optimum dose of 24 hours pterostilbene treatment using MTT assays. Then, effects of pterostilbene (0-50 μM) on GST and NQO1 activity and GSH levels were determined using GST, NQO1 and Ellman assays, respectively. MTT assay of pterostilbene (0-100 μM) showed no cytotoxicity toward the HT-29 cell line. Treatment increased GST activity in the cell line significantly (p<0.05) at 12.5 and 25.0 μM. In addition, treatment at 50 μM increased the GSH level significantly (p<0.05). Pterostilbene also enhanced NQO1 activity significantly (p<0.05) at 12.5 μM and 50 μM. Hence, pterostilbene is a potential chemopreventive agent capable of modulation of detoxifying enzyme levels in HT-29 cells.

PMID: 23464466

Influence of berry polyphenols on receptor signaling and cell-death pathways: implications for breast cancer prevention.

Aiyer HS¹, Warri AM, Woode DR, Hilakivi-Clarke L, Clarke R.

Author information

Abstract

Breast cancer is the most commonly diagnosed cancer among women worldwide. Many women have become more aware of the benefits of increasing fruit consumption, as part of a healthy lifestyle, for the prevention of cancer. The mechanisms by which fruits, including berries, prevent breast cancer can be partially explained by exploring their interactions with pathways known to influence cell proliferation and evasion of cell-death. Two receptor pathways, estrogen receptor (ER) and tyrosine kinase receptors, especially the epidermal growth factor receptor (EGFR) family, are drivers of cell proliferation and play a significant role in the development of both primary and recurrent breast cancer. There is strong evidence to show that several phytochemicals present in berries such as cyanidin, delphinidin, quercetin, kaempferol, ellagic acid, resveratrol, and pterostilbene interact with and alter the effects of these pathways. Furthermore, they also induce cell death (apoptosis and autophagy) via their influence on kinase signaling. This review summarizes in vitro data regarding the interaction of berry polyphenols with the specific receptors and the mechanisms by which they induce cell death. This paper also presents in vivo data of primary breast cancer prevention by individual compounds and whole berries. Finally, a possible role for berries and berry compounds in the prevention of breast cancer and a perspective on the areas that require further research are presented.

PMID: 22300613


Pterostilbene, a natural analogue of resveratrol, potently inhibits 7,12-dimethylbenz[a]anthracene (DMBA)/12-O-tetradecanoylphorbol-13-acetate (TPA)-induced mouse skin carcinogenesis.

Tsai ML¹, Lai CS, Chang YH, Chen WJ, Ho CT, Pan MH.

Author information

Abstract
We reported previously that pterostilbene, a natural analogue of resveratrol from blueberries, strongly suppressed lipopolysaccharide-induced up-expression of inducible NO synthase (iNOS) and cyclooxygenase-2 (COX-2) in murine macrophages. In this study, we further investigated pterostilbene's molecular mechanism of action and its anti-tumor properties. Pretreatment with pterostilbene has resulted in the reduction of 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced nuclear translocation of the nuclear factor-κB (NFκB) subunits. Pterostilbene also reduced TPA-induced phosphorylation of IκBα and p65 and caused subsequent degradation of IκBα. Moreover, pterostilbene markedly suppressed TPA-induced activation of extracellular signal-regulated kinase (ERK)1/2, p38 mitogen-activated protein kinase (MAPK), c-Jun N-terminal kinase (JNK)1/2, phosphatidylinositol 3-kinase (PI3K) and Akt, which are upstream of NFκB and activator protein 1 (AP-1). Furthermore, pterostilbene significantly inhibited 7,12-dimethylbenz[a]anthracene (DMBA)/TPA-induced skin tumor formation measured by the tumor multiplicity of papillomas at 20 weeks. The presented data has, for the first time, revealed that pterostilbene is an effective anti-tumor agent that functions by downregulating inflammatory iNOS and COX-2 gene expression in mouse skin. It is suggested that pterostilbene is a novel functional agent capable of preventing inflammation-associated tumorigenesis.

PMID: 22842666

Chemopreventive effects of pterostilbene on urethane-induced lung carcinogenesis in mice via the inhibition of EGFR-mediated pathways and the induction of apoptosis and autophagy.

Chen RJ¹, Tsai SJ, Ho CT, Pan MH, Ho YS, Wu CH, Wang YJ.

Author information

Abstract

Lung cancer is the most commonly diagnosed cancer and the leading cause of cancer deaths globally. Due to the lack of successful chemopreventive agents for lung cancer, there is an emerging need to evaluate new and effective agents for lung cancer prevention. Pterostilbene, a naturally occurring analogue of resveratrol, has been reported to be an effective chemopreventive agent against many cancers. The aim of this study is to investigate the chemopreventive effects of pterostilbene in urethane-induced murine lung tumors. Pretreatment with pterostilbene at 50 or 250 mg/kg significantly reduced tumor multiplicity by 26 and 49%, respectively. Pterostilbene also significantly inhibited tumor volume by 25 and 34% and decreased the tumor burden per mouse by 45 and 63%, respectively. The mechanisms by which pterostilbene suppresses lung tumorigenesis have been investigated in lung tissues and homogenates. The results indicate that the pterostilbene-mediated chemopreventive effects in vivo were a result of the inhibition of epidermal growth factor receptor (EGFR) and its downstream pathways, leading to retarded cell...
cycle progression, and of the induction of apoptosis and autophagy during urethane-induced lung tumorigenesis.

PMID: 23113763


Topical treatment with pterostilbene, a natural phytoalexin, effectively protects hairless mice against UVB radiation-induced skin damage and carcinogenesis.

Sirerol JA¹, Feddi F², Mena S¹, Rodríguez ML¹, Sirera P¹, Aupí M¹, Pérez S¹, Asensi M³, Ortega A³, Estrela JM⁴.

Author information

Abstract

The aim of our study was to investigate in the SKH-1 hairless mouse model the effect of pterostilbene (Pter), a natural dimethoxy analog of resveratrol (Resv), against procarcinogenic ultraviolet B radiation (UVB)-induced skin damage. Pter prevented acute UVB (360 mJ/cm²)-induced increase in skin fold, thickness, and redness, as well as photoaging-associated skin wrinkling and hyperplasia. Pter, but not Resv, effectively prevented chronic UVB (180 mJ/cm², three doses/week for 6 months)-induced skin carcinogenesis (90% of Pter-treated mice did not develop skin carcinomas, whereas a large number of tumors were observed in all controls). This anticarcinogenic effect was associated with (a) maintenance of skin antioxidant defenses (i.e., glutathione (GSH) levels, catalase, superoxide, and GSH peroxidase activities) close to control values (untreated mice) and (b) an inhibition of UVB-induced oxidative damage (using as biomarkers 8-hydroxy-2'-deoxyguanosine, protein carbonyls, and isoprostanes). The molecular mechanism underlying the photoprotective effect elicited by Pter was further evaluated using HaCaT immortalized human keratinocytes and was shown to involve potential modulation of the Nrf2-dependent antioxidant response.

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KEYWORDS:
Free radicals; Oxidative stress; Photocarcinogenesis; Phytochemicals; Polyphenols; Pterostilbene; Resveratrol; Skin damage; Stilbenes; UV radiation

PMID: 25845487

Enhanced chemoprevention by the combined treatment of pterostilbene and lupeol in B[a]P-induced mouse skin tumorigenesis.

Singh P¹, Arora D¹, Shukla Y².

Author information

Abstract

The present study is aimed to evaluate the inhibitory effect of the combination of two phytochemicals; pterostilbene and lupeol (generally obtained from blue berries, grapes, white cabbage, green pepper, olive and mangoes) on mouse skin tumorigenesis. We hypothesized that the concomitant topical treatment of selected phytochemicals would lead to improved impediment of skin cancer. Swiss albino mice (n = 25) received a topical dose of Benzo[a]pyrene (B[a]P, 5 μg/animal) with pre/post application of pterostilbene (16 μM/0.2 ml acetone/animal) and/or lupeol (500 μM/0.2 ml acetone/animal) for 32 weeks. Results showed that pterostilbene and/or lupeol treatment resulted in a significant delay in onset of tumorigenesis. However, a more promising effect on tumor suppression was noted with the combination of both the phytochemicals. A significant reduction in average tumor volume, cumulative number of tumors and tumor multiplicity was recorded in combination treated group. The histopathological analysis illustrated the marked suppression in epidermal hyperplasia and necrotic cells in combination treated groups. Our study suggests that the combination of pterostilbene and lupeol was more effective in prevention of skin cancer as compared to either of the phytochemical alone. Therefore, the combined treatment of phytochemicals has better potential to prevent skin carcinogenesis.

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KEYWORDS:
Benzo[a]pyrene; Chemoprevention; Lupeol; Phytochemical; Pterostilbene

PMID: 27836749
Association between pterostilbene and quercetin inhibits metastatic activity of B16 melanoma.

Ferrer P¹, Asensi M, Segarra R, Ortega A, Benlloch M, Obrador E, Varea MT, Asensio G, Jordá L, Estrela JM.

Abstract

Inhibition of cancer growth by resveratrol (trans-3,5,4′-trihydroxystilbene; RESV), a phytoalexin present in many plant species, is limited by its low bioavailability. Pterostilbene (3,5-dimethoxy-4′-hydroxystilbene; PTER) and quercetin (3,3′,4′,5,6-pentahydroxyflavone; QUER), two structurally related and naturally occurring small polyphenols, show longer half-life in vivo. In vitro growth of highly malignant B16 melanoma F10 cells (B16M-F10) is inhibited (56%) by short-time exposure (60 min/day) to PTER (40 microm) and QUER (20 microm) (approximate mean values of plasma concentrations measured within the first hour after intravenous administration of 20 mg/kg each polyphenol). Intravenous administration of PTER and QUER (20 mg/kg per day) to mice inhibits (73%) metastatic growth of B16M-F10 cell in the liver, a common site for metastasis development. The anti-metastatic mechanism involves: 1) a PTER-induced inhibition of vascular adhesion molecule 1 expression in the hepatic sinusoidal endothelium, which consequently decreases B16M-F10 cell adhesion to the endothelium through very late activation antigen 4; and 2) a QUER- and PTER-induced inhibition of Bcl-2 expression in metastatic cells, which sensitizes them to vascular endothelium-induced cytotoxicity. Our findings demonstrate that the association of PTER and QUER inhibits metastatic melanoma growth and extends host survival.

PMID: 15736313

Nitric oxide mediates natural polyphenol-induced Bcl-2 down-regulation and activation of cell death in metastatic B16 melanoma.
Abstract

Intravenous administration to mice of trans-pterostilbene (t-PTER; 3,5-dimethoxy-4'-hydroxystilbene) and quercetin (QUER; 3,3',4',5,6-pentahydroxyflavone), two structurally related and naturally occurring small polyphenols, inhibits metastatic growth of highly malignant B16 melanoma F10 (B16M-F10) cells. t-PTER and QUER inhibit bcl-2 expression in metastatic cells, which sensitizes them to vascular endothelium-induced cytotoxicity. However, the molecular mechanism(s) linking polyphenol signaling and bcl-2 expression are unknown. NO is a potential bioregulator of apoptosis with controversial effects on Bcl-2 regulation. Polyphenols may affect NO generation. Short-term exposure (60 min/day) to t-PTER (40 microM) and QUER (20 microM) (approximate mean values of the plasma concentrations measured within the first hour after intravenous administration of 20 mg of each polyphenol/kg) down-regulated inducible NO synthetase in B16M-F10 cells and up-regulated endothelial NO synthetase in the vascular endothelium and thereby facilitated endothelium-induced tumor cytotoxicity. Very low and high NO levels down-regulated bcl-2 expression in B16M-F10 cells. t-PTER and QUER induced a NO shortage-dependent decrease in cAMP-response element-binding protein phosphorylation, a positive regulator of bcl-2 expression, in B16M-F10 cells. On the other hand, during cancer and endothelial cell interaction, t-PTER- and QUER-induced NO release from the vascular endothelium up-regulated neutral sphingomyelinase activity and ceramide generation in B16M-F10 cells. Direct NO-induced cytotoxicity and ceramide-induced mitochondrial permeability transition and apoptosis activation can explain the increased endothelium-induced death of Bcl-2-depleted B16M-F10 cells.

PMID: 17135264


Effects of pterostilbene on melanoma alone and in synergy with inositol hexaphosphate.

Schneider JG, Alosi JA, McDonald DE, McFadden DW.

Author information

Abstract
BACKGROUND:
Pterostilbene and inositol-6-phosphate (IP6) have been shown to inhibit melanoma growth in vitro. However, pterostilbene's mechanism of action has not been clearly demonstrated. We aimed to further investigate the mechanism of action for pterostilbene and to determine whether combination treatment with IP6 produced synergistic growth inhibition.

METHODS:
Melanoma cells were treated with increasing doses of pterostilbene, IP6, or combinations thereof. Cell viability was measured at 24 hours, 48 hours, and 72 hours using a MTT assay. Caspase activity and vascular endothelial growth factor (VEGF) production were measured using enzyme-linked immunosorbent assay (ELISA). Analysis of variance (ANOVA) and t tests were used for statistical analysis.

RESULTS:
Pterostilbene inhibits melanoma growth in vitro in association with increased effector caspase activity. Combination treatment with inositol hexaphosphate produces synergistic growth inhibition, greater than either treatment alone.

CONCLUSIONS:
Pterostilbene produces caspase-dependent apoptosis in melanoma cell lines. Combination treatment with IP6 produces synergistic growth inhibition. Both compounds have significant potential for a therapeutic role in the treatment of melanoma.

PMID: 19887199

Enhanced antitumor efficacy with combined administration of astragalus and pterostilbene for melanoma.

Huang XY¹, Zhang SZ, Wang WX.

Author information

Abstract

Astragalus, a commonly used traditional Chinese medicine, has exhibited antitumor actions in patients. In this study, in vitro and in vivo antitumor effects of astragalus and synergistic antitumor efficacy in combination with pterostilbene were investigated. Melanoma cells were treated with pterostilbene (Pt), graduated doses of astragalus injection (AI), or these in combination. Cell viability was measured using a MTT assay. Released nucleosomes and
caspase activity were measured using enzyme-linked immunosorbent assay. Growth inhibition in vitro and in vivo was also assessed. Analysis of variance and t tests were used for statistical analysis. Significant reduction (p<0.05) in cellular proliferation were observed with AI and AI-Pt in a time- and concentration-dependent manner. Apoptosis and caspase-3/7 activity were significantly increased by AI and AI-Pt treatment (p<0.05). In vivo, AI inhibited melanoma tumor growth, with inhibition rates ranging from 36.5 to 62.3%, by inducing apoptosis via up-regulation Bax expression and the Bax/Bcl-2 ratio and down-regulating Bcl-2 expression. AI significantly inhibits the growth of melanoma in vitro and in vivo by inducing apoptosis. These data suggest that combined treatment of astragalus with pterostilbene enhances antitumor efficacy.

PMID: 24606435


**Pterostilbene Decreases the Antioxidant Defenses of Aggressive Cancer Cells In Vivo: A Physiological Glucocorticoids- and Nrf2-Dependent Mechanism.**

Benlloch M¹, Obrador E², Valles SL², Rodriguez ML², Sirerol JA², Alcácer J³, Pellicer JA², Salvador R², Cerdá C⁴, Sáez GT⁴, Estrela JM².

**Author information**

**Abstract**

**AIMS:** Polyphenolic phytochemicals have anticancer properties. However, in mechanistic studies, lack of correlation with the bioavailable concentrations is a critical issue. Some reports had suggested that these molecules downregulate the stress response, which may affect growth and the antioxidant protection of malignant cells. Initially, we studied this potential underlying mechanism using different human melanomas (with genetic backgrounds correlating with most melanomas), growing in nude mice as xenografts, and pterostilbene (Pter, a natural dimethoxylated analog of resveratrol).
RESULTS:
Intravenous administration of Pter decreased human melanoma growth in vivo. However, Pter, at levels measured within the tumors, did not affect melanoma growth in vitro. Pter inhibited pituitary production of the adrenocorticotropic hormone (ACTH), decreased plasma levels of corticosterone, and thereby downregulated the glucocorticoid receptor- and nuclear factor (erythroid-derived 2)-like 2 (Nrf2)-dependent antioxidant defense system in growing melanomas. Exogenous corticosterone or genetically induced Nrf2 overexpression in melanoma cells prevented the inhibition of tumor growth and decreased antioxidant defenses in these malignant cells. These effects and mechanisms were also found in mice bearing different human pancreatic cancers. Glutathione depletion (selected as an antimelanoma strategy) facilitated the complete elimination by chemotherapy of melanoma cells isolated from mice treated with Pter.

INNOVATION:
Although bioavailability-related limitations may preclude direct anticancer effects in vivo, natural polyphenols may also interfere with the growth and defense of cancer cells by downregulating the pituitary gland-dependent ACTH synthesis.

CONCLUSIONS:
Pter downregulates glucocorticoid production, thus decreasing the glucocorticoid receptor and Nrf2-dependent signaling/transcription and the antioxidant protection of melanoma and pancreatic cancer cells. Antioxid. Redox Signal. 24, 974-990.

PMID: 26651028
Pterostilbene and 3'-hydroxypterostilbene are effective apoptosis-inducing agents in MDR and BCR-ABL-expressing leukemia cells.


Abstract

Pterostilbene and 3,5-hydroxypterostilbene are the natural 3,5-dimethoxy analogs of trans-resveratrol and piceatannol, two compounds which can induce apoptosis in tumor cells. In previous studies we demonstrated the importance of a 3,5-dimethoxy motif in conferring pro-apoptotic activity to stilbene based compounds so we now wanted to evaluate the ability of pterostilbene and 3,5-hydroxypterostilbene in inducing apoptosis in sensitive and resistant leukemia cells. When tested in sensitive cell lines, HL60 and HUT78, 3'-hydroxypterostilbene was 50-97 times more potent than trans-resveratrol in inducing apoptosis, while pterostilbene appeared barely active. However, both compounds, but not trans-resveratrol and piceatannol, were able to induce apoptosis in the two Fas-ligand resistant lymphoma cell lines, HUT78B1 and HUT78B3, and the multi drug-resistant leukemia cell lines HL60-R and K562-ADR (a Bcr-Abl-expressing cell line resistant to imatinib mesylate). Of note, pterostilbene-induced apoptosis was not inhibited by the pancaspase-inhibitor Z-VAD-fmk, suggesting that this compound acts through a caspase-independent pathway. On the contrary, 3'-hydroxypterostilbene seemed to trigger apoptosis through the intrinsic apoptotic pathway: indeed, it caused a marked disruption of the mitochondrial membrane potential delta psi and its apoptotic effects were inhibited by Z-VAD-fmk and the caspase-9-inhibitor Z-LEHD-fmk. Moreover, pterostilbene and 3'-hydroxypterostilbene, when used at concentrations that elicit significant apoptotic effects in tumor cell lines, did not show any cytotoxicity in normal hemopoietic stem cells. In conclusion, our data show that pterostilbene and particularly 3'-hydroxypterostilbene are interesting antitumor natural compounds that may be useful in the treatment of resistant hematological malignancies, including imatinib, non-responsive neoplasms.

PMID: 15878840

3,5-dibenzylxyl-4'-hydroxystilbene induces early caspase-9 activation during apoptosis in human K562 chronic myelogenous leukemia cells.

Roslie H1, Chan KM, Rajab NF, Velu SS, Kadir SA, Bunyamin I, Weber JF, Thomas NF, Majeed AB, Myatt G, Inayat-Hussain SH.

Author information

Abstract

A series of 22 stilbene derivatives based on resveratrol were synthesized incorporating acetoxy-, benzyloxy-, carboxy-, chloro-, hydroxy- and methoxy functional groups. We examined the cytotoxicity of these 22 stilbenes in human K562 chronic myelogenous leukemia cells. Only four compounds were cytotoxic namely 4'-hydroxy-3-methoxystilbene (15), 3'-acetoxy-4-chlorostilbene (19), 4'-hydroxy-3,5-dimethoxystilbene or pterostilbene (3) and 3,5-dibenzylxyl-4'-hydroxystilbene (28) with IC(50)s of 78 µM, 38 µM, 67 µM and 19.5 µM respectively. Further apoptosis assessment on the most potent compound, 28, confirmed that the cells underwent apoptosis based on phosphatidylserine externalization and loss of mitochondrial membrane potential. Importantly, we observed a concentration-dependent activation of caspase-9 as early as 2 hr with resultant caspase-3 cleavage in 28-induced apoptosis. Additionally, a structure-activity relationship (SAR) study proposed a possible mechanism of action for compound 28. Taken together, our data suggests that the pro-apoptotic effects of 28 involve the intrinsic mitochondrial pathway characterized by an early activation of caspase-9.

PMID: 22293408


Pterostilbene induces cell cycle arrest and apoptosis in MOLT4 human leukemia cells.

Siedlecka-Kroplewska K1, Jozwik A, Kaszubowska L, Kowalczyk A, Boguslawski W.

Author information

Abstract

Pterostilbene, a polyphenolic compound present in grapes and other fruits, has been demonstrated to inhibit growth and induce apoptosis and autophagy in some cancer cell types. We found that pterostilbene at the IC(90) concentration of 44 µM inhibited proliferation and induced apoptosis in MOLT4 human leukemia cells. Treatment with pterostilbene resulted in a transient accumulation of cells in the G(0)/G(1)-cell cycle phase followed by the S-phase arrest. Pterostilbene-induced apoptotic death of MOLT4 cells was mediated by caspase-3 activation and
was accompanied by the disruption of mitochondrial membrane potential, phosphatidylserine externalization and internucleosomal DNA fragmentation. Our results suggest that pterostilbene could serve as a potential additional chemotherapeutic agent for the treatment of leukemia.

PMID: 23264221


**Pterostilbene induces accumulation of autophagic vacuoles followed by cell death in HL60 human leukemia cells.**

Siedlecka-Kroplewska K¹, Jozwik A, Boguslawski W, Wozniak M, Zauszkiewicz-Pawlak A, Spodnik JH, Rychlowski M, Kmiec Z.

Author information

Abstract

Pterostilbene, a naturally occurring structural analog of resveratrol, has been reported to exert antiproliferative and proapoptotic effects in various cancer types. Recently, it has been demonstrated to induce both autophagy and apoptosis in human bladder and breast cancer cell lines. The aim of this study was to evaluate the effects of pterostilbene on HL60 human leukemia cells. Cell morphology was examined using confocal and electron microscopy. Cell viability was determined by MTT, neutral red uptake and trypan blue exclusion assays. LC3 processing was studied based on Western blotting and immunofluorescence analyses. Flow cytometry was used to study cell cycle distribution, phosphatidylserine externalization, caspase activation, disruption of mitochondrial membrane potential and intracellular production of reactive oxygen species. DNA degradation was examined by gel electrophoresis. We found that treatment of HL60 cells with pterostilbene at the IC90 concentration resulted in the G0/G1 cell cycle arrest. Pterostilbene induced conversion of cytosolic LC3-I to membrane-bound LC3-II and accumulation of large LC3-positive vacuolar structures. Pterostilbene also led to phosphatidylserine externalization, internucleosomal DNA fragmentation, caspase activation and disruption of mitochondrial membrane potential. Moreover, it did not induce oxidative stress. Our results suggest that pterostilbene induces accumulation of autophagic vacuoles followed by cell death in HL60 cells.

PMID: 24304568


**Pterostilbene simultaneously induced G0/G1-phase arrest and MAPK-mediated mitochondrial-derived apoptosis in human acute myeloid leukemia cell lines.**
Abstract

BACKGROUND: Pterostilbene (PTER) is a dimethylated analog of the phenolic phytoalexin, resveratrol, with higher anticancer activity in various tumors. Herein, the molecular mechanisms by which PTER exerts its anticancer effects against acute myeloid leukemia (AML) cells were investigated.

METHODOLOGY AND PRINCIPAL FINDINGS: Results showed that PTER suppressed cell proliferation in various AML cell lines. PTER-induced G0/G1-phase arrest occurred when expressions of cyclin D3 and cyclin-dependent kinase (CDK)2/6 were inhibited. PTER-induced cell apoptosis occurred through activation of caspases-8-9,-3, and a mitochondrial membrane permeabilization (MMP)-dependent pathway. Moreover, treatment of HL-60 cells with PTER induced sustained activation of extracellular signal-regulated kinase (ERK)1/2 and c-Jun N-terminal kinase (JNK)1/2, and inhibition of both MAPKs by their specific inhibitors significantly abolished the PTER-induced activation of caspases-8/-9/-3. Of note, PTER-induced cell growth inhibition was only partially reversed by the caspase-3-specific inhibitor, Z-DEVE-FMK, suggesting that this compound may also act through a caspase-independent pathway. Interestingly, we also found that PTER promoted disruption of lysosomal membrane permeabilization (LMP) and release of activated cathepsin B.

CONCLUSION: Taken together, our results suggest that PTER induced HL-60 cell death via MAPKs-mediated mitochondria apoptosis pathway and loss of LMP might be another cause for cell apoptosis induced by PTER.

PMID: 25144448

Pterostilbene induces apoptosis and cell cycle arrest in diffuse large B-cell lymphoma cells.

Kong Y1, Chen G1, Xu Z2, Yang G1, Li B2, Wu X1, Xiao W1, Xie B1, Hu L1, Sun X1, Chang G1, Gao M1, Gao L1, Dai B1, Tao Y1, Zhu W2, Shi J1.

Author information
Abstract

Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma (NHL). Pterostilbene, a natural dimethylated analog of resveratrol, has been shown to possess diverse pharmacological activities, including anti-inflammatory, antioxidant and anticancer properties. However, to the best of our knowledge, there has been no study of the effects of pterostilbene upon hematological malignancies. Herein, we report the antitumor activity and mechanism of pterostilbene against DLBCL cells both in vitro and in vivo. We found that pterostilbene treatment resulted in a dose-dependent inhibition of cell viability. In addition, pterostilbene exhibited a strong cytotoxic effect, as evidenced not only by reductions of mitochondrial membrane potential (MMP) but also by increases in cellular apoptotic index and reactive oxygen species (ROS) levels, leading to arrest in the S-phase of the cell cycle. Furthermore, pterostilbene treatment directly up-regulated p-p38MAPK and down-regulated p-ERK1/2. In vivo, intravenous administration of pterostilbene inhibited tumor development in xenograft mouse models. Overall, the results suggested that pterostilbene is a potential anticancer pharmaceutical against human DLBCL by a mechanism involving the suppression of ERK1/2 and activation of p38MAPK signaling pathways.

PMID: 27869173


Pterostilbene Inhibits Human Multiple Myeloma Cells via ERK1/2 and JNK Pathway In Vitro and In Vivo.


Author information

Abstract

Multiple myeloma (MM) is the second most common malignancy in the hematologic system, which is characterized by accumulation of plasma cells in bone marrow. Pterostilbene (PTE) is a natural dimethylated analog of resveratrol, which has anti-oxidant, anti-inflammatory and anti-tumor properties. In the present study, we examined the anti-tumor effect of PTE on MM cell lines both in vitro and in vivo using the cell counting kit (CCK)-8, apoptosis assays, cell cycle analysis, reactive oxygen species (ROS) generation, JC-1 mitochondrial membrane potential assay, Western blotting and tumor xenograft models. The results demonstrated that PTE induces apoptosis in the H929 cell line and causes cell cycle arrest at G0/G1 phase by enhancing ROS generation and reducing mitochondrial membrane potential. The anti-tumor effect of PTE may be caused by the activation of the extracellular regulated protein kinases (ERK) 1/2 and c-Jun N-terminal kinase (JNK) signaling pathways. Additionally, mice treated with PTE by intraperitoneal injection demonstrated reduced tumor volume. Taken together, the results of this
study indicate that the anti-tumor effect of PTE on MM cells may provide a new therapeutic option for MM patients.

**KEYWORDS:**
ERK1/2; JNK; apoptosis; cell cycle; multiple myeloma; pterostilbene

PMID: 27869675
**Stomach Cancer**


**Pterostilbene induces apoptosis and cell cycle arrest in human gastric carcinoma cells.**

Pan MH¹, Chang YH, Badmaev V, Nagabhushanam K, Ho CT.

**Author information**

**Abstract**

Pterostilbene, an active constituent of blueberries, is known to possess anti-inflammatory activity and also induces apoptosis in various types of cancer cells. Here, the effects of pterostilbene on cell viability in human gastric carcinoma AGS cells were investigated. This study demonstrated that pterostilbene was able to inhibit cell proliferation and induce apoptosis in a concentration- and time-dependent manner. Pterostilbene-induced cell death was characterized with changes in nuclear morphology, DNA fragmentation, and cell morphology. The molecular mechanism of pterostilbene-induced apoptosis was also investigated. The results show the caspase-2, -3, -8, and -9 are all activated by pterostilbene, together with cleavage of the downstream caspase-3 target DNA fragmentation factor (DFF-45) and poly(ADP-ribose) polymerase. Moreover, the results indicate that the Bcl-family of proteins, the mitochondrial pathway, and activation of the caspase cascade are responsible for pterostilbene-induced apoptosis. Pterostilbene markedly enhanced the expression of growth arrest DNA damage-inducible gene 45 and 153 (GADD45 and GADD153) in a time-dependent manner. Flow cytometric analysis indicated that pterostilbene blocked cell cycle progression at G1 phase in a dose- and time-dependent manner. Pterostilbene increased the p53, p21, p27, and p16 proteins and decreased levels of cyclin A, cyclin E, cyclin-dependent kinase 2 (Cdk2), Cdk4, and Cdk6, but the expression of cyclin D1 was not affected. Over a 24 h exposure to pterostilbene, the degree of phosphorylation of Rb was decreased after 6 h. In summary, pterostilbene induced apoptosis in AGS cells through activating the caspase cascade via the mitochondrial and Fas/FasL pathway, GADD expression, and by modifying cell cycle progress and changes in several cycle-regulating proteins. The induction of apoptosis by pterostilbene may provide a pivotal mechanism of the antitumor effects and for treatment of human gastric cancer.

PMID: 17696482
Natural polyphenols facilitate elimination of HT-29 colorectal cancer xenografts by chemoradiotherapy: a Bcl-2- and superoxide dismutase 2-dependent mechanism.

Priego S\textsuperscript{1}, Feddi F, Ferrer P, Mena S, Benlloch M, Ortega A, Carretero J, Obrador E, Asensi M, Estrela JM.

**Author information**

**Abstract**

Colorectal cancer is one of the most common malignancies worldwide. The treatment of advanced colorectal cancer with chemotherapy and radiation has two major problems: development of tumor resistance to therapy and nonspecific toxicity towards normal tissues. Different plant-derived polyphenols show anticancer properties and are pharmacologically safe. In vitro growth of human HT-29 colorectal cancer cells is inhibited (approximately 56%) by bioavailable concentrations of trans-pterostilbene (trans-3,5-dimethoxy-4'-hydroxystilbene; t-PTER) and quercetin (3,3',4',5,6-pentahydroxyflavone; QUER), two structurally related and naturally occurring small polyphenols. I.v. administration of t-PTER and QUER (20 mg/kg x day) inhibits growth of HT-29 xenografts (approximately 51%). Combined administration of t-PTER + QUER, FOLFOX6 (oxaliplatin, leucovorin, and 5-fluorouracil; a first-line chemotherapy regimen), and radiotherapy (X-rays) eliminates HT-29 cells growing in vivo leading to long-term survival (>120 days). Gene expression analysis of a Bcl-2 family of genes and antioxidant enzymes revealed that t-PTER + QUER treatment preferentially promotes, in HT-29 cells growing in vivo, (a) superoxide dismutase 2 overexpression (approximately 5.7-fold, via specificity protein 1-dependent transcription regulation) and (b) down-regulation of bcl-2 expression (approximately 3.3-fold, via inhibition of nuclear factor-kappaB activation). Antisense oligodeoxynucleotides to human superoxide dismutase 2 and/or ectopic bcl-2 overexpression avoided polyphenols and chemoradiotherapy-induced colorectal cancer elimination and showed that the mangano-type superoxide dismutase and Bcl-2 are key targets in the molecular mechanism activated by the combined application of t-PTER and QUER.

PMID: 18852136

Anti-inflammatory action of pterostilbene is mediated through the p38 mitogen-activated protein kinase pathway in colon cancer cells.

Paul S¹, Rimando AM, Lee HJ, Ji Y, Reddy BS, Suh N.

Author information

Abstract

Oxidative/nitrosative stress and generation of proinflammatory cytokines are hallmarks of inflammation. Because chronic inflammation is implicated in several pathologic conditions in humans, including cancers of the colon, anti-inflammatory compounds may be useful chemopreventive agents against colon cancer. Stilbenes, such as resveratrol, have diverse pharmacologic activities, which include anti-inflammation, cancer prevention, a cholesterol-lowering effect, enhanced insulin sensitivity, and increased life span. We previously showed that pterostilbene (trans-3,5-dimethoxy-4'-hydroxystilbene), a structural analogue of resveratrol, is present in blueberries and that pterostilbene inhibited expression of certain inflammation-related genes in the colon and suppressed aberrant crypt foci formation in rats. Here, we examined molecular mechanisms of the action of pterostilbene in colon cancer. Pterostilbene reduced cell proliferation, down-regulated the expression of c-Myc and cyclin D1, and increased the level of cleaved poly(ADP-ribose) polymerase. A combination of cytokines (tumor necrosis factor-alpha, IFN-gamma, and bacterial endotoxin lipopolysaccharide) induced inflammation-related genes such as inducible nitric oxide synthase and cyclooxygenase-2, which was significantly suppressed by treatment with pterostilbene. We further identified upstream signaling pathways contributing to the anti-inflammatory activity of pterostilbene by investigating multiple signaling pathways, including nuclear factor-kappaB, Janus-activated kinase-signal transducer and activator of transcription, extracellular signal-regulated kinase, p38, c-Jun NH(2)-terminal kinase, and phosphatidylinositol 3-kinase. Cytokine induction of the p38-activating transcription factor 2 pathway was markedly inhibited by pterostilbene among the different mediators of signaling evaluated. By silencing the expression of the p38 alpha isoform, there was significant reduction in cytokine induction of inducible nitric oxide synthase and cyclooxygenase-2. Our data suggest that the p38 mitogen-activated protein kinase cascade is a key signal transduction pathway for eliciting the anti-inflammatory action of pterostilbene in cultured HT-29 colon cancer cells.

PMID: 19549798

Inhibitory effects of resveratrol and pterostilbene on human colon cancer cells: a side-by-side comparison.
Nutakul W, Sobers HS, Qiu P, Dong P, Decker EA, McClements DJ, Xiao H.

Author information

Abstract

The effects of resveratrol and pterostilbene (two structurally related stilbene compounds) on three human colon cancer cells were systematically compared. Cell viability tests indicated that IC(50) values of pterostilbene were 2-5-fold lower than those of resveratrol in all three cancer cells. Pterostilbene was also more potent in inhibiting colony formation of all three cancer cells. Annexin V/propidium iodide costaining assay and Western blotting analysis showed pterostilbene had a stronger apoptosis-inducing effect, which was evidenced by the higher percentage of annexin V positive cells and higher levels of cleaved caspase-3 and poly(ADP-ribose) polymerase proteins in cancer cells treated with pterostilbene compared with resveratrol. High-performance liquid chromatography analysis demonstrated that intracellular levels of pterostilbene were 2-4-fold higher than those of resveratrol after treatments with individual compounds at the same concentration. Overall, the results demonstrated that pterostilbene had more potent inhibitory effects on colon cancer cells than resveratrol, which may be associated with the superior bioavailability of pterostilbene to resveratrol.

PMID: 21936500


In vitro evaluation of antiproliferative and cytotoxic properties of pterostilbene against human colon cancer cells.

Wawszczyk J, Kapral M, Hollek A, Węglarz L.

Abstract

Colon cancer has been remaining the second leading cause of cancer mortality in Poland in the last years. Epidemiological, preclinical and clinical studies reveal that dietary phytochemicals may exert chemopreventive and therapeutic effect against colorectal cancer. There is a growing interest in identifying new biologically active agents from dietary sources in this respect. Pterostilbene (trans-3,5-dimethoxy-4-hydroxystilbene) is a naturally occurring stilbene, that has been found to have antioxidative, anti-inflammatory and antiproliferative properties. Compared to other stilbenes, pterostilbene has greater bioavailability, and so, a greater potential for clinical applications. Recent studies showed that pterostilbene exhibits the hallmark characteristics of an anticancer agent. The aim of this study was to analyze antiproliferative and cytotoxic effects of pterostilbene on human colon cancer Caco-2 cells. They were cultured using standard techniques and exposed to increasing doses of pterostilbene (5-100 μM) for 48 and 72 h. Cell proliferation was determined by sulforhodamine B assay. The growth of treated cells was expressed as a percentage of that of untreated control cells. Pterostilbene decreased proliferation rate of Caco-2 cells in a dose- and time-dependent manner. Its concentrations = 25 μM did not affect cell
growth after 48 h treatment period. Significant growth inhibition was observed in cultures incubated with higher concentrations of pterostilbene (40-100 μM). Pterostilbene at all concentrations used (5-100 μM) caused significant inhibition of cell proliferation when the experimental time period was elongated to 72 h. The maximum growth reduction was observed at 100 mM pterostilbene. The cytotoxicity of pterostilbene was evaluated in 48 h cultures based on lactate dehydrogenase (LDH) leakage into the culture medium and showed dose-related pattern. The findings of this study showed significant dose-dependent antiproliferative and cytotoxic effects of pterostilbene against human colon cancer cells in vitro.

PMID: 25745778


Pterostilbene, an active component of blueberries, sensitizes colon cancer cells to 5-fluorouracil cytotoxicity.

Tolba MF¹,², Abdel-Rahman SZ³.

Author information

Abstract

Although colorectal cancer (CRC) treatment with 5-fluorouracil (5-FU) is the first line of therapy for this debilitating disease, treatment effectiveness is often hampered by the development of drug resistance and toxicity at high doses. ER-β can play an important role in CRC development and possibly in its response to therapy. Pterostilbene (PT) possesses antioxidant and anticancer effects that are mediated by ER-β. In the current study, we test the hypothesis that PT sensitizes colon cancer cells to 5-FU and we examine the underlying mechanism(s) by which PT exerts its cytotoxic effects in CRC cells. Our data indicate that PT exhibited a more potent cytotoxic effect in Caco-2 compared to HCT-116 cells. PT/5-FU co-treatment was more effective in Caco-2 cells. Our data indicate that ER-β is expressed at higher levels in Caco-2 cells and its levels are further boosted with PT treatment. PT significantly suppressed Akt and ERK phosphorylations, and enhanced FOXO-1 and p27(kip1) levels in Caco-2 cells. PT also induced a significant increase in Caco-2 cells at pre-G phase coupled with increased Bax/Bcl-2 ratio and PARP cleavage. These results provide a rationale for novel combination treatment strategies, especially for patients with 5-FU-resistant tumors expressing ER-β protein.

PMID: 26472352


Identification of pinostilbene as a major colonic metabolite of pterostilbene and its inhibitory effects on colon cancer cells.
SCOPE:
Pterostilbene (PTE) is a resveratrol derivative mainly found in blueberries, and it has been shown to inhibit colon carcinogenesis in multiple animal models. To shed light on the mechanism of PTE in inhibiting colon carcinogenesis, we investigated the PTE metabolites in the mouse colon and in the human colon cancer cells.

METHODS AND RESULTS:
CD-1 mice were fed PTE-containing diet for 3 weeks, and colonic content and colonic mucosa were collected and subjected to LC-MS analysis. Pinostilbene (PIN) was identified as a major metabolite of PTE in the mouse colon. Importantly, the level of PIN was found to be approximately equivalent to that of PTE in the colonic mucosa. PIN significantly inhibited the growth of human colon cancer cells, i.e., HCT116 and HT29. These inhibitory effects were similar to those produced by PTE. Moreover, under physiologically relevant conditions, 20 and 40 μM of PIN caused cell cycle arrest at S phase and induced apoptosis in colon cancer cells. These effects were associated with profound modulation of signaling proteins related with cell proliferation and programmed cell death.

CONCLUSION:
Our results demonstrated that PIN is a major metabolite of PTE in the colon of mice fed with PTE, and PIN may play important roles in the anti-colon cancer effects elicited by orally administered PTE.

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KEYWORDS:
Apoptosis; Cell cycle arrest; Colon cancer; Metabolite; Pinostilbene; Pterostilbene

PMID: 26990242
Liver Cancer


Pterostilbene inhibited tumor invasion via suppressing multiple signal transduction pathways in human hepatocellular carcinoma cells.

Pan MH¹, Chiou YS, Chen WJ, Wang JM, Badmaev V, Ho CT.

Author information

Abstract

Pterostilbene, a natural dimethylated analog of resveratrol, is known to have diverse pharmacologic activities including anticancer, anti-inflammation, antioxidant, apoptosis, anti-proliferation and analgesic potential. However, the effects of pterostilbene in preventing invasion of cancer cells have not been studied. Here, we report our finding that pterostilbene significantly suppressed 12-O-tetradecanoylphorbol 13-acetate (TPA)-induced invasion, migration and metastasis of human hepatoma cells (HepG(2) cells). Increase in the enzyme activity, protein and messenger RNA levels of matrix metalloproteinase (MMP)-9 were observed in TPA-treated HepG(2) cells, and these were blocked by pterostilbene. In addition, pterostilbene can inhibit TPA-induced expression of vascular endothelial growth factor, epidermal growth factor and epidermal growth factor receptor. Transient transfection experiments also showed that pterostilbene strongly inhibited TPA-stimulated nuclear factor kappa B (NF-kappaB) and activator protein-1 (AP-1)-dependent transcriptional activity in HepG(2) cells. Moreover, pterostilbene can suppress TPA-induced activation of extracellular signal-regulated kinase 1/2, p38 mitogen-activated protein kinase, c-Jun N-terminal kinases 1/2 and phosphatidylinositol 3-kinase/Akt and protein kinase C that are upstream of NF-kappaB and AP-1. Significant therapeutic effects were further demonstrated in vivo by treating nude mice with pterostilbene (50 and 250 mg/kg intraperitoneally) after inoculation with HepG(2) cells into the tail vein. Presented data reveal that pterostilbene is a novel, effective, anti-metastatic agent that functions by downregulating MMP-9 gene expression.

PMID: 19447859


Long-term ethanol exposure-induced hepatocellular carcinoma cell migration and invasion through lysyl oxidase
activation are attenuated by combined treatment with pterostilbene and curcumin analogues.

Huang CS¹, Ho CT, Tu SH, Pan MH, Chuang CH, Chang HW, Chang CH, Wu CH, Ho YS.

Author information

Abstract

Ethanol consumption induces hepatocellular carcinoma (HCC) cell metastasis by changing the extracellular matrix (ECM). Lysyl oxidase (LOX) catalyzes the cross-linkage of collagen or elastin in the ECM. LOX protein and mRNA overexpression (>21-fold compared with controls, n = 6) was detected in cirrhotic HCC patients with a history of alcoholism. LOX protein expression was induced in HCC cells after long-term treatment with ethanol (10 mM) for 20-40 passages (denoted E20-E40 cells). Pterostilbene (PSB, 1 μM) displayed significant potency to reduce LOX-mediated activity in E40 cells when combined with curcumin and its analogues. The ability of E40 cells to form colonies in soft agar was reduced by both genetic depletion of LOX and by chemical inhibitors of LOX expression. This study suggests that targeting LOX expression with food components such as PSB and curcumin may be a novel strategy to overcome ethanol-induced HCC cell metastasis in liver cancer patients.

PMID: 23560895


In Vitro Safety/Protection Assessment of Resveratrol and Pterostilbene in a Human Hepatoma Cell Line (HepG2).


Abstract

The aim of this work was to evaluate in vitro the genotoxic and/or antigenotoxic effects of resveratrol (RESV) and pterostilbene (PTER) on HepG2 cells. Moreover, additional tests were performed to evaluate early and late apoptosis events induced by the tested stilbenes. RESV and PTER did not show any genotoxic activity. As regards antigenotoxicity testing, RESV and PTER showed a typical, U-shaped hormetic dose-response relationship characterized by a biphasic trend with small quantities having opposite effects to large ones. HepG2 cells treated with PTER exhibited a marked increase in early apoptosis (40.1%) at 250 microM; whereas, the highest concentration tested for both RESV and PTER significantly increased the proportion of HepG2 cells undergoing late apoptosis (32.5 and 51.2%, respectively). The observed pro-apoptotic activity could, at least in part, explain the hormetic response observed when the compounds were tested for antigenotoxicity (i.e., in the presence of induced DNA damage).
Pterostilbene inhibits hepatocellular carcinoma through p53/SOD2/ROS-mediated mitochondrial apoptosis.


Author information

Abstract

Hepatocellular carcinoma (HCC) is one of the most common malignancies and the second cause of cancer-related deaths around the world. Pterostilbene (PTE), is a natural analog of resveratrol, possessing diverse pharmacological activities. In the present study, we aimed to examine the effect of PTE on tumor growth in mouse models of HCC and to elucidate the possible molecular mechanism in vivo and in vitro. We showed that PTE dose-dependently suppressed tumor growth in mice induced by diethylnitrosamine plus carbon tetrachloride, as evidenced by a decrease in the number of tumors and in the maximum size of the tumors. PTE concentration-dependently inhibited cell viability and proliferation in HepG2 cells. PTE increased caspase-3 activities and apoptosis in liver tumor tissues and cells, indicating the activation of the mitochondrial apoptotic pathway. PFTα, superoxide dismutase 2 (SOD2) lentivirus and N-acetylcysteine (NAC) significantly inhibited PTE-induced inhibition of tumor growth and cell proliferation and increase in apoptosis. PTE dose-dependently increased reactive oxygen species (ROS) levels both in liver tumor tissues and cells, which were inhibited by PFTα, SOD2 lentivirus and NAC. PTE resulted in a significant decrease in SOD2 expression in liver tumor tissues and cells, which were inhibited by PFTα, but not NAC, indicating that PTE-induced ROS generation was attributed to p53-mediated downregulation of SOD2. Collectively, PTE increased p53 expression, decreased SOD2 expression, and resulted in an increase in the ROS levels and the activation of the mitochondrial apoptotic pathway, leading to inhibition of tumor growth and cell proliferation. These data demonstrated that the p53/SOD2/ROS pathway is critical for PTE-mediated inhibition of tumor growth and HCC cell proliferation.
Suppression of Heregulin-β1/HER2-Modulated Invasive and Aggressive Phenotype of Breast Carcinoma by Pterostilbene via Inhibition of Matrix Metalloproteinase-9, p38 Kinase Cascade and Akt Activation.

Pan MH¹, Lin YT, Lin CL, Wei CS, Ho CT, Chen WJ.

Author information

Abstract

Invasive breast cancer is the major cause of death among females and its incidence is closely linked to HER2 (human epidermal growth factor receptor 2) overexpression. Pterostilbene, a natural analog of resveratrol, exerts its cancer chemopreventive activity similar to resveratrol by inhibiting cancer cell proliferation and inducing apoptosis. However, the anti-invasive effect of pterostilbene on HER2-bearing breast cancer has not been evaluated. Here, we used heregulin-β1 (HRG-β1), a ligand for HER3, to transactivate HER2 signaling. We found that pterostilbene was able to suppress HRG-β1-mediated cell invasion, motility and cell transformation of MCF-7 human breast carcinoma through down-regulation of matrix metalloproteinase-9 (MMP-9) activity and growth inhibition. In parallel, pterostilbene also inhibited protein and mRNA expression of MMP-9 driven by HRG-β1, suggesting that pterostilbene decreased HRG-β1-mediated MMP-9 induction via transcriptional regulation. Examining the signaling pathways responsible for HRG-β1-associated MMP-9 induction and growth inhibition, we observed that pterostilbene, as well as SB203580 (p38 kinase inhibitor), can abolish the phosphorylation of p38 mitogen-activated protein kinase (p38 kinase), a downstream HRG-β1-responsive kinase responsible for MMP-9 induction. In addition, HRG-β1-driven Akt phosphorylation required for cell proliferation was also suppressed by pterostilbene. Taken together, our present results suggest that pterostilbene may serve as a chemopreventive agent to inhibit HRG-β1/HER2-mediated aggressive and invasive phenotype of breast carcinoma through down-regulation of MMP-9, p38 kinase and Akt activation.

PMID: 19617202
Pterostilbene inhibits breast cancer in vitro through mitochondrial depolarization and induction of caspase-dependent apoptosis.

Alosi JA¹, McDonald DE, Schneider JS, Privette AR, McFadden DW.

Author information

Abstract

BACKGROUND:
Epidemiologic studies suggest that diets high in fruits and vegetables reduce cancer risk. Resveratrol, a compound present in grapes, has been shown to inhibit a variety of primary tumors. Pterostilbene, an analogue of resveratrol found in blueberries, has both antioxidant and antiproliferative properties. We hypothesized that pterostilbene would induce apoptosis and inhibit breast cancer cell growth in vitro.

METHODS:
Breast cancer cells were treated with graduated doses of pterostilbene. Cell viability was measured by MTT assay. Apoptosis was evaluated via DNA fragmentation assay and TUNEL assay. Apo-ONE caspase-3/7 assay was used to evaluate caspase activity. Flow cytometry was used to evaluate mitochondrial depolarization, superoxide formation, and cell cycle. Student's t-test and two-way ANOVA with Bonferroni posttests were utilized for statistical analysis.

RESULTS:
Pterostilbene decreased breast cancer cell viability in a concentration- and time-dependent manner. Pterostilbene treatment increased caspase-3/7 activity and apoptosis in both cell lines. Caspase-3/7 inhibitors completely reversed pterostilbene's effects on cell viability. Pterostilbene treatment triggered mitochondrial depolarization, increased superoxide anion, and caused alteration in cell cycle.

CONCLUSIONS:
Pterostilbene treatment inhibits the growth of breast cancer in vitro through caspase-dependent apoptosis. Mitochondrial membrane depolarization and increased superoxide anion may contribute to the activation downstream effector caspases. Caspase inhibition leads to complete reversal of pterostilbene's effect on cell viability. Further in vitro mechanistic studies and in vivo experiments are warranted to determine its potential for the treatment of breast cancer.

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Pterostilbene and tamoxifen show an additive effect against breast cancer in vitro.

Mannal P¹, McDonald D, McFadden D.

Abstract

BACKGROUND:
Tamoxifen is widely used for the treatment of breast cancer. Pterostilbene, a bioavailable stilbenoid found in blueberries, has been found to inhibit breast cancer growth in vitro. It was hypothesized that combining pterostilbene with tamoxifen would produce additive effects on estrogen receptor-positive breast cancer cells.

METHODS:
Two estrogen receptor-positive breast cancer cell lines, MCF7 and ZR-751, were pretreated with graduated doses of pterostilbene for 24 hours, followed by 5 μmol/L tamoxifen. MTT proliferation assays and Cell Death Detection ELISA(PLUS) tests evaluated cell viability and apoptosis.

RESULTS:
MCF7 cells showed inhibition (10 and 20 μmol/L, P < .001; 30 μmol/L, P < .05) at all time points when combined with tamoxifen. ZR-751 cells showed additive reductions in cell viability (P < .001). Cell Death Detection ELISA(PLUS) indicated increased apoptosis (P < .01).

CONCLUSIONS:
Pterostilbene shows an additive inhibitory effect on breast cancer cells when combined with tamoxifen, most likely from augmented cancer cell apoptosis.

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The antiproliferative effects of pterostilbene on breast cancer in vitro are via inhibition of constitutive and leptin-induced Janus kinase/signal transducer and activator of transcription activation.

McCormack D\textsuperscript{1}, Schneider J, McDonald D, McFadden D.

Author information

Abstract

BACKGROUND:
The hormone leptin is implicated in breast carcinogenesis in obese women. One mechanism is through its activation of Janus kinase/signal transducer and activator of transcription (JAK/STAT3) and apoptosis dysregulation. We have shown that the antioxidant pterostilbene inhibits proliferation and induces apoptosis in breast cancer. Therefore, the goal of this study was to evaluate the effect of pterostilbene on cell proliferation and JAK/STAT3 signaling in leptin-stimulated breast cancer.

METHODS:
Breast cancer cells were treated with leptin alone or in combination with pterostilbene. Detection of cell proliferation and JAK/STAT3 signaling were performed using enzyme-linked immunosorbent assay protocols. Statistical analysis was performed with analysis of variance and Tukey post hoc analysis.

RESULTS:
Pterostilbene suppresses constitutive as well as leptin-induced JAK/STAT3 activation. Pterostilbene treatment also inhibited leptin-induced cell proliferation.

CONCLUSIONS:
Pterostilbene has an inhibitory effect on leptin-stimulated breast cancer in vitro through reduction of cell proliferation and JAK/STAT3 signaling, a critical regulatory component of tumorigenesis in obesity-related breast cancer.

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PMID: 21944294

Long term induction by pterostilbene results in autophagy and cellular differentiation in MCF-7 cells via ROS dependent pathway.

Chakraborty A¹, Bodipati N, Demonacos MK, Peddinti R, Ghosh K, Roy P.

Author information

Abstract

This study shows the effect of pterostilbene on intracellular neutral lipid accumulation in MCF-7 breast cancer cells leading to growth arrest and autophagy. On exposing the breast cancer cells with 30 μM pterostilbene for 72 h there was almost 2-folds increase in neutral lipids and triglycerides. Also the phytochemical caused a 4-folds increase in the expression of adipogenic differentiation marker c/EBPα. Further, pterostilbene inhibited 3β-hydroxysterol-Δ(7)-reductase, the enzyme which catalyzes the last step conversion of 7-dehydrocholesterol to cholesterol, and thereby causes the intracellular accumulation of the former sterol. These results were associated with over-expression of oxysterol binding protein homologue and liver X receptor (LXR) by ~7-folds. Pterostilbene also caused a simultaneous increase in the expression autophagic marker proteins Beclin 1 and LC3 II (microtubule-associated protein 1 light chain 3) by approximately 6-folds, which leads to an alternative pathway of autophagy. These effects were observed in association with the loss of mitotic and metastatic potential of MCF-7 cells which was abolished in the presence of catalase (ROS scavenger) or 3MA (autophagic inhibitor). Thus the present data shows that the long term exposure to pterostilbene causes growth arrest in MCF-7 cells which may be due to differentiation of the mammary carcinoma cells into normal epithelial cell like morphology and activation of autophagy.

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PMID: 22273805


Pterostilbene simultaneously induces apoptosis, cell cycle arrest and cyto-protective autophagy in breast cancer cells.


Abstract

As a nature phytoalexin found in grapes, resveratrol has been proposed as a potential drug for cancer chemoprevention and treatment. However, its poor bioavailability limits its potential clinical application. Pterostilbene, the natural dimethylated analog of resveratrol with greater bioavailability, was confirmed to inhibit tumor growth both in vivo and in vitro, demonstrating
its potential for further clinical application. In the current study, we found that pterostilbene could markedly inhibit the growth of two independent breast cancer cell lines. Both apoptosis and cell cycle arrest as well as the inhibition of wnt singling was induced by pterostilbene. The dominant-active mutant of β-catenin could reverse the growth inhibitory effect of pterostilbene, indicating that the inhibition of wnt signaling is important to the growth inhibitory effect of pterostilbene. Interestingly, pterostilbene induced autophagy and blockage of autophagy augmented pterostilbene-induced growth inhibition, suggesting that the combination of autophagy inhibitors with pterostilbene and other therapeutics such as endocrine drugs could serve as a new and promising strategy for the treatment of breast cancer cells.

**KEYWORDS:**
Pterostilbene; apoptosis; phytoalexins; tumor growth inhibition; wnt singling

PMID: 22347521


**Pterostilbene induces mitochondrially derived apoptosis in breast cancer cells in vitro.**

Moon D, McCormack D, McDonald D, McFadden D.

**Author information**

**Abstract**

**BACKGROUND:**
The ability of a breast cancer cell to evade apoptosis has a key role in tumor progression and sensitivity to treatment. High levels of Bcl-2-associated X protein (Bax) in tumor cells have been found to promote apoptosis and sensitize cells to anti-cancer therapies. Bcl-2-associated X protein redistribution to the mitochondrial membrane results in the release of proapoptotic factors including cytochrome C, second-mitochondrial-derived activator of caspase/direct inhibitor of apoptosis-binding protein with low PI (Smac/DIABLO), and Ca(2+). We aimed to explore this pathway in cancerous breast cell lines treated with the naturally occurring antioxidant 3,5-dimethoxy-4-hydroxystilbene (pterostilbene).

**METHODS:**
We used whole cell lysates +/- Bax SiRNA from the cell lines MCF-7 and MDA-MB-231 in an enzyme-linked immunosorbent assay to quantify Bax, cytochrome C, Smac/DIABLO expression, and manganese superoxide dismutase (MnSOD) activity after treatment with pterostilbene. We quantified cell death using histone-related DNA complexes from cytosolic and mitochondrial fractions and used methylthiazol tetrazolium assay to analyze cell proliferation, in the presence of Bax-silencing or scrambled RNA. We measured changes in cytosolic calcium using the ratiometric calcium-sensitive dye fura-2-AM using an inverted ratiometric monochromator microscope.
RESULTS:
Treatment of MCF-7 and MDA-MB-231 (MDA) cells with pterostilbene caused concentration-dependent increases in intracellular Bax at all doses tested. RNA silencing of Bax resulted in reduced rates of apoptosis in both cells types and increased cell survival when treated with pterostilbene. We observed an increase in cytochrome C in MDA cells after treatment with pterostilbene. The MCF-7 cells showed a net increase in cytosolic cytochrome C, with a corresponding reduction in mitochondrial cytochrome C after treatment with 50 and 75 μmol/L pterostilbene. We observed this again in Smac/DIABLO expression in both cell types. In MCF-7 cells, pterostilbene treatment caused an increase in cytosolic but a decrease in mitochondrial Smac/DIABLO protein concentrations. Pterostilbene significantly increase MnSOD activity in MDA-MB-231 cells. Finally, pterostilbene resulted in significant increases in cytosolic calcium concentrations.

CONCLUSIONS:
The natural dietary compound pterostilbene has an anti-proliferative effect and induces apoptosis in breast cancer cells in vitro via Bax activation and overexpression, resulting in increased MnSOD, Smac/DIABLO, and cytochrome C activity and cytosolic Ca(2+) overload.

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PMID: 22572619

Invadopodia-associated proteins blockade as a novel mechanism for 6-shogaol and pterostilbene to reduce breast cancer cell motility and invasion.

Hong BH1, Wu CH, Yeh CT, Yen GC.

Author information
Abstract

SCOPE:
Invadopodia are actin-rich membrane protrusions of tumor cells that are thought to initiate the local migration and invasion during cancer metastasis. The blockade of invadopodia-associated proteins has been reported as a promising approach for prevention of tumor metastasis. The aim of this study was to investigate the modulatory effects of 6-shogaol and pterostilbene on invadopodia in aggressive breast cancer cells.
METHODS AND RESULTS:
By wound-healing, transwell, and gelatin zymography assays, we found that 6-shogaol and pterostilbene effectively attenuated the motility and invasion of MDA-MB-231 cells, and suppressed the activities of matrix metalloproteinase-2 (MMP-2) and matrix metalloproteinase-9 (MMP-9). Further investigation into the underlying molecular mechanisms revealed that the levels of key modulators of invadopodium maturation, including c-Src kinase, cortactin, and membrane type 1-matrix metalloproteinase (MT1-MMP) decreased when cells were treated with 6-shogaol or pterostilbene.

CONCLUSION:
These data suggest that the repression of these factors might affect the maturation of invadopodia, inhibiting the metastasis of MDA-MB-231 cells. In conclusion, the present study demonstrates for the first time that 6-shogaol and pterostilbene can inhibit invadopodium formation and MMP activity in highly invasive breast cancer cells. We suggest that these compounds may be clinically useful in chemopreventive treatments for metastatic breast cancer.

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PMID: 23417847


The anti-tumor efficiency of pterostilbene is promoted with a combined treatment of Fas signaling or autophagy inhibitors in triple negative breast cancer cells.

Chen WC, Hsu KY, Hung CM, Lin YC, Yang NS, Ho CT, Kuo SC, Way TD.

Author information

Abstract

High expression of vimentin, a canonical mesenchymal marker, is linked with poor prognosis in triple negative breast cancer (TNBC), implying that vimentin may be a potential biomarker in the application of TNBC therapy. Pterostilbene (PTE) has shown anti-invasion activity, and thus, we investigated whether PTE inhibited the epithelial-mesenchymal transition (EMT) in TNBC. Here, we show that PTE decreases the vimentin expression, but that the effect was transient. PTE stimulated Fas signaling, which drives EMT by the ERK1/2 and GSK3β/β-catenin pathways, supporting Fas signaling induction involved in EMT regulation. PTE also triggered autophagy in TNBC. The treatment of TNBC with 3-methyladenine an autophagy inhibitor, not only sustained PTE-inhibited EMT but also significantly promoted anti-proliferation, which indicates that autophagy plays a cyto-protective role and is associated with EMT. Taken together, these data
showed that Fas signaling and autophagy accelerated the aggressiveness of TNBC. Inhibition of autophagy or Fas signaling may provide novel targets for TNBC therapy.

PMID: 24944076


**Estrogen receptor-α36 is involved in pterostilbene-induced apoptosis and anti-proliferation in in vitro and in vivo breast cancer.**

Pan C¹, Hu Y², Li J³, Wang Z¹, Huang J⁵, Zhang S¹, Ding L⁵.

**Author information**

**Abstract**

Pterostilbene (trans-3,5-dimethoxy-4'-hydroxystilbene) is an antioxidant primarily found in blueberries. It also inhibits breast cancer regardless of conventional estrogen receptor (ER-α66) status by inducing both caspase-dependent and caspase-independent apoptosis. However, the pterostilbene-induced apoptosis rate in ER-α66-negative breast cancer cells is much higher than that in ER-α66-positive breast cancer cells. ER-α36, a variant of ER-α66, is widely expressed in ER-α66-negative breast cancer, and its high expression mediates the resistance of ER-α66-positive breast cancer patients to tamoxifen therapy. The aim of the present study is to determine the relationship between the antiproliferation activity of pterostilbene and ER-α36 expression in breast cancer cells. Methylthiazolyltetrazolium (MTT) assay, apoptosis analysis, and an orthotropic xenograft mouse model were used to examine the effects of pterostilbene on breast cancer cells. The expressions of ER-α36 and caspase 3, the activation of ERK and Akt were also studied through RT-PCR, western blot analysis, and immunohistochemical (IHC) staining. ER-α36 knockdown was found to desensitize ER-α66-negative breast cancer cells to pterostilbene treatment both in vitro and in vivo, and high ER-α36 expression promotes pterostilbene-induced apoptosis in breast cancer cells. Western blot analysis data indicate that MAPK/ERK and PI3K/Akt signaling in breast cancer cells with high ER-α36 expression are mediated by ER-α36, and are inhibited by pterostilbene. These results suggest that ER-α36 is a therapeutic target in ER-α36-positive breast cancer, and pterostilbene is an inhibitor that targets ER-α36 in the personalized therapy against ER-α36-positive breast cancer.

PMID: 25127034

Pterostilbene inhibits triple-negative breast cancer metastasis via inducing microRNA-205 expression and negatively modulates epithelial-to-mesenchymal transition.

Su CM¹, Lee WH², Wu AT³, Lin YK⁴, Wang LS⁵, Wu CH⁶, Yeh CT⁷.

Author information

Abstract

Breast cancer is the leading cause of cancer-related deaths among females in economically developing countries. Greater than 95% of breast malignancies are of epithelial origin; the induction of epithelial-to-mesenchymal transition (EMT) has been shown to initiate the metastatic process in breast carcinoma and remains the key target for drug development. Here, we examine the anti-metastatic potential of pterostilbene in modulating EMT process in breast cancer cells both in vitro and in vivo. The differential invasive ability among MCF7, Hs578t and MDA-MB-231 breast cancer cell lines were closely correlated with the expression of EMT markers, determined by Western blots and Matrigel-coated transwells assay. Pterostilbene inhibited the migratory and invasive potential of triple-negative MDA-MB-231 and Hs578t cells, accompanied by the up-regulation of E-cadherin and down-regulation of Snail, Slug, vimentin and ZEB1. Mechanistic investigations revealed a significant up-regulation of miR-205, which resulted in the reduction of Src expression in pterostilbene-treated breast cancer cells. Importantly, pterostilbene suppressed tumor growth and metastasis in MDA-MB-231-bearing NOD/SCID mice by reducing Src/Fak signaling; this observation was consistent with the negative correlations between miR-205 and Src expression in both normal and malignant breast tissues. Our findings provide supports for the usage of pterostilbene as an inhibitor of EMT process and potential candidate for adjuvant therapy.

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KEYWORDS:
Epithelial-to-mesenchymal transition (EMT); Metastasis; Pterostilbene; Triple-negative breast cancer; miR-205

PMID: 25792283


Epigenetic-based combinatorial resveratrol and pterostilbene alters DNA damage response by affecting SIRT1 and DNMT enzyme expression, including SIRT1-
dependent γ-H2AX and telomerase regulation in triple-negative breast cancer.

Kala R¹, Shah HN², Martin SL³, Tollefsbol TO⁴,⁵,⁶,⁷,⁸.

Author information

Abstract

BACKGROUND:
Nutrition is believed to be a primary contributor in regulating gene expression by affecting epigenetic pathways such as DNA methylation and histone modification. Resveratrol and pterostilbene are phytoalexins produced by plants as part of their defense system. These two bioactive compounds when used alone have been shown to alter genetic and epigenetic profiles of tumor cells, but the concentrations employed in various studies often far exceed physiologically achievable doses. Triple-negative breast cancer (TNBC) is an often fatal condition that may be prevented or treated through novel dietary-based approaches.

METHODS:
HCC1806 and MDA-MB-157 breast cancer cells were used as TNBC cell lines in this study. MCF10A cells were used as control breast epithelial cells to determine the safety of this dietary regimen. CompuSyn software was used to determine the combination index (CI) for drug combinations.

RESULTS:
Combinatorial resveratrol and pterostilbene administered at close to physiologically relevant doses resulted in synergistic (CI <1) growth inhibition of TNBCs. SIRT1, a type III histone deacetylase (HDAC), was down-regulated in response to this combinatorial treatment. We further explored the effects of this novel combinatorial approach on DNA damage response by monitoring γ-H2AX and telomerase expression. With combination of these two compounds there was a significant decrease in these two proteins which might further resulted in significant growth inhibition, apoptosis and cell cycle arrest in HCC1806 and MDA-MB-157 breast cancer cells, while there was no significant effect on cellular viability, colony forming potential, morphology or apoptosis in control MCF10A breast epithelial cells. SIRT1 knockdown reproduced the effects of combinatorial resveratrol and pterostilbene-induced SIRT1 down-regulation through inhibition of both telomerase activity and γ-H2AX expression in HCC1806 breast cancer cells. As a part of the repair mechanisms and role of SIRT1 in recruiting DNMTs, the effects of this combination treatment was also explored on DNA methyltransferases (DNMTs) expression. Interestingly, the compounds resulted in a significant down-regulation of DNMT enzymes with no significant effects on DNMT enzyme expression in MCF10A control cells.
CONCLUSION:
Collectively, these results provide new insights into the epigenetic mechanisms of a novel combinatorial nutrient control strategy that exhibits synergy and may contribute to future recalcitrant TNBC prevention and/or therapy.

PMID: 26459286


A Novel Combinatorial Epigenetic Therapy Using Resveratrol and Pterostilbene for Restoring Estrogen Receptor-α (ERα) Expression in ERα-Negative Breast Cancer Cells.

Kala R¹, Tollefsbol TO¹,²,³,⁴,⁵.

Author information

Abstract

Breast cancer is the second most common cancer and a leading cause of cancer death in women. Specifically, estrogen receptor-α (ERα)-negative breast cancers are clinically more aggressive and normally do not respond to conventional hormone-directed therapies such as tamoxifen. Although epigenetic-based therapies such as 5-aza-2'-deoxycytidine and/or trichostatin A as DNA methyltransferase (DNMT) and histone deacetylase (HDAC) inhibitors, respectively, can regulate the expression of ERα, this can often lead to a number of side effects. Plant-based dietary compounds such as resveratrol and pterostilbene in novel combinatorial therapy provides new avenues to target these side effects and provide similar results with a higher level of safety. Here, we report that combinatorial resveratrol and pterostilbene leads to the reactivation of ERα expression in ERα-negative breast cancer cells in a time-dependent manner. Chromatin immunoprecipitation analysis of the ERα promoter in each cell type revealed an increase in enrichment of acetyl-H3, acetyl-H3lysine9 (H3K9) and acetyl-H4 active chromatin markers in the ERα promoter region after combinatorial treatment. This treatment also resulted in a significant change in HDAC and histone acetyl transferase (HAT) enzyme activity in these cells after 3 days of treatments. The combination resulted in a significant decrease in DNMT enzyme activity and 5-methylcytosine levels in MDA-MB-157 breast cancer cells. Moreover, reactivation of ERα expression by resveratrol combined with pterostilbene was found to sensitize ERα-dependent response to 17β-estradiol (E2)-mediated cellular proliferation and antagonist 4-hydroxytamoxifen (4-OHT)-mediated inhibition of cellular proliferation in ERα-negative breast cancer cells. E2 and 4-OHT further affected the ERα-responsive downstream progesterone receptor (PGR) gene in ERα reactivated MDA-MB-157 cells. Collectively, our findings provide a new and safer way of restoring ERα expression by regulating epigenetic mechanisms with the
use of phytochemicals in combinatorial therapy. This combination can further provide effective treatment options for hormonal refractory breast cancer with available anti-hormonal therapy.

PMID: 27159275


Stilbenoids remodel the DNA methylation patterns in breast cancer cells and inhibit oncogenic NOTCH signaling through epigenetic regulation of MAML2 transcriptional activity.

Lubecka K¹, Kurzava L¹, Flower K², Buvala H¹, Zhang H³, Teegarden D⁴, Camarillo I⁵, Suderman M⁶, Kuang S⁷, Andrisani O⁸, Flanagan JM², Stefanska B⁹.

Author information

Abstract

DNA hypomethylation was previously implicated in cancer progression and metastasis. The purpose of this study was to examine whether stilbenoids, resveratrol and pterostilbene thought to exert anticancer effects, target genes with oncogenic function for de novo methylation and silencing, leading to inactivation of related signaling pathways. Following Illumina 450K, genome-wide DNA methylation analysis reveals that stilbenoids alter DNA methylation patterns in breast cancer cells. On average, 75% of differentially methylated genes have increased methylation, and these genes are enriched for oncogenic functions, including NOTCH signaling pathway. MAML2, a coactivator of NOTCH targets, is methylated at the enhancer region and transcriptionally silenced in response to stilbenoids, possibly explaining the downregulation of NOTCH target genes. The increased DNA methylation at MAML2 enhancer coincides with increased occupancy of repressive histone marks and decrease in activating marks. This condensed chromatin structure is associated with binding of DNMT3B and decreased occupancy of OCT1 transcription factor at MAML2 enhancer, suggesting a role of DNMT3B in increasing methylation of MAML2 after stilbenoid treatment. Our results deliver a novel insight into epigenetic regulation of oncogenic signals in cancer and provide support for epigenetic-targeting strategies as an effective anticancer approach.

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PMID: 27207652
Pterostilbene inhibits lung cancer through induction of apoptosis.

Schneider JG¹, Alosi JA, McDonald DE, McFadden DW.

Author information

Abstract

BACKGROUND:
Lung cancer remains the leading cause of cancer mortality in the United States. Resveratrol is a potent antioxidant found in grapes that inhibits several types of cancer, including lung cancer. Herein, we investigated the effects of pterostilbene, an analog of resveratrol found in blueberries, on lung cancer, in vitro. We hypothesized that pterostilbene would inhibit lung cancer cell growth in vitro by a pro-apoptotic mechanism.

METHODS:
Two lung cancer cell lines (NCI-H460 and SK-MES-1) were cultured using standard techniques. Cells were treated with increasing doses of pterostilbene (10-100 microM). Cell viability was measured at 24, 48, and 72h using a MTT assay. Apo-ONE Caspase-3/7 assay was used to evaluate caspase activity. T-test and two-way ANOVA were used for statistical analysis.

RESULTS:
Pterostilbene significantly decreased cell viability in lung cancer cells in a concentration- and time-dependent manner (P<0.001). Concentrations greater than 20 microM of pterostilbene produced significant growth inhibition by 72h (P<0.001). Apoptosis and caspase-3/7 activity were significantly increased by pterostilbene treatment (P<0.05).

CONCLUSIONS:
Pterostilbene inhibits growth via apoptosis induction in vitro. Further in vitro mechanistic studies and in vivo experiments are warranted to determine the potential role for pterostilbene in lung cancer treatment or prevention.

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Pterostilbene exerts antitumor activity via the Notch1 signaling pathway in human lung adenocarcinoma cells.


Abstract

Although pterostilbene (PTE) has been shown to have potent antitumor activities against various cancer types, the molecular mechanisms of these activities remain unclear. In this study, we investigated the antitumor activity of PTE against human lung adenocarcinoma in vitro and in vivo and explored the role of the Notch1 signaling pathway in this process. PTE treatment resulted in a dose- and time-dependent decrease in the viability of A549 cells. Additionally, PTE exhibited strong antitumor activity, as evidenced not only by a reduced mitochondrial membrane potential (MMP) and a decreased intracellular glutathione content but also by increases in the apoptotic index and the level of reactive oxygen species (ROS). Furthermore, PTE treatment induced the activation of the Notch1 Intracellular Domain (NICD) protein and activated Hes1. DAPT (a gamma secretase inhibitor) and Notch1 siRNA prevented the induction of NICD and Hes1 activation by PTE treatment and sensitized the cells to PTE treatment. The down-regulation of Notch signaling also prevented the activation of pro-survival pathways (most notably the PI3K/Akt pathway) after PTE treatment. In summary, lung adenocarcinoma cells may enhance Notch1 activation as a protective mechanism in response to PTE treatment. Combining a gamma secretase inhibitor with PTE treatment may represent a novel approach for treating lung adenocarcinoma by inhibiting the survival pathways of cancer cells.

A combination of pterostilbene with autophagy inhibitors exerts efficient apoptotic characteristics in both chemosensitive and chemoresistant lung cancer cells.

Hsieh MJ, Lin CW, Yang SF, Sheu GT, Yu YY, Chen MK, Chiou HL.

Abstract
The emergence of multidrug resistance (MDR), meaning that cancer cells develop simultaneous resistance to different drugs, has limited the clinical efficacy and application of chemotherapy. Pterostilbene, a naturally occurring phytoalexin exerts a variety of pharmacologic activities, including cancer prevention, cytotoxicity, and antioxidant activity. In this study, results proved the capability of pterostilbene to effectively inhibit the cell viability of docetaxel-induced MDR human lung cancer cell lines through cell cycle arrest and apoptosis. Meanwhile, the observation of LC3-II production and formation of acidic vesicular organelles revealed an induction of autophagy at an early stage by pterostilbene, which was triggered by an inhibition of the AKT and JNK pathways and activation of ERK1/2. Furthermore, pretreatment with the autophagy inhibitors 3-methyladenine and bafilomycin A1 or with beclin-1 small interfering RNA was able to enhance pterostilbene-triggered apoptosis. In conclusion, this study demonstrated that pterostilbene causes autophagy and apoptosis in lung cancer cells. Furthermore, pterostilbene in combination with autophagy inhibitors may strengthen the efficiency of chemotherapeutic strategies in both chemosensitive and chemoresistant lung cancer cells, which may be of immense value for the clinical management of lung cancer patients with MDR.

**KEYWORDS:** apoptosis; autophagy; multidrug resistance; pterostilbene

PMID: 24154491


**UPLC-MS method for quantification of pterostilbene and its application to comparative study of bioavailability and tissue distribution in normal and Lewis lung carcinoma bearing mice.**

Deng L¹, Li Y², Zhang X³, Chen B¹, Deng Y¹, Li Y¹.

**Author information**

**Abstract**

A UPLC-MS method was developed for determination of pterostilbene (PTS) in plasma and tissues of mice. PTS was separated on Agilent Zorbax XDB-C18 column (50 × 2.1 mm, 1.8 μm) with gradient mobile phase at the flow rate of 0.2 ml/min. The detection was performed by negative ion electrospray ionization in multiple reaction monitoring mode. The linear calibration curve of PTS in mouse plasma and tissues ranged from 1.0 to 5000 and 0.50 to 500 ng/ml \((r^2>0.9979)\), respectively, with lowest limits of quantification (LLOQ) were between 0.5 and 2.0 ng/ml, respectively. The accuracy and precision of the assay were satisfactory. The validated method was applied to the study of bioavailability and tissue distribution of PTS in normal and Lewis lung carcinoma (LLC) bearing mice. The bioavailability of PTS (dose 14, 28 and 56
mg/kg) in normal mice were 11.9%, 13.9% and 26.4%, respectively; and the maximum level (82.1 ± 14.2 μg/g) was found in stomach (dose 28 mg/kg). The bioavailability, peak concentration (Cmax), time to peak concentration (Tmax) of PTS in LLC mice was increased compared with normal mice. The results indicated the UPLC-MS method is reliable and bioavailability and tissue distribution of PTS in normal and LLC mice were dramatically different.

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KEYWORDS:
Bioavailability; Pterostilbene; Tissue distribution; UPLC–MS

PMID: 26070162


ATM/CHK/p53 Pathway Dependent Chemopreventive and Therapeutic Activity on Lung Cancer by Pterostilbene.

Lee H1, Kim Y2, Jeong JH1, Ryu JH1, Kim WY1.

Author information

Abstract

Among the many stilbenoids found in a variety of berries, resveratrol and pterostilbene are of particular interest given their potential for use in cancer therapeutics and prevention. We purified four stilbenoids from R. undulatum and found that pterostilbene inhibits cancer cell proliferation more efficiently than rhapontigenin, piceatannol and resveratrol. To investigate the underlying mechanism of this superior action of pterostilbene on cancer cells, we utilized a reverse-phase protein array followed by bioinformatic analysis and found that the ATM/CHK pathway is modified by pterostilbene in a lung cancer cell line. Given that ATM/CHK signaling requires p53 for its biological effects, we hypothesized that p53 is required for the anticancer effect of pterostilbene. To test this hypothesis, we used two molecularly defined precancerous human bronchial epithelial cell lines, HBECR and HBECR/p53i, with normal p53 and suppressed p53 expression, respectively, to represent premalignant states of squamous lung carcinogenesis. Pterostilbene inhibited the cell cycle more efficiently in HBECR cellglis compared to HBECR/p53i cells, suggesting that the presence of p53 is required for the action of pterostilbene. Pterostilbene also activated ATM and CHK1/2, which are upstream of p53, in both cell lines, though pterostilbene-induced senescence was dependent on the presence of p53. Finally, pterostilbene more effectively inhibited p53-dependent cell proliferation compared to the other three stilbenoids. These results strongly support the potential chemopreventive effect of pterostilbene on p53-positive cells during early carcinogenesis.

PMID: 27612029
Pterostilbene prevents AKT-ERK axis-mediated polymerization of surface fibronectin on suspended lung cancer cells independently of apoptosis and suppresses metastasis.

Wang YJ¹,²,³, Lin JF¹, Cheng LH⁵, Chang WT⁵,⁶, Kao YH⁷, Chang MM⁶, Wang BJ¹,⁸,⁹, Cheng HC¹⁰,¹¹.

Author information

Abstract

BACKGROUND: Polymeric fibronectin (polyFN) assembled on suspended breast cancer cells is required for metastasis. Conceivably, drugs that target such polyFN may fight against cancer metastasis. While stilbene analogs trigger pro-apoptotic effect on attached cancer cells, whether they prevent polyFN assembly and metastasis of suspended cancer cells via an apoptosis-independent manner remains unexplored.

METHODS: We depleted suspended Lewis lung carcinoma (LLC) cells of polyFN by silencing the endogenous FN expression or pterostilbene (PS) to examine whether metastasis of lung cancer cells could thus be suppressed. We investigated whether PS regulates AKT-ERK signaling axis to suppress polyFN assembly in suspended LLC cells independently of apoptosis. We tested the therapeutic effects of orally administered PS against cancer metastasis.

RESULTS: Both FN-silencing and PS among the three stilbenoids indeed significantly reduced polyFN assembly and lung metastasis of suspended LLC cells in an apoptosis-independent manner. Mechanistically, PS-induced AKT phosphorylation (pAKT) and suppressed ERK phosphorylation (pERK) in suspended LLC cells, whereas pretreatment with a PI3K inhibitor, LY294002, effectively reduced pAKT, rescued pERK, and consequently reversed the PS-suppressed polyFN assembly on LLC cells; these pretreatment effects were then overturned by the ERK inhibitor U0126. Indeed, PS-suppressed lung metastasis was counteracted by LY294002, which was further overruled with U0126. Finally, we found that PS, when orally administered in experimental metastasis assays, both significantly prevented lung colonization and metastasis of LLC cells and reduced the already established tumor growth in the mouse lungs.
CONCLUSIONS:
PS suppressed AKT/ERK-regulated polyFN assembly on suspended LLC cells and pulmonary metastasis. PS possesses potency in both preventing and treating lung metastasis of lung cancer cells in apoptosis-independent and apoptosis-dependent manners, respectively.

KEYWORDS:
Fibronectin; PI3K/AKT/ERK signaling; Pericellular assembly; Pterostilbene; Pulmonary localization

PMID: 28327179
Pterostilbene suppresses human endometrial cancer cells in vitro by down-regulating miR-663b.

Wang YL¹, Shen Y², Xu JP², Han K¹, Zhou Y¹, Yang S¹, Yin JY¹, Min DL¹, Hu HY¹.

Author information

Abstract

Resveratrol has long been known as an antioxidant and a chemopreventive agent. Similar to resveratrol, pterostilbene (PT) is also a phenolic compound extracted from the Vitis species. However, there are few studies on the antitumor effect of PT. Thus, we investigated the effects of PT on the endometrial cancer (EC) cells in vitro and the related molecular mechanisms. Treatment of EC cell lines HTB-111 and Ishikawa with PT (25-100 μmol/L) dose-dependently suppressed the cell viability and induced apoptosis. Using miR microarrays, we examined the miR expression profile in Ishikawa cells with or without PT, and revealed that miR-663b was the most decreased in PT-treated Ishikawa cells. Furthermore, we predicted and verified that the pro-apoptosis factor BCL2L14 is the direct target of miR-663b. Over-expression of miR-663b and knock-down of BCL2L14 counteracted the suppressing effects of PT on HTB-111 and Ishikawa cells. In addition, we evaluated the miR-663b levels in EC tissues of 51 patients using an in situ hybridization technique. With the median of the score of miR-663b as a cut-off value, these EC patients were divided into two groups, and the patients with high miR-663b expression had significantly poor prognosis.

PMID: 28552912
**Prostate Cancer**


**Differential effects of resveratrol and its naturally occurring methylether analogs on cell cycle and apoptosis in human androgen-responsive LNCaP cancer cells.**

Wang TT¹, Schoene NW, Kim YS, Mizuno CS, Rimando AM.

**Author information**

**Abstract**

Stilbenes are phytoalexins that become activated when plants are stressed. These compounds exist in foods and are widely consumed. Resveratrol is a grape-derived stilbene, which possesses a wide range of health-promoting activities, including anticancer properties. Several other stilbenes structurally similar to resveratrol are also available in food, but their biological activities remain largely unknown. In this study, we compared the effects of resveratrol and its natural derivatives pterostilbene, trans-resveratrol trimethylether, trans-pinostilbene and trans-desoxyrhapontigenin on androgen-responsive human prostate cancer LNCaP cells. We found that these compounds exert differential effects on LNCaP cell growth, cell cycle and apoptosis. Trans-resveratrol trimethylether appeared to be the most potent compound among the stilbenes tested. Treatment of LNCaP cells with trans-resveratrol trimethylether resulted in G2/M blockage while other compounds, including resveratrol, induced G1/S arrest. Moreover, different from other compounds, trans-resveratrol trimethylether induced apoptosis. At the molecular level, the effects of these compounds on cell cycle correlated with induction of the cyclin-dependent kinase inhibitor 1A and B mRNA levels. Additionally, these compounds also inhibited both androgen- as well as estrogen-mediated pathways. These results provide mechanistic information on how resveratrol and its methylether analogs may act to contribute to potential antiprostate cancer activity.

PMID: 20077416


**Activation of AMPK by pterostilbene suppresses lipogenesis and cell-cycle progression in p53 positive and negative human prostate cancer cells.**

Lin VC¹, Tsai YC, Lin JN, Fan LL, Pan MH, Ho CT, Wu JY, Way TD.
Prostate cancer is one of the leading causes of cancer death in men in Western countries. Epidemiological studies have linked the consumption of fruits and vegetables to a reduced risk of prostate cancer, and small fruits are particularly rich sources of many active phytochemical stilbenes, such as pterostilbene. As a constituent of small fruits such as grapes, berries, and their products, pterostilbene is under intense investigation as a cancer chemopreventive agent. Using the p53 wild type LNCaP and p53 null PC3 cells, we found that treatment with pterostilbene resulted in dose-dependent inhibition of cellular proliferation, which suggested that the interaction of pterostilbene with the p53 might not fully explain its inhibitory effect on proliferation. In this study, we found that pterostilbene activated AMPK in both p53 positive and negative human prostate cancer cells. Pterostilbene-activated AMPK decreased the activity and/or expression of lipogenic enzymes, such as fatty acid synthase (FASN) and acetyl-CoA carboxylase (ACC). Interestingly, the resolution between apoptosis and growth arrest following AMPK activation is greatly influenced by p53 status. In p53 positive LNCaP cells, pterostilbene blocked the progression of cell cycle at G1 phase by inducing p53 expression and further up-regulating p21 expression. However, pterostilbene induced apoptosis in p53 negative PC3 cells. Our results suggest that pterostilbene may be a functional chemopreventive agent and that dietary exposure to pterostilbene would be helpful for antiprostate cancer activity.

PMID: 22670709


Pterostilbene acts through metastasis-associated protein 1 to inhibit tumor growth, progression and metastasis in prostate cancer.

Li K, Dias SJ, Rimando AM, Dhar S, Mizuno CS, Penman AD, Lewin JR, Levenson AS.
acetylation, confirming superior potency over resveratrol as dietary epigenetic agent. In orthotopic PCa xenografts, resveratrol and PTER significantly inhibited tumor growth, progression, local invasion and spontaneous metastasis. Furthermore, MTA1-knockdown sensitized cells to these agents resulting in additional reduction of tumor progression and metastasis. The reduction was dependent on MTA1 signaling showing increased p53 acetylation, higher apoptotic index and less angiogenesis in vivo in all xenografts treated with the compounds, and particularly with PTER. Altogether, our results indicate MTA1 as a major contributor in prostate tumor malignant progression, and support the use of strategies targeting MTA1. Our strong pre-clinical data indicate PTER as a potent, selective and pharmacologically safe natural product that may be tested in advanced PCa.

PMID: 23469203


Epigenetic potential of resveratrol and analogs in preclinical models of prostate cancer.

Kumar A1, Dhar S1, Rimando AM2, Lage JM3, Lewin JR3, Zhang X4, Levenson AS1,3.

Author information

Abstract

Lifestyle, particularly diet, is a risk factor for prostate cancer. Dietary polyphenols such as resveratrol possess anticancer properties and therefore have chemopreventive and therapeutic potential. Resveratrol has pleiotropic effects, exerting its biological activity through multiple pathways and targets, including those associated with cancer. Numerous studies have demonstrated the anticancer effects of resveratrol and, to a lesser extent, its analogs, in tissue culture, while in vivo observations are limited. Here, we provide a concise summary of our results on epigenetic mechanisms of resveratrol and analogs mediated through regulation of chromatin modifier metastasis-associated protein 1 (MTA1) and microRNAs (miRNAs), and highlight the anticancer effects of these compounds in preclinical models of prostate cancer. We suggest that the identified stilbene responsive mechanism-based biomarkers, such as MTA1 and oncogenic miRNAs, may become indicative of treatment efficacy in prostate cancer. Resveratrol analogs with better bioavailability, conferring superior pharmacological potencies and greater anticancer effects, may become stronger candidates for clinical development.


KEYWORDS:
MTA1; miRNA; preclinical models; prostate cancer epigenetics; pterostilbene; resveratrol

PMID: 26214308
**Resveratrol and pterostilbene epigenetically restore PTEN expression by targeting oncomiRs of the miR-17 family in prostate cancer.**

Dhar S\(^1\), Kumar A\(^1\), Rimando AM\(^2\), Zhang X\(^3\), Levenson AS\(^1,4\).

**Author information**

**Abstract**

In recent years, not only has the role of miRNAs in cancer become increasingly clear but also their utilization as potential biomarkers and therapeutic targets has gained ground. Although the importance of dietary stilbenes such as resveratrol and pterostilbene as anti-cancer agents is well recognized, our understanding of their miRNA-targeting capabilities is still limited. In our previous study, we reported that resveratrol downregulates PTEN-targeting members of the oncogenic miR-17 family, which are overexpressed in prostate cancer. This study investigates the resveratrol and pterostilbene induced miRNA-mediated regulation of PTEN in prostate cancer. Here, we show that both compounds decrease the levels of endogenous as well as exogenously expressed miR-17, miR-20a and miR-106b thereby upregulating their target PTEN. Using functional luciferase reporter assays, we demonstrate that ectopically expressed miR-17, miR-20a and miR-106b directly target PTEN 3'UTR to reduce its expression, an effect rescued upon treatment with resveratrol and pterostilbene. Moreover, while stable lentiviral expression of miR-17/106a significantly decreased PTEN mRNA and protein levels and conferred survival advantage to the cells, resveratrol and more so pterostilbene was able to dramatically suppress these effects. Further, pterostilbene through downregulation of miR-17-5p and miR-106a-5p expression both in tumors and systemic circulation, rescued PTEN mRNA and protein levels leading to reduced tumor growth in vivo. Our findings implicate dietary stilbenes as an attractive miRNA-mediated chemopreventive and therapeutic strategy, and circulating miRNAs as potential chemopreventive and predictive biomarkers for clinical development in prostate cancer.

**KEYWORDS:**
PTEN; oncomiRs; prostate cancer epigenetics; pterostilbene; resveratrol

PMID: 26318586

**Dietary pterostilbene is a novel MTA1-targeted chemopreventive and therapeutic agent in prostate cancer.**
Overexpression of the epigenetic modifier metastasis-associated protein 1 (MTA1) is associated with aggressive human prostate cancer. The purpose of this study was to determine MTA1-targeted chemopreventive and therapeutic efficacy of pterostilbene, a natural potent analog of resveratrol, in pre-clinical models of prostate cancer. Here, we show that high levels of MTA1 expression in Pten-loss prostate cooperate with key oncogenes, including c-Myc and Akt among others, to promote prostate cancer progression. Loss-of-function studies using human prostate cancer cells indicated direct involvement of MTA1 in inducing inflammation and epithelial-to-mesenchymal transition. Importantly, pharmacological inhibition of MTA1 by pterostilbene resulted in decreased proliferation and angiogenesis and increased apoptosis. This restrained prostatic intraepithelial neoplasia (PIN) formation in prostate-specific Pten heterozygous mice and reduced tumor development and progression in prostate-specific Pten-null mice. Our findings highlight MTA1 as a key upstream regulator of prostate tumorigenesis and cancer progression. More significantly, it offers pre-clinical proof for pterostilbene as a promising lead natural agent for MTA1-targeted chemopreventive and therapeutic strategy to curb prostate cancer.

KEYWORDS:
MTA1; chemoprevention; prostate cancer; pterostilbene; therapy

PMID: 26943043

Resveratrol and pterostilbene as a microRNA-mediated chemopreventive and therapeutic strategy in prostate cancer.

Kumar A, Rimando AM, Levenson AS.

Author information

Abstract

Growing evidence indicates that deregulation of the epigenetic machinery comprising the microRNA (miRNA) network is a critical factor in the progression of various diseases, including cancer. Concurrently, dietary phytochemicals are being intensively studied for their miRNA-mediated health-beneficial properties, such as anti-inflammatory, cardioprotective, antioxidative,
and anticancer properties. Available experimental data have suggested that dietary polyphenols may be effective miRNA-modulating chemopreventive and therapeutic agents. Moreover, noninvasive detection of changes in miRNA expression in liquid biopsies opens enormous possibilities for their clinical utilization as novel prognostic and predictive biomarkers. In our published studies, we identified resveratrol-regulated miRNA profiles in prostate cancer. Resveratrol downregulated the phosphatase and tensin homolog (PTEN)-targeting members of the oncogenic miR-17 family of miRNAs, which are overexpressed in prostate cancer. We have functionally validated the miRNA-mediated ability of resveratrol and its potent analog pterostilbene to rescue the tumor suppressor activity of PTEN in vitro and in vivo. Taken together, our findings implicate the use of resveratrol and its analogs as an attractive miRNA-mediated chemopreventive and therapeutic strategy in prostate cancer and the use of circulating miRNAs as potential predictive biomarkers for clinical development.


**KEYWORDS:**
biomarkers; microRNAs; prostate cancer; pterostilbene; resveratrol

PMID: 28662290
Pterostilbene inhibits pancreatic cancer in vitro.

Mannal PW\textsuperscript{1}, Alosi JA, Schneider JG, McDonald DE, McFadden DW.

Author information

Abstract

INTRODUCTION:
Stilbenes are phenolic compounds present in grapes and blueberries. Resveratrol, a naturally occurring compound present in grapes, has been shown to have potent antioxidant properties as well as an ability to induce apoptosis. Resveratrol has also been reported to have significant inhibitory effects against a variety of primary tumors including breast, colon, and prostate. Pterostilbene, a naturally occurring analogue of resveratrol found in blueberries, also has antioxidant and antiproliferative properties. It is also substantially more bioavailable orally than resveratrol. These effects have not been studied in pancreatic cancer. We hypothesized that pterostilbene would inhibit pancreatic cancer cell growth in vitro.

MATERIALS AND METHODS:
Two pancreatic cancer cell lines (MIA PaCa and PANC-1) were cultured using standard techniques. Cells were treated with graduated doses of pterostilbene ranging from 10 to 100 microM. Cell viability was measured by MTT at 24, 48, and 72 h.

RESULTS:
Pterostilbene decreases cell viability in both cancer cell lines in a concentration- and time-dependent manner. Higher doses (75-100 microM) caused a significant reduction in cell viability at 24 and 48 h. However, by 72 h, all tested concentrations of pterostilbene (10 to 100 microM) resulted in significantly reduced cell viability in both pancreatic cancer cell lines in a dose-dependent fashion. Pterostilbene caused a dose-dependent 10-63% inhibition in MIA PaCa-2 cells and 10-75% inhibition in PANC-1 cells.
DISCUSSION:
Treatment of pancreatic cancer cells in vitro with Pterostilbene leads to inhibition of cell proliferation and/or cell death, cell cycle arrest, mitochondrial membrane depolarization, and activation of effector caspases. This naturally occurring agent may have a role in treating pancreatic cancer.

CONCLUSIONS:
Pterostilbene inhibits the growth of pancreatic cancer in vitro. Further, in vitro mechanistic studies and in vivo experiments are warranted to determine its potential for the treatment of pancreatic cancer.

PMID: 20140535

Genomic analysis of pterostilbene predicts its antiproliferative effects against pancreatic cancer in vitro and in vivo.

McCormack DE¹, Mannal P, McDonald D, Tighe S, Hanson J, McFadden D.

Author information

Abstract

BACKGROUND:
To investigate the inhibitory role of pterostilbene in pancreatic cancer, we conducted a genomic analysis of pterostilbene-treated pancreatic cancer cells. We also investigated the effect of pterostilbene upon the carcinogenic markers, manganese superoxide dismutase, cytochrome C, Smac/DIABLO, and STAT3 phosphorylation in vitro. The antiproliferative effects of pterostilbene were further evaluated in an in vivo model.

METHODS:
Pancreatic cancer cells were treated with pterostilbene and evaluated with DNA microarray analysis. Pterostilbene-treated cells were analyzed for cytochrome C, Smac/DIABLO, manganese superoxide dismutase (MnSOD)/antioxidant activity, and STAT3 phosphorylation using ELISA. Data were statistically analyzed using ANOVA. Pterostilbene was then administered to nude mice for 8 weeks, and tumor growth rates were recorded and statistically analyzed.
RESULTS:
Microarray analysis of pterostilbene-treated cells revealed upregulation of pro-apoptosis genes. In vitro, pterostilbene treatment altered levels of phosphorylated STAT3, MnSOD/antioxidant activity, cytochrome C, and Smac/DIABLO. In nude mice, oral pterostilbene inhibited tumor growth rates.

CONCLUSION:
Pterostilbene alters gene expression in pancreatic cancer and increases the antiproliferative markers cytochrome C, Smac/DIABLO, and MnSOD/antioxidant activity. It was also shown to inhibit phosphorylated STAT3, a marker of accelerated tumorigenesis, and decrease pancreatic tumor growth in vivo. Further studies are warranted to elucidate the effects of pterostilbene in humans.

PMID: 22450950


Inhibitory effects of (-)-epigallocatechin-3-gallate and pterostilbene on pancreatic cancer growth in vitro.

Kostin SF¹, McDonald DE, McFadden DW.

Author information

Abstract

BACKGROUND:
It has been previously shown that the naturally occurring antioxidant (-)-epigallocatechin-3-gallate (EGCG), found in green tea, and pterostilbene, a stilbenoid derived from blueberries, inhibit pancreatic cancer in vitro when used individually. We hypothesized that the combination of EGCG and pterostilbene would reveal additive effects in vitro.

METHODS:
Using the pancreatic cancer cell lines MIA PaCa-2 and PANC-1, efficacy and synergism were evaluated for cell proliferation and viability (3-(4,5-dimethylthiazol-2-y1)-2,5-diphenltetrazolium bromide assays, cell cycle analysis) and mitochondrial apoptosis (mitochondrial depolarization, cytochrome C release, caspase-3/7 activity, cell death detection using enzyme-linked immunosorbent assay).
RESULTS:
Cell proliferation assays revealed significant additive antiproliferative effects with pterostilbene and EGCG in both cell lines at the later, 72-h, point (P < 0.05). MIA underwent S-phase arrest with the combination (10-12% increase); however, cell cycle arrest was not observed in PANC. The combination induced mitochondrial depolarization and upregulated cytochrome C (P < 0.05) in MIA, but these effects were not observed in PANC. EGCG increased caspase-3/7 in MIA; however, the combination did not significantly increase the activity in either cell line (P < 0.05). Apoptosis was only observed in PANC (P < 0.05). The reduction in proliferation in MIA in the 3-(4,5-dimethylthiazol-2-y1)-2,5-diphenltetrazolium bromide assays with the combination indicated that cell death occurs, possibly through another mechanism.

CONCLUSIONS:
Our results are encouraging regarding the future use of EGCG and pterostilbene to improve traditional pancreatic cancer therapies. In conclusion, EGCG and pterostilbene have additive, antiproliferative effects in vitro and alter the apoptotic mechanisms in both cell lines by modulation at different points in the mechanism.

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PMID: 22583593
Pterostilbene induces autophagy and apoptosis in sensitive and chemoresistant human bladder cancer cells.

Chen RJ¹, Ho CT, Wang YJ.

Author information

Abstract

SCOPE:
Bladder cancer is one of the most common malignancies in the world. The majority of bladder cancer deaths are due to unresectable lesions that are resistant to chemotherapy. Pterostilbene (PT), a naturally occurring phytoalexin, possesses a variety of pharmacologic activities, including antioxidant, cancer prevention activity and cytotoxicity to many cancers. We found that PT effectively inhibits the growth of sensitive and chemoresistant human bladder cancer cells by inducing cell cycle arrest, autophagy and apoptosis. Down-regulations of Cyclin A, B and D1 and pRB are the results of PT-induced cell cycle arrest.

METHODS AND RESULTS:
Autophagy occurred at an early stage and was observed through the formation of acidic vesicular organelles (the marker for autophagy) and microtubule-associated protein 1 light chain 3-II production. Apoptosis occurred at a later stage and was detected by Annexin V and 4’,6-diamidino-2-phenylindole staining. PT-induced autophagy was triggered by the inhibition of active human protein kinase/the mammalian TOR/p70S6K pathway and activation of extracellular signal-regulated kinase pathway. Inhibition of autophagy by pretreatment with 3-methyladenine, bafilomycin A1, Beclin 1 or extracellular signal-regulated kinase short hairpin RNA enhanced PT-triggered apoptosis.

CONCLUSION:
This is the first study to demonstrate that PT causes autophagy in cancer cells and suggests that PT could serve as a new and promising agent for the treatment of sensitive and chemoresistant bladder cancer cells.

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PMID: 20603834
Pterostilbene exerts antitumor activity against human osteosarcoma cells by inhibiting the JAK2/STAT3 signaling pathway.


Abstract

Osteosarcoma is a high-grade malignant bone tumor. Pterostilbene (PTE) is a natural, dimethylated analog of resveratrol with higher bioavailability. While PTE has been shown to have potent antitumor activity against various types of cancer, the molecular mechanisms underlying the effects of PTE remain largely unknown. The Janus kinase 2/Signal Transducer and Activator of Transcription 3 (JAK2/STAT3) signaling pathway plays a crucial role in tumorigenesis and immune development. In this study, we assessed the antitumor activity of PTE against human osteosarcoma cells and explored the role of JAK2/STAT3 and apoptosis-related signaling pathways on the activity of PTE. PTE treatment resulted in a dose- and time-dependent inhibition of osteosarcoma cell viability. Additionally, PTE exhibited strong antitumor activity, as evidenced not only by reductions in tumor cell adhesion, migration and mitochondrial membrane potential (MMP) but also by increases in the apoptotic index, reactive oxygen species (ROS) and several biochemical parameters. Furthermore, PTE treatment directly inhibited the phosphorylation of JAK2 at Tyr 1007 and the downstream activation of STAT3. PTE also down-regulated the expression of STAT3 target genes, including the anti-apoptotic proteins Bcl-xL and Mcl-1, leading to the up-regulation of mitochondrial apoptosis pathway-related proteins (Bax, Bak, cytosolic Cytochrome c, and cleaved Caspase3) and cyclin-dependent kinase inhibitors such as p21 and p27. PTE, used in combination with a known JAK2/STAT3 inhibitor, AG490, further decreased the viability of osteosarcoma cells. Taken together, PTE is a potent inhibitor of osteosarcoma cell growth that targets the JAK2/STAT3 signaling pathway. These data suggest that inhibition of JAK2/STAT3 signaling is a novel mechanism of action for PTE during therapeutic intervention in osteosarcoma cancers.
Oral Cancer


Pterostilbene suppresses oral cancer cell invasion by inhibiting MMP-2 expression.

Lin CW¹, Chou YE, Chiou HL, Chen MK, Yang WE, Hsieh MJ, Yang SF.

Abstract

OBJECTIVE:
Polyphenol compounds, present in a wide variety of natural plants, exhibit antioxidant and free radical scavenging ability and induce apoptosis in various cancer cells. However, the effect of pterostilbene on oral cancer cell metastasis has not been clarified.

RESEARCH DESIGN AND METHODS:
The present study aimed to examine the anti-metastatic properties of pterostilbene in human oral squamous cell carcinoma (SCC)-9 cells.

RESULTS:
In this study, pterostilbene treatment significantly inhibited migration/invasion capacities of SCC-9 cells in vitro. The results of zymography and western blotting revealed that the activities and protein levels of the MMP-2 and urokinase-type plasminogen activator (u-PA) was inhibited by pterostilbene. Western blot analysis also showed that pterostilbene inhibits the phosphorylation of Akt, extracellular signal-regulated kinase 1/2 and p38. Determinations of the mRNA levels, real-time polymerase chain reaction and promoter assays were conducted to evaluate the inhibitory effects of pterostilbene on MMP-2 and u-PA expression in SCC-9 cells. Such inhibitory effects were associated with the upregulation of tissue inhibitor of metalloproteinase-2, plasminogen activator inhibitor-1 and the downregulation of the transcription factors of NF-κB, SP-1 and CREB signaling pathways.

CONCLUSIONS:
Pterostilbene may have potential use as a chemopreventive agent against oral cancer metastasis.
KEYWORDS:
MMP-2; migration; oral cancer; pterostilbene; urokinase-type plasminogen activator

PMID: 25109417


**Pterostilbene induce autophagy on human oral cancer cells through modulation of Akt and mitogen-activated protein kinase pathway.**

Ko CP¹, Lin CW², Chen MK³, Yang SF⁴, Chiou HL⁵, Hsieh MJ⁶.

**Author information**

**Abstract**

**OBJECTIVES:**
Extensive research supports the administration of herbal medicines or natural foods during cancer therapy. Pterostilbene, a naturally occurring phytoalexin, has various pharmacological activities, including antioxidant activity, cancer prevention activity, and cytotoxicity to many cancers. However, the effect of pterostilbene on the autophagy of tumor cells has not been clarified.

**MATERIALS AND METHODS:**
In this study, the unique effects of pterostilbene on the autophagy of human oral cancer cells were investigated.

**RESULTS:**
The results of this study showed that pterostilbene effectively inhibited the growth of human oral cancer cells by inducing cell cycle arrest and apoptosis. In addition, the formation of acidic vesicular organelles and LC3-II production also demonstrated that pterostilbene induced autophagy. Administering 3-methylamphetamime (3-MA) and bafilomycin A1 (BafA1) exerted differing effects on the pterostilbene-induced death of human oral cancer cells. Pterostilbene-induced autophagy was triggered by activation of JNK1/2 and inhibition of Akt, ERK1/2, and p38.
CONCLUSION:
In conclusion, this study demonstrated that pterostilbene caused autophagy and apoptosis in human oral cancer cells, suggesting that pterostilbene could serve as a new and promising agent for treating human oral cancer.

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KEYWORDS:
Apoptosis; Autophagy; MAPK; Oral cancer; Phytoalexin; Pterostilbene

PMID: 25883032


Potential Compounds for Oral Cancer Treatment:
Resveratrol, Nimbolide, Lovastatin, Bortezomib, Vorinostat, Berberine, Pterostilbene, Deguelin, Andrographolide, and Colchicine.

Bundela S1,2, Sharma A2, Bisen PS1,3.

Author information

Abstract

Oral cancer is one of the main causes of cancer-related deaths in South-Asian countries. There are very limited treatment options available for oral cancer. Research endeavors focused on discovery and development of novel therapies for oral cancer, is necessary to control the ever rising oral cancer related mortalities. We mined the large pool of compounds from the publicly available compound databases, to identify potential therapeutic compounds for oral cancer. Over 84 million compounds were screened for the possible anti-cancer activity by custom build SVM classifier. The molecular targets of the predicted anti-cancer compounds were mined from reliable sources like experimental bioassays studies associated with the compound, and from protein-compound interaction databases. Therapeutic compounds from DrugBank, and a list of natural anti-cancer compounds derived from literature mining of published studies, were used for building partial least squares regression model. The regression model thus built, was used for the estimation of oral cancer specific weights based on the molecular targets. These weights were used to compute scores for screening the predicted anti-cancer compounds for their potential to treat oral cancer. The list of potential compounds was annotated with corresponding physicochemical properties, cancer specific bioactivity evidences, and literature evidences. In all, 288 compounds with the potential to treat oral cancer were identified in the current study. The majority of the compounds in this list are natural products, which are well-tolerated and have minimal side-effects compared to the synthetic counterparts. Some of the potential therapeutic
compounds identified in the current study are resveratrol, nimbolide, lovastatin, bortezomib, vorinostat, berberine, pterostilbene, deguelin, andrographolide, and colchicine.

PMID: 26536350


Pterostilbene Inhibits the Growth of Human Esophageal Cancer Cells by Regulating Endoplasmic Reticulum Stress.


Abstract

BACKGROUND/AIMS: Pterostilbene (PTE), a natural dimethylated resveratrol analog from blueberries, is known to have diverse pharmacological activities, including anticancer properties. In this study, we investigated the anticancer activity of PTE against human esophageal cancer cells both in vitro and in vivo and explored the role of endoplasmic reticulum (ER) stress (ERS) signaling in this process.

METHODS: Cell viability, the apoptotic index, Caspase 3 activity, adhesion, migration, reactive oxygen species (ROS) levels, and glutathione (GSH) levels were detected to explore the effect of PTE on human EC109 esophageal cancer cells. Furthermore, siRNA transfection and a chemical inhibitor were employed to confirm the role of ERS.

RESULTS: PTE treatment dose- and time-dependently decreased the viability of human esophageal cancer EC109 cells. PTE also decreased tumor cell adhesion, migration and intracellular GSH levels while increasing the apoptotic index, Caspase 3 activity and ROS levels, which suggest the strong anticancer activity of PTE. Furthermore, PTE treatment increased the expression of ERS-related molecules (GRP78, ATF6, p-PERK, p-eIF2α and CHOP), upregulated the pro-apoptosis-related protein PUMA and downregulated the anti-apoptosis-related protein Bcl-2 while promoting the translocation of cytochrome c from mitochondria to cytosol and the activation of Caspase 9 and Caspase 12. The downregulation of ERS signaling by CHOP siRNA desensitized esophageal cancer cells to PTE treatment, whereas upregulation of ERS signaling by thapsigargin (THA) had the opposite effect. N-Acetylcysteine (NAC), a ROS scavenger, also desensitized esophageal cancer cells to PTE treatment.
CONCLUSIONS:
Overall, the results indicate that PTE is a potent anti-cancer pharmaceutical against human esophageal cancer, and the possible mechanism involves the activation of ERS signaling pathways.

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PMID: 26982591
Ovarian Cancer


Pterostilbene induces apoptosis through caspase activation in ovarian cancer cells.

Dong J, Guo H, Chen Y.

Abstract

AIM:
Pterostilbene, an analog of resveratrol increasing bioavailability has shown to offer antioxidant and anticancer properties in vitro and in vivo. Dietary compounds with anti-oxidant properties have been shown to gain importance due to therapeutic applications. In addition, compounds with higher bioavailability levels show great interest in present scenario. Thus, the present study aimed at investigating the cytotoxic role of pterostilbene and its mechanism of cell death in ovarian cancer cells line.

MATERIALS AND METHODS:
The effect of pterostilbene was determined on SKOV-3 cells, by cytotoxicity assays, oxidative stress levels, [Ca2+]i levels, mitochondrial depolarization, cell cycle analysis and caspase 3, 8, and 9 activities.

RESULTS:
The study revealed that pterostilbene offered cytotoxic effect at a concentration of IC50-55 uM. Further, pterostilbene induced reactive oxygen species (ROS) mediated intrinsic pathway of apoptosis through enhancing oxidative stress, [Ca2+]i levels, mitochondrial depolarization, Sub G1 accumulation, and activation of caspase 3 and 9.

CONCLUSION:
The study demonstrates for the first time the cytotoxic potential of pterostilbene against ovarian cancer cells.

PMID: 27352561
Anticancer Activity of Pterostilbene in Human Ovarian Cancer Cell Lines.

Pei HL\textsuperscript{1}, Mu DM\textsuperscript{2}, Zhang B\textsuperscript{2}.

Author information

Abstract

BACKGROUND Epithelial ovarian cancer is a major cause of mortality in women and one of the most common gynecologic disorders. Pterostilbene (PTS), a trans-3,5-dimethoxy-4'-hydroxystilbene, was chosen for this work due to its reported effectiveness as a chemotherapeutic agent in cancer studies. In this work, we studied underlying molecular mechanisms of PTS treatment in various ovarian cancer cell lines such as OVCAR8, OV1063, IGROV-1, and SKOV3. MATERIAL AND METHODS We used the cytometric bead array (CBA) method and real-time PCR analysis to analyze the secretion level of tumor necrosis factor alpha (TNF-\textalpha) and to measure the TNF-\textalpha mRNA expression. NF-kappa B (NF-\kappa B) promoter analysis, Western blot analysis, electrophoresis mobility shift assay (EMSA), and immunostaining analyses were performed to measure the NF-\kappa B activity and other relative proteins levels. RESULTS The PTS treatment decreased the release of TNF-\textalpha in IGROV-1 ovarian cancer cells. It also showed significant inhibitory effect on nuclear NF-\kappa B p50, and NF-\kappa B p65 protein levels. CONCLUSIONS From the results obtained, we suggest that PTS has the potential to treat ovarian cancer by reducing the level of TNF-\textalpha cytokine and to have a limited effect on NF-\kappa B, AKT, and ERK signaling pathways.

PMID: 28664898
Comparative drug pair screening across multiple glioblastoma cell lines reveals novel drug-drug interactions.


Abstract

BACKGROUND: Glioblastoma multiforme (GBM) is the most aggressive brain tumor in adults, and despite state-of-the-art treatment, survival remains poor and novel therapeutics are sorely needed. The aim of the present study was to identify new synergistic drug pairs for GBM. In addition, we aimed to explore differences in drug-drug interactions across multiple GBM-derived cell cultures and predict such differences by use of transcriptional biomarkers.

METHODS: We performed a screen in which we quantified drug-drug interactions for 465 drug pairs in each of the 5 GBM cell lines U87MG, U343MG, U373MG, A172, and T98G. Selected interactions were further tested using isobole-based analysis and validated in 5 glioma-initiating cell cultures. Furthermore, drug interactions were predicted using microarray-based transcriptional profiling in combination with statistical modeling.

RESULTS: Of the 5 × 465 drug pairs, we could define a subset of drug pairs with strong interaction in both standard cell lines and glioma-initiating cell cultures. In particular, a subset of pairs involving the pharmaceutical compounds rimcazole, sertraline, pterostilbene, and gefitinib showed a strong interaction in a majority of the cell cultures tested. Statistical modeling of microarray and interaction data using sparse canonical correlation analysis revealed several predictive biomarkers, which we propose could be of importance in regulating drug pair responses.
CONCLUSION:
We identify novel candidate drug pairs for GBM and suggest possibilities to prospectively use transcriptional biomarkers to predict drug interactions in individual cases.

KEYWORDS:
drug combination responses; glioblastoma stem cell cultures; glioblastoma therapy; predictive medicine

PMID: 24101737


Pterostilbene suppressed irradiation-resistant glioma stem cells by modulating GRP78/miR-205 axis.

Huynh TT1, Lin CM2, Lee WH3, Wu AT4, Lin YK5, Lin YF6, Yeh CT7, Wang LS8

Author information

Abstract

Glioblastoma multiforme (GBM) is the most aggressive type characterized by relapse and resistance even with the combination of radio- and chemotherapy. The presence of glioma stem cells (GSCs) has been shown to contribute to tumorigenesis, recurrence and treatment resistance. Particularly, CD133-positive glioma cells have been shown to represent the subpopulation that confers glioma radioresistance and suggested to be the source of tumor recurrence after radiation. Thus, a better understanding and the development of agents which target GSCs could potentially lead to a significant improvement in treating GBM patients. Here, we demonstrated that GRP78 (an antistress protein) was highly expressed in GBM cells along with β-catenin and Notch and correlated to the development of GSCs. CD133+ GSCs exhibited enhanced migration/invasion and self-renewal abilities. When GRP78 was silenced, GSC properties were suppressed and the sensitivity towards irradiation increased. In addition, the level of microRNA 205 appeared to be negatively associated with GRP78 expression. Our previous study indicated that pterostilbene (PT) possessed anticancer stem cell properties in hepatocellular carcinoma. Thus, we examined whether PT is also effective against GSCs. We found that PT-treated GSCs exhibited suppressed self-renewal and irradiation-resistant abilities. PT-mediated effects were associated with an increase of miR-205. Finally, we showed that PT treatment suppressed tumorigenesis in GSC xenograft mice. In conclusion, we provided evidence that GRP78/miR-205 axis played an important role in GSC maintenance and irradiation resistance. PT treatment suppressed GSC development via negatively modulating GRP78 signaling. PT may be considered for combined therapeutic agent to enhance irradiation efficacy in GBM patients.

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Activation of the c-Met Pathway Mobilizes an Inflammatory Network in the Brain Microenvironment to Promote Brain Metastasis of Breast Cancer.


Author information

Abstract

Brain metastasis is one of the chief causes of mortality in breast cancer patients, but the mechanisms that drive this process remain poorly understood. Here, we report that brain metastatic cells expressing high levels of c-Met promote the metastatic process via inflammatory cytokine upregulation and vascular reprogramming. Activated c-Met signaling promoted adhesion of tumor cells to brain endothelial cells and enhanced neovascularization by inducing the secretion of IL8 and CXCL1. Additionally, stimulation of IL1β secretion by activation of c-Met induced tumor-associated astrocytes to secrete the c-Met ligand HGF. Thus, a feed-forward mechanism of cytokine release initiated and sustained by c-Met fed a vicious cycle that generated a favorable microenvironment for metastatic cells. Reinforcing our results, we found that pterostilbene, a compound that penetrates the blood-brain barrier, could suppress brain metastasis by targeting c-Met signaling. These findings suggest a potential utility of this natural compound for chemoprevention. Cancer Res; 76(17); 4970-80. ©2016 AACR.

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PMID: 27364556


Case-specific potentiation of glioblastoma drugs by pterostilbene.
Glioblastoma multiforme (GBM, astrocytoma grade IV) is the most common malignant primary brain tumor in adults. Addressing the shortage of effective treatment options for this cancer, we explored repurposing of existing drugs into combinations with potent activity against GBM cells. We report that the phytoalexin pterostilbene is a potentiator of two drugs with previously reported anti-GBM activity, the EGFR inhibitor gefitinib and the antidepressant sertraline. Combinations of either of these two compounds with pterostilbene suppress cell growth, viability, sphere formation and inhibit migration in tumor GBM cell (GC) cultures. The potentiating effect of pterostilbene was observed to a varying degree across a panel of 41 patient-derived GCs, and correlated in a case specific manner with the presence of missense mutation of EGFR and PIK3CA and a focal deletion of the chromosomal region 1p32. We identify pterostilbene-induced cell cycle arrest, synergistic inhibition of MAPK activity and induction of Thioredoxin interacting protein (TXNIP) as possible mechanisms behind pterostilbene's effect. Our results highlight a nontoxic stilbenoid compound as a modulator of anticancer drug response, and indicate that pterostilbene might be used to modulate two anticancer compounds in well-defined sets of GBM patients.

KEYWORDS: cancer therapeutics; drug repurposing; glioblastoma; glioblastoma initiating cells; stilbenoids

PMID: 27689322

The effect of resveratrol, its naturally occurring derivatives and tannic acid on the induction of cell cycle arrest and apoptosis in rat C6 and human T98G glioma cell lines.

Zielińska-Przyjemska M¹, Kaczmarek M², Krajka-Kuźniak V¹, Łuczak M³, Baer-Dubowska W⁴.

Author information

Resveratrol (3,5,4′-trihydroxy-trans-stilbene) is a potent chemopreventive and potentially cancer therapeutic agent. Since rapid metabolism limits resveratrol bioavailability, derivatives less prone to metabolic transformation are being sought and tested. We evaluated the effect of
resveratrol, and its analogs (pterostilbene and 3,5,4'-trimethoxystilbene) along with tannic acid, on cell cycle and apoptosis in rat C6 and human T98G glioma cells. At concentration ranges both lower and higher than IC_{50} calculated based on MTT assay, all these polyphenols affected the cell cycle distribution. However, resveratrol and pterostilbene increased the percentage of the cells in S phase, while trimethoxystilbene (TMS) caused a massive accumulation of cells at the G2/M phase of the cell cycle. Tannic acid had no effect on cell cycle distribution in C6 cells, but increased the number of dead cells in both glioma cell lines. The ability to induce apoptosis by tannic acid and stilbenes was confirmed by phosphatidylserine externalization, the loss of mitochondrial membrane potential and the level of cleaved caspase-3. The apoptosis rate was most significantly increased by TMS and this was related to p53 induction. These results indicate that methoxylated stilbenes are efficient inhibitors of glioma cell proliferation and apoptosis inducers and might be considered adjuvants in glioma therapy.

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**KEYWORDS:**
Apoptosis; Cell cycle; Human T98G glioblastoma cells; Rat C6 glioma cells; Stilbene derivatives; Tannic acid

PMID: 28595835
Pterostilbene, a bioactive component of blueberries, suppresses the generation of breast cancer stem cells within tumor microenvironment and metastasis via modulating NF-κB/microRNA 448 circuit.

Mak KK¹, Wu AT, Lee WH, Chang TC, Chiou JF, Wang LS, Wu CH, Huang CY, Shieh YS, Chao TY, Ho CT, Yen GC, Yeh CT.

Abstract information

SCOPE:
Tumor-associated macrophages (TAMs) have been shown to promote metastasis and malignancy. Pterostilbene, a natural stilbene isolated from blueberries, has been suggested for anti-cancer effects. Here, we explored the potential cancer stem cells (CSCs)/TAM modulating effects of pterostilbene in breast cancer.

METHODS AND RESULTS:
Using flowcytometric and Boyden chamber assay, we showed MCF7 and MDA-MB-231 cells cocultured with M2 TAMs exhibited increased percentage of CD44(+)/CD24(-) CSC population and migratory/invasive abilities. RT-PCR results showed that CD44(+)/CD24(-) cells expressed an increased level of HIF-1α, β-catenin, Twist1, and NF-κB and enhanced tumor sphere forming ability. Additionally, pterostilbene treatment dose dependently overcame M2 TAM-induced enrichment of CSCs and metastatic potential of breast cancer cells. Mechanistically, pterostilbene suppressed NFκB, Twist1, vimentin, and increased E-cadherin expression. Using siRNA technique, we demonstrated that pterostilbene-mediated NFκB downregulation was correlated to an increased amount of microRNA 448. Finally, pterostilbene-mediated suppression in tumorigenesis and metastasis was validated by noninvasive bioluminescence in mice bearing M2 TAM cocultured MDA-MB-231 tumor.
CONCLUSION:
Pterostilbene effectively suppresses the generation of CSCs and metastatic potential under the influence of M2 TAMs via modulating EMT associated signaling pathways, specifically NF-κB/miR488 circuit. Thus, pterostilbene could be an ideal anti-CSC agent in clinical settings.

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KEYWORDS:
Breast cancer stem cells; Epithelial-to-mesenchymal transition; Pterostilbene; Tumor-associated macrophages; miR448

PMID: 23504987

BlueBerry Isolate, Pterostilbene, Functions as a Potential Anticancer Stem Cell Agent in Suppressing Irradiation-Mediated Enrichment of Hepatoma Stem Cells.

Lee CM¹, Su YH, Huynh TT, Lee WH, Chiou JF, Lin YK, Hsiao M, Wu CH, Lin YF, Wu AT, Yeh CT.

Author information

Abstract

For many malignancies, radiation therapy remains the second option only to surgery in terms of its curative potential. However, radiation-induced tumor cell death is limited by a number of factors, including the adverse response of the tumor microenvironment to the treatment and either intrinsic or acquired mechanisms of evasive resistance, and the existence of cancer stem cells (CSCs). In this study, we demonstrated that using different doses of irradiation led to the enrichment of CD133(+) Mahlavu cells using flow cytometric method. Subsequently, CD133(+) Mahlavu cells enriched by irradiation were characterized for their stemness gene expression, self-renewal, migration/invasion abilities, and radiation resistance. Having established irradiation-enriched CD133(+) Mahlavu cells with CSC properties, we evaluated a phytochemical, pterostilbene (PT), found abundantly in blueberries, against irradiation-enriched CSCs. It was shown that PT treatment dose-dependently reduced the enrichment of CD133(+) Mahlavu cells upon irradiation; PT treatment also prevented tumor sphere formation, reduced stemness gene expression, and suppressed invasion and migration abilities as well as increasing apoptosis of CD133(+) Mahlavu CSCs. Based on our experimental data, pterostilbene could be used to prevent the enrichment of CD133(+) hepatoma CSCs and should be considered for future clinical testing as a combined agent for HCC patients.
Targeting cancer stem cells in breast cancer: potential anticancer properties of 6-shogaol and pterostilbene.

Wu CH, Hong BH, Ho CT, Yen GC.

Abstract

Breast cancer stem cells (BCSCs) constitute a small fraction of the primary tumor that can self-renew and become a drug-resistant cell population, thus limiting the treatment effects of chemotherapeutic drugs. The present study evaluated the cytotoxic effects of five phytochemicals including 6-gingerol (6-G), 6-shogaol (6-S), 5-hydroxy-3,6,7,8,3',4'-hexamethoxyflavone (5-HF), nobiletin (NOL), and pterostilbene (PTE) on MCF-7 breast cancer cells and BCSCs. The results showed that 6-G, 6-S, and PTE selectively killed BCSCs and had high sensitivity for BCSCs isolated from MCF-7 cells that expressed the surface antigen CD44(+)/CD24(-). 6-S and PTE induced cell necrosis phenomena such as membrane injury and bleb formation in BCSCs and inhibited mammosphere formation. In addition, 6-S and PTE increased the sensitivity of isolated BCSCs to chemotherapeutic drugs and significantly increased the anticancer activity of paclitaxel. Analysis of the underlying mechanism showed that 6-S and PTE decreased the expression of the surface antigen CD44 on BCSCs and promoted β-catenin phosphorylation through the inhibition of hedgehog/Akt/GSK3β signaling, thus decreasing the protein expression of downstream c-Myc and cyclin D1 and reducing BCSC stemness.

KEYWORDS:
6-shogaol; breast cancer stem cells; hedgehog; mammospheres; pterostilbene

Pterostilbene suppressed irradiation-resistant glioma stem cells by modulating GRP78/miR-205 axis.

Huynh TT, Lin CM, Lee WH, Wu AT, Lin YK, Lin YF, Yeh CT, Wang LS.
Abstract

Glioblastoma multiforme (GBM) is the most aggressive type characterized by relapse and resistance even with the combination of radio- and chemotherapy. The presence of glioma stem cells (GSCs) has been shown to contribute to tumorigenesis, recurrence and treatment resistance. Particularly, CD133-positive glioma cells have been shown to represent the subpopulation that confers glioma radioresistance and suggested to be the source of tumor recurrence after radiation. Thus, a better understanding and the development of agents which target GSCs could potentially lead to a significant improvement in treating GBM patients. Here, we demonstrated that GRP78 (an antistress protein) was highly expressed in GBM cells along with β-catenin and Notch and correlated to the development of GSCs. CD133+ GSCs exhibited enhanced migration/invasion and self-renewal abilities. When GRP78 was silenced, GSC properties were suppressed and the sensitivity towards irradiation increased. In addition, the level of microRNA 205 appeared to be negatively associated with GRP78 expression. Our previous study indicated that pterostilbene (PT) possessed anticancer stem cell properties in hepatocellular carcinoma. Thus, we examined whether PT is also effective against GSCs. We found that PT-treated GSCs exhibited suppressed self-renewal and irradiation-resistant abilities. PT-mediated effects were associated with an increase of miR-205. Finally, we showed that PT treatment suppressed tumorigenesis in GSC xenograft mice. In conclusion, we provided evidence that GRP78/miR-205 axis played an important role in GSC maintenance and irradiation resistance. PT treatment suppressed GSC development via negatively modulating GRP78 signaling. PT may be considered for combined therapeutic agent to enhance irradiation efficacy in GBM patients.

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KEYWORDS:
CD133+ glioma stem cells; Glucose-regulated protein, 78 kDa (GRP78); Irradiation resistance; Pterostilbene; miR-205

PMID: 25736407


Modulation of macrophage polarization and lung cancer cell stemness by MUC1 and development of a related small-molecule inhibitor pterostilbene.

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Author information

Abstract
Tumor-associated macrophages (TAMs) polarized to the M2 phenotype play key roles in tumor progression in different cancer types, including lung cancer. MUC1 expression in various types of cancer is an indicator of poorer prognosis. Elevated MUC1 expression has been reported in inflammatory lung macrophages and is associated with lung cancer development. Here, we investigated the role of M2-polarized TAMs (M2-TAMs) in the generation of lung cancer stem cells (LCSCs) and tested pterostilbene, a small-molecule agent that modulates MUC1 expression in lung cancer cells, with the goal of subverting the microenvironment toward a favorable anti-tumor impact. We found that MUC1 was overexpressed in lung cancer patients, which was associated with poor survival rates. M2-TAMs and cancer cell lines were co-cultured in an experimental tumor microenvironment model. The expression levels of MUC1 and cancer stemness genes significantly increased in lung cancer cells in the presence of the M2-TAM cells. Intriguingly, pterostilbene dose-dependently suppressed self-renewal ability in M2-TAMs-co-cultured lung cancer cells, and this suppression was accompanied by downregulation of MUC1, NF-κB, CD133, β-catenin, and Sox2 expression. Moreover, MUC1-silenced M2-TAMs exhibited a significantly lower ability to promote LCSC generation and decreased levels of NF-κB, CD133, and Sox2. The results suggest that MUC1 plays an important role in TAM-induced LCSC progression. Pterostilbene may have therapeutic potential for modulating the unfavorable effects of TAMs in lung cancer progression.

KEYWORDS: Immune response; Immunity; Immunology and Microbiology Section; M2 polarization; MUC1; lung cancer stem cells (CSCs); pterostilbene; tumor-associated macrophages (TAMs)

PMID: 27276704
Antibacterial nanocarriers of resveratrol with gold and silver nanoparticles.

Park S1, Cha SH2, Cho I3, Park S2, Park Y1, Cho S2, Park Y4.

Author information

Abstract

This study focused on the preparation of resveratrol nanocarrier systems and the evaluation of their in vitro antibacterial activities. Gold nanoparticles (AuNPs) and silver nanoparticles (AgNPs) for resveratrol nanocarrier systems were synthesized using green synthetic routes. During the synthesis steps, resveratrol was utilized as a reducing agent to chemically reduce gold and silver ions to AuNPs and AgNPs. This system provides green and eco-friendly synthesis routes that do not involve additional chemical reducing agents. Resveratrol nanocarriers with AuNPs (Res-AuNPs) and AgNPs (Res-AgNPs) were observed to be spherical and to exhibit characteristic surface plasmon resonance at 547 nm and at 412-417 nm, respectively. The mean size of the nanoparticles ranged from 8.32 to 21.84 nm, as determined by high-resolution transmission electron microscopy. The face-centered cubic structure of the Res-AuNPs was confirmed by high-resolution X-ray diffraction. Fourier-transform infrared spectra indicated that the hydroxyl groups and C=C in the aromatic ring of resveratrol were involved in the reduction reaction. Res-AuNPs retained excellent colloidal stability during ultracentrifugation and re-dispersion, suggesting that resveratrol also played a role as a capping agent. Zeta potentials of Res-AuNPs and Res-AgNPs were in the range of -20.58 to -48.54 mV. Generally, against Gram-positive and Gram-negative bacteria, the Res-AuNPs and Res-AgNPs exhibited greater antibacterial activity compared to that of resveratrol alone. Among the tested strains, the highest antibacterial activity of the Res-AuNPs was observed against Streptococcus pneumoniae. The addition of sodium dodecyl sulfate during the synthesis of Res-AgNPs slightly increased their antibacterial activity. These results suggest that the newly developed resveratrol nanocarrier systems with metallic nanoparticles show potential for application as nano-antibacterial agents with enhanced activities.

KEYWORDS:
Antibacterial activity; Gold nanoparticles; Nanocarriers; Resveratrol; Silver nanoparticles

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DOI: 10.1016/j.msec.2015.09.068
Pterostilbene enhanced anti-methicillin resistant staphylococcus aureus (MRSA) activity of oxacillin

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Diagnostic & Applied Health Sciences

Abstract

Methicillin-resistant Staphylococcus aureus (MRSA) is a deadly pathogen that initially was limited to hospital and healthcare facilities but has gradually became a growing problem in healthy children and adults. Pterostilbene belongs to the phenylpropanoid phytoalexin which is involved in plant response to various pathogen and herbivores attack. The aim of this study is to evaluate the anti-MRSA action of pterostilbene in combination with selected antibiotics; vancomycin, linezolid and oxacillin against ATCC 43300 and ATCC 33591. The minimum inhibitory concentration (MIC), minimum bactericidal concentration (MBC) and fractional inhibitory concentration (FIC) index values were determined. Microbroth dilution technique and microdilution checkerboard (MDC) assay were employed. The MIC and MBC of pterostilbene against ATCC 33591 was 31.25 and 62.50 µg mL⁻¹, respectively. While for ATCC 43300, the MBC value was also twice (62.50 µg mL⁻¹) its MIC value of 31.25 µg mL⁻¹. This indicated that pterostilbene was bacteriostatic against both MRSA strains. Our MIC/MBC study also showed that linezolid exhibited bacteriostatic action but, oxacillin and vancomycin were bactericidal. MDC study showed that pterostilbene-oxacillin combination exhibited lowest FIC value (0.56) against both MRSA strains which indicated partial synergistic interaction. On the other hand, pterostilbene was additive (FIC 1.00) in combination with vancomycin whereas pterostilbene-linezolid combination displayed indifference effect with FIC of 1.25 against both MRSA strains. Pterostilbene in combination with oxacillin partially enhanced anti-MRSA activity with twofold reduction in MIC of oxacillin by acting at different site at the bacterial cell wall from that of oxacillin but more specific to the site of action of vancomycin.

Keywords
Bacteriostatic FIC MIC MRSA Pterostilbene Synergism

In Vitro and In Vivo Activities of Pterostilbene against Candida albicans Biofilms

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http://aac.asm.org/content/58/4/2344.full

Author information
ABSTRACT

Pterostilbene (PTE) is a stilbene-derived phytoalexin that originates from several natural plant sources. In this study, we evaluated the activity of PTE against Candida albicans biofilms and explored the underlying mechanisms. In 2,3-bis-(2-methoxy-4-nitro-5-sulfophenyl)-2H-tetrazolium-5-carboxanilide (XTT) reduction assays, biofilm biomass measurement, confocal laser scanning microscopy, and scanning electron microscopy, we found that ≤16 μg/ml PTE had a significant effect against C. albicans biofilms in vitro, while it had no fungicidal effect on planktonic C. albicans cells, which suggested a unique antibiofilm effect of PTE. Then we found that PTE could inhibit biofilm formation and destroy the maintenance of mature biofilms. At 4 μg/ml, PTE decreased cellular surface hydrophobicity (CSH) and suppressed hyphal formation. Gene expression microarrays and real-time reverse transcription-PCR showed that exposure of C. albicans to 16 μg/ml PTE altered the expression of genes that function in morphological transition, ergosterol biosynthesis, oxidoreductase activity, and cell surface and protein unfolding processes (heat shock proteins). Filamentation-related genes, especially those regulated by the Ras/cyclic AMP (cAMP) pathway, including ECE1, ALS3, HWP1, HGC1, and RAS1 itself, were downregulated upon PTE treatment, indicating that the antibiofilm effect of PTE was related to the Ras/cAMP pathway. Then, we found that the addition of exogenous cAMP reverted the PTE-induced filamentous growth defect. Finally, with a rat central venous catheter infection model, we confirmed the in vivo activity of PTE against C. albicans biofilms. Collectively, PTE had strong activities against C. albicans biofilms both in vitro and in vivo, and these activities were associated with the Ras/cAMP pathway.


Pterostilbene, a Methoxylated Resveratrol Derivative, Efficiently Eradicates Planktonic, Biofilm, and Intracellular MRSA by Topical Application.

Yang SC1, Tseng CH2,3,4,5, Wang PW6, Lu PL7,8, Weng YH1, Yen FL5,9, Fang JY1,10,11.

Author information

Abstract

Pterostilbene is a methoxylated derivative of resveratrol originated from natural sources. We investigated the antibacterial activity of pterostilbene against drug-resistant Staphylococcus aureus and the feasibility of using it to treat cutaneous bacteria. The antimicrobial effect was evaluated using an in vitro culture model and an in vivo mouse model of cutaneous infection. The minimum inhibitory concentration (MIC) assay demonstrated a superior biocidal activity of pterostilbene compared to resveratrol (8~16-fold) against methicillin-resistant S. aureus (MRSA) and clinically isolated vancomycin-intermediate S. aureus (VISA). Pterostilbene was found to reduce MRSA biofilm thickness from 18 to 10 μm as detected by confocal microscopy. Pterostilbene showed minimal toxicity to THP-1 cells and was readily engulfed by the macrophages, facilitating the eradication of intracellular MRSA. Pterostilbene exhibited
increased skin absorption over resveratrol by 6-fold. Topical pterostilbene application improved the abscess formation produced by MRSA by reducing the bacterial burden and ameliorating the skin architecture. The potent anti-MRSA capability of pterostilbene was related to bacterial membrane leakage, chaperone protein downregulation, and ribosomal protein upregulation. This mechanism of action was different from that of resveratrol according to proteomic analysis and molecular docking. Pterostilbene has the potential to serve as a novel class of topically applied agents for treating MRSA infection in the skin while demonstrating less toxicity to mammalian cells.

**KEYWORDS:**
MRSA; biofilm; proteomics; pterostilbene; resveratrol; skin infection

PMID: 28659908 PMCID: PMC5468402 DOI: 10.3389/fmicb.2017.01103
Pharmacokinetics, oral bioavailability, and metabolic profile of resveratrol and its dimethylether analog, pterostilbene, in rats

Izet M. Kapetanovic, Miguel Muzzio, Zhihua Huang, Thomas N. Thompson, and David L. McCormick

Abstract

Resveratrol (3,5,4′-trihydroxy-trans-stilbene) is a naturally occurring polyphenol with a broad range of possible health benefits, including anti-cancer activity. However, the biological activity of resveratrol may be limited by poor absorption and first-pass metabolism: only low plasma concentrations of resveratrol are seen following oral administration, and metabolism to glucuronide and sulfate conjugates is rapid. Methylated polyphenol analogs (such as pterostilbene [3,5-dimethoxy-4’-hydroxy-trans-stilbene], the dimethylether analog of resveratrol) may overcome these limitations to pharmacologic efficacy. The present study was designed to compare the bioavailability, pharmacokinetics, and metabolism of resveratrol and pterostilbene following equimolar oral dosing in rats.

Methods

The agents were administered orally via gavage for 14 consecutive days at 50 or 150 mg/kg/day for resveratrol and 56 or 168 mg/kg/day for pterostilbene. Two additional groups were dosed once intravenously with 10 and 11.2 mg/kg for resveratrol and pterostilbene, respectively. Plasma concentrations of agents and metabolites were measured using a high-pressure liquid chromatograph-tandem mass spectrometer system. Noncompartmental analysis was used to derive pharmacokinetic parameters.

Results

Resveratrol and pterostilbene were approximately 20 and 80% bioavailable, respectively. Following oral dosing, plasma levels of pterostilbene and pterostilbene sulfate were markedly greater than were plasma levels of resveratrol and resveratrol sulfate. Although plasma levels of resveratrol glucuronide exceeded those of pterostilbene glucuronide, those differences were smaller than those of the parent drugs and sulfate metabolites.
Conclusions
When administered orally, pterostilbene demonstrates greater bioavailability and total plasma levels of both the parent compound and metabolites than does resveratrol. These differences in agent pharmacokinetics suggest that the in vivo biological activity of equimolar doses of pterostilbene may be greater than that of resveratrol.

Keywords: Resveratrol, Pterostilbene, Pharmacokinetics, Bioavailability, Metabolites, Rat

PMCID: PMC3090701
NIHMSID: NIHMS265180


Pharmacometrics of pterostilbene: preclinical pharmacokinetics and metabolism, anticancer, antiinflammatory, antioxidant and analgesic activity.

Remsberg CM, Yáñez JA, Ohgami Y, Vega-Villa KR, Rimando AM, Davies NM.

Author information

Abstract

The present study evaluated the preclinical pharmacokinetics and pharmacodynamics of trans-pterostilbene, a constituent of some plants. Right jugular vein cannulated male Sprague-Dawley rats were dosed i.v. with 20 mg/kg of pterostilbene and samples were analysed by the reverse phase HPLC method. Serum AUC, serum t(1/2), urine t(1/2), Cl(total) and Vd(beta) were 17.5 +/- 6.6 microg/h/mL, 1.73 +/- 0.78 h, 17.3 +/- 5.6 h, 0.960 +/- 0.025 L/h/kg and 2.41 +/- 1.13 L/kg (mean +/- SEM), respectively. A pterostilbene glucuronidated metabolite was detected in both serum and urine. The in vitro metabolism in rat liver microsomes furthermore suggests phase II metabolism of pterostilbene. Pterostilbene demonstrated concentration-dependent anticancer activity in five cancer cell lines (1-100 microg/mL). An in vitro colitis model showed concentration-dependent suppression of PGE(2) production in the media of HT-29 cells. Antiinflammatory activity was examined by inducing inflammation in canine chondrocytes followed by treatment with pterostilbene (1-100 microg/mL). The results showed decreased levels of MMP-3, sGAG and TNF-alpha compared with control levels. Pterostilbene exhibited concentration-dependent antioxidant capacity measured by the ABTS method. Pterostilbene increased the latency period to response in both tail-flick and hot-plate analgesic tests.

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Pterostilbene alleviates polymicrobial sepsis-induced liver injury: Possible role of SIRT1 signaling.

Liu X1, Yang X1, Han L2, Ye F1, Liu M1, Fan W1, Zhang K1, Kong Y1, Zhang J3, Shi L1, Chen Y1, Zhang X4, Lin S5.

Author information

Abstract

Liver injury occurs frequently during sepsis. Pterostilbene (Pte), a natural dimethylated analog of resveratrol from blueberries, exerts anti-inflammatory and anti-apoptotic effects in various diseases. However, the role of Pte in sepsis-induced liver injury and its underlying mechanisms remain unknown. The current study aimed to evaluate the protective effects of Pte on sepsis-induced liver injury and its potential mechanisms. Sepsis was induced using cecal ligation and puncture (CLP) in C57BL/6 mice. Mice were administered Pte (5, 10, 15mg/kg, i.p.) at 0.5h, 2h, and 8h after CLP induction. The pathological changes of the liver were evaluated using hematoxylin and eosin (H&E) staining. The serum levels of alanine transaminase (ALT) and aspartate aminotransferase (AST) were measured. The levels of tumor necrosis factor-alpha (TNF-α), interleukin (IL-6), myeloperoxidase (MPO), p38 mitogen-activated protein kinase (p38MAPK), Bax, and B-cell lymphoma 2 (Bcl-2) were also evaluated. Pte treatment attenuated the CLP-induced liver injury, as evidenced by the attenuated histopathologic injuries and the decreased serum aminotransferase levels. Pte reduced the serum inflammatory cytokine (TNF-α and IL-6) levels and hepatic mRNA levels of TNF-α and IL-6. Pte also reduced MPO activity and p38MAPK activation in the liver. Additionally, Pte significantly inhibited Bax expression and increased Bcl-2 expression. Moreover, Pte increased the expression of sirtuin-1 (SIRT1) and reduced the expression of acetylated forkhead box O1 (Ac-FoxO1), acetylated Ac-p53, and acetylated nuclear factor-kappa beta (Ac-NF-κB). However, SIRT1 small interfering RNA (siRNA) abolished Pte's effects on the expression levels of those protein. Notably, Pte improved the survival rate in septic mice. In conclusion, Pte alleviates sepsis-induced liver injury by reducing inflammatory response and inhibiting hepatic apoptosis, and the potential mechanism is associated with SIRT1 signaling activation.

KEYWORDS:
Inflammation; Liver injury; Pterostilbene; SIRT1 signaling; Sepsis

PMID: 28550734 DOI: 10.1016/j.intimp.2017.05.022


Pterostilbene, a dimethylated analog of resveratrol, promotes energy metabolism in obese rats.

Nagao K1, Jinnouchi T2, Kai S2, Yanagita T3.
Pterostilbene (trans-3,5-dimethoxy-4-hydroxystilbene) is a dimethylated analog of resveratrol and has been reported to exert various pharmacological effects. In this study, we evaluated the effect of pterostilbene on the pathogenesis of obesity and energy metabolism in obese rats. Pterostilbene significantly activates silent mating type information regulation 2 homolog-1 and peroxisome proliferator-activated receptor-alpha in vitro. At 4 weeks a 0.5% pterostilbene diet markedly suppressed the abdominal white adipose tissue (WAT) accumulation in obese rats. The oxygen consumption and energy expenditure were significantly higher in the pterostilbene group, and pterostilbene increased the fat metabolism rather than the carbohydrate metabolism in obese rats. The mRNA level of uncoupling protein, a thermogenic regulator, was increased and the mRNA levels of fatty acid synthase and leptin, which are involved in lipogenesis and fat storage, were markedly decreased in WAT after the pterostilbene feeding. These results suggest that pterostilbene prevents WAT accumulation through the enhancement of energy metabolism and partly the suppression of lipogenesis in obese OLETF rats.

KEYWORDS:
Energy expenditure; Obesity; PPARα; Pterostilbene; SIRT1

PMID: 28319852 DOI: 10.1016/j.jnutbio.2017.02.009


SIRT1 activation by pterostilbene attenuates the skeletal muscle oxidative stress injury and mitochondrial dysfunction induced by ischemia reperfusion injury.

Cheng Y1,2, Di S3, Fan C3, Cai L4, Gao C4, Jiang P4, Hu W5, Ma Z3, Jiang S6, Dong Y7, Li T5, Wu G5, Lv J5, Yang Y8.

Author information

Abstract

Ischemia reperfusion (IR) injury is harmful to skeletal muscles and causes mitochondrial oxidative stress. Pterostilbene (PTE), an analogue of resveratrol, has organic protective effects against oxidative stress. However, no studies have investigated whether PTE can protect against IR-related skeletal muscular injury. In this study, we sought to evaluate the protective effect of PTE against IR-related skeletal muscle injury and to determine the mechanisms in this process. Male Sprague-Dawley rats were pretreated with PTE for a week and then underwent limb IR surgery. The IR injury induced segmental necrosis and apoptosis, myofilament disintegration, thicker interstitial spaces, and inflammatory cell infiltration. Furthermore, mitochondrial...
respiratory chain activity in the muscular tissue was inhibited, methane dicarboxylic aldehyde concentration and myeloperoxidase activity were up-regulated, and superoxide dismutase was down-regulated after IR. However, these effects were significantly inhibited by PTE in a dose-dependent manner. The mechanism underlying IR injury is attributed to the down-regulation of silent information regulator 1 (SIRT1)-FOXO1/p53 pathway and the increase of the Bax/Bcl2 ratio, Cleaved poly ADP-ribose polymerase 1, Cleaved Caspase 3, which can be reversed with PTE. Furthermore, EX527, an SIRT1 inhibitor, counteracted the protective effects of PTE on IR-related muscle injury. In conclusion, PTE has protective properties against IR injury of the skeletal muscles. The mechanism of this protective effect depends on the activation of the SIRT1-FOXO1/p53 signaling pathway and the decrease of the apoptotic ratio in skeletal muscle cells.

KEYWORDS: Ischemia reperfusion injury; Mitochondrial function; Pterostilbene; Silent information regulator 1; Skeletal muscle

PMID: 27270300 DOI: 10.1007/s10495-016-1258-x


Restoration of sirt1 function by pterostilbene attenuates hypoxia-reoxygenation injury in cardiomyocytes.

Guo Y1, Zhang L2, Li F2, Hu CP3, Zhang Z4.

Author information

Abstract

Restoration of blood supply to ischemic myocardium causes cardiomyocyte damage, a process known as ischemia-reperfusion injury. Excess reactive oxygen species and intracellular calcium contribute to cell damage but the involvement of sirt1, a versatile protein deacetylase in reperfusion-induced cell damage remains unknown. Here, we found that hypoxia-reoxygenation, an in vitro model of ischemia-reperfusion injury, induced H9c2 cardiomyocyte apoptosis as revealed by caspase-3 assay, Hoechst 33258 staining, flow cytometric analysis and JC-1 staining. Molecular docking analysis showed that, pterostilbene, a natural dimethyl ether derivative of resveratrol, binds to the enzymatic active pocket of sirt1. Importantly, application of pterostilbene at low concentrations of 0.1-3.0 μM rescued H9c2 cells from apoptosis, an effect comparable with resveratrol at 20 μM. Mechanistically, pterostilbene exerted its cardioprotective effects via 1) stimulation of sirt1 activity, since pretreatment of H9c2 cells with splitomicin, an antagonist of sirt1, removed the effects of pterostilbene, and 2) enhancement of sirt1 expression. Therefore, the present study demonstrates that activation of sirt1 during ischemia-reperfusion is cardioprotective and that the natural compound-pterostilbene-could be used therapeutically to alleviate ischemia-reperfusion injury.

KEYWORDS:
Epigenetic-based combinatorial resveratrol and pterostilbene alters DNA damage response by affecting SIRT1 and DNMT enzyme expression, including SIRT1-dependent γ-H2AX and telomerase regulation in triple-negative breast cancer.

Kala R1, Shah HN2, Martin SL3, Tollefsbol TO4,5,6,7,8.

Author information

Abstract

BACKGROUND:
Nutrition is believed to be a primary contributor in regulating gene expression by affecting epigenetic pathways such as DNA methylation and histone modification. Resveratrol and pterostilbene are phytoalexins produced by plants as part of their defense system. These two bioactive compounds when used alone have been shown to alter genetic and epigenetic profiles of tumor cells, but the concentrations employed in various studies often far exceed physiologically achievable doses. Triple-negative breast cancer (TNBC) is an often fatal condition that may be prevented or treated through novel dietary-based approaches.

METHODS:
HCC1806 and MDA-MB-157 breast cancer cells were used as TNBC cell lines in this study. MCF10A cells were used as control breast epithelial cells to determine the safety of this dietary regimen. CompuSyn software was used to determine the combination index (CI) for drug combinations.

RESULTS:
Combinatorial resveratrol and pterostilbene administered at close to physiologically relevant doses resulted in synergistic (CI <1) growth inhibition of TNBCs. SIRT1, a type III histone deacetylase (HDAC), was down-regulated in response to this combinatorial treatment. We further explored the effects of this novel combinatorial approach on DNA damage response by monitoring γ-H2AX and telomerase expression. With combination of these two compounds there was a significant decrease in these two proteins which might further resulted in significant growth inhibition, apoptosis and cell cycle arrest in HCC1806 and MDA-MB-157 breast cancer cells, while there was no significant effect on cellular viability, colony forming potential, morphology or apoptosis in control MCF10A breast epithelial cells. SIRT1 knockdown reproduced the effects of combinatorial resveratrol and pterostilbene-induced SIRT1 down-
regulation through inhibition of both telomerase activity and $\gamma$-H2AX expression in HCC1806 breast cancer cells. As a part of the repair mechanisms and role of SIRT1 in recruiting DNMTs, the effects of this combination treatment was also explored on DNA methyltransferases (DNMTs) expression. Interestingly, the compounds resulted in a significant down-regulation of DNMT enzymes with no significant effects on DNMT enzyme expression in MCF10A control cells.

CONCLUSION:
Collectively, these results provide new insights into the epigenetic mechanisms of a novel combinatorial nutrient control strategy that exhibits synergy and may contribute to future recalcitrant TNBC prevention and/or therapy.

PMID: 26459286 PMCID: PMC4603342 DOI: 10.1186/s12885-015-1693-z


Synergistic induction of human cathelicidin antimicrobial peptide gene expression by vitamin D and stilbenoids.

Guo C#1,2, Sinnott B#1,2, Niu B3, Lowry MB1,4, Fantcone ML1,2, Gombart AF1,2.

Abstract information

SCOPE:
The cathelicidin antimicrobial peptide (CAMP) gene is induced by 1\alpha,25-dihydroxyvitamin D3 (1\alpha,25(OH)2 D3), lithocholic acid, curcumin, nicotinamide, and butyrate. Discovering additional small molecules that regulate its expression will identify new molecular mechanisms involved in CAMP regulation and increase understanding of how diet and nutrition can improve immune function.

METHODS AND RESULTS:
We discovered that two stilbenoids, resveratrol and pterostilbene, induced CAMP promoter-luciferase expression. Synergistic activation was observed when either stilbenoid was combined with 1\alpha,25(OH)2 D3. Both stilbenoids increased CAMP mRNA and protein levels in the monocyte cell line U937 and synergy was observed in both U937 and the keratinocyte cell line, HaCaT. Inhibition of resveratrol targets sirtuin-1, cyclic AMP production and the c-Jun N-terminal, phosphoinositide 3 and AMP-activated kinases did not block induction of CAMP by resveratrol or synergy with 1\alpha,25(OH)2 D3. Nevertheless, inhibition of the extracellular signal regulated 1/2 and p38 mitogen-activated protein kinases, increased CAMP gene expression in combination with 1\alpha,25(OH)2 D3 suggesting that inhibition of these kinases by resveratrol may explain, in part, its synergy with vitamin D.

CONCLUSION:
Our findings demonstrate for the first time that stilbenoid compounds may have the potential to boost the innate immune response by increasing CAMP gene expression, particularly in combination with 1α,25(OH)2 D3.

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**KEYWORDS:**
Cathelicidin antimicrobial peptide; Innate immunity; Resveratrol; Stilbenoid; Vitamin D receptor

PMID: 24039193 PMCID: PMC3947465 DOI: 10.1002/mnfr.201300266


**Low-dose pterostilbene, but not resveratrol, is a potent neuromodulator in aging and Alzheimer's disease.**


**Author information**

**Abstract**

Recent studies have implicated resveratrol and pterostilbene, a resveratrol derivative, in the protection against age-related diseases including Alzheimer's disease (AD). However, the mechanism for the favorable effects of resveratrol in the brain remains unclear and information about direct cross-comparisons between these analogs is rare. As such, the purpose of this study was to compare the effectiveness of diet-achievable supplementation of resveratrol to that of pterostilbene at improving functional deficits and AD pathology in the SAMP8 mouse, a model of accelerated aging that is increasingly being validated as a model of sporadic and age-related AD. Furthermore we sought to determine the mechanism of action responsible for functional improvements observed by studying cellular stress, inflammation, and pathology markers known to be altered in AD. Two months of pterostilbene diet but not resveratrol significantly improved radial arm water maze function in SAMP8 compared with control-fed animals. Neither resveratrol nor pterostilbene increased sirtuin 1 (SIRT1) expression or downstream markers of sirtuin 1 activation. Importantly, markers of cellular stress, inflammation, and AD pathology were positively modulated by pterostilbene but not resveratrol and were associated with upregulation of peroxisome proliferator-activated receptor (PPAR) alpha expression. Taken together our findings indicate that at equivalent and diet-achievable doses pterostilbene is a more potent modulator of cognition and cellular stress than resveratrol, likely driven by increased peroxisome proliferator-activated receptor alpha expression and increased lipophilicity due to substitution of hydroxy with methoxy group in pterostilbene.

PMID: 21982274 DOI: 10.1016/j.neurobiolaging.2011.08.015
Activator of NRF2


Pterostilbene protects against uraemia serum-induced endothelial cell damage via activation of Keap1/Nrf2/HO-1 signaling.

Chen ZW1, Miu HF1, Wang HP2, Wu ZN2, Wang WJ1, Ling YJ2, Xu XH2, Sun HJ2, Jiang X3.

Author information

Abstract

Chronic kidney disease causes uremia-related endothelial cell dysfunction associated with high risk for cardiovascular diseases. The vascular endothelium is permanently exposed to uraemic toxins including indoxyl sulfate, which provokes endothelial damage in subjects with end-stage renal disease. Pterostilbene (PT) is identified to be homologous derivative of resveratrol and exerts antioxidant and anti-inflammatory actions. However, the effects of PT on uraemic serum-induced endothelial cell damage have not been elucidated. In this study, we investigated the effects and mechanisms of PT on uraemic serum (US)-mediated injury in human umbilical vein endothelial cells (HUVECs). Treatment of US obviously reduced cell viability, inhibited superoxide dismutase activity and catalase activity, suppressed phosphorylated endothelial nitric oxide synthase (eNOS) protein level and eNOS activity, whereas promoted lactate dehydrogenase leakage, increased malondialdehyde, hydrogen peroxide, superoxide anions levels and NAD(P)H activity accompanied with increased nitrative stress and inflammatory response in HUVECs, and these changes were reversed after PT treatment. Under US environment, PT downregulated Kelch-like ECH-associated protein 1 (Keap1) and upregulated nuclear factor erythroid-2-related factor 2 (Nrf2) and its downstream target heme oxygenase-1 (HO-1) protein levels. Of note, the level of HO-1 was decreased after the transfection of cells with Nrf2-siRNA, and HO-1 inhibitor Snpp abolished the protective effects of PT on HUVECs in response to US. Collectively, our study demonstrated that PT is effective in reducing US-evoked endothelial cell dysfunction via suppression of oxidative/nitrative stress and inflammatory response, which at least partly depended on Keap1/Nrf2/HO-1 signaling pathway.

KEYWORDS:
Chronic kidney disease; Endothelial cell; Nrf2; Pterostilbene; Uremia

PMID: 29094331 DOI: 10.1007/s11255-017-1734-4
Pterostilbene protects against UVB-induced photo-damage through a phosphatidylinositol-3-kinase-dependent Nrf2/ARE pathway in human keratinocytes.

Li H1, Jiang N1,2, Liang B1, Liu Q1,3, Zhang E1, Peng L1, Deng H1, Li R1, Li Z1, Zhu H1.

Author information

Abstract

OBJECTIVE: Ultraviolet B (UVB) irradiation is the initial etiological factor for various skin disorders, including erythema, sunburn, photoaging, and photocarcinogenesis. Pterostilbene (Pter) displayed remarkable antioxidant, anti-inflammatory, and anticarcinogenic activities. This study aimed to investigate the effective mechanism of Pter against UVB-induced photodamage in immortalized human keratinocytes.

METHODS: Human keratinocytes were pretreated with Pter (5 and 10 μM) for 24 h prior to UVB irradiation (300 mJ/cm2). Harvested cells were analyzed by MTT, DCFH-DA, comet, western blotting, luciferase promoter, small interference RNA transfection, and quantitative real-time polymerase chain reaction assay.

RESULTS: Pter significantly attenuated UVB-induced cell death and reactive oxygen species (ROS) generation, and effectively increased nuclear translocation of NF-E2-related factor-2 (Nrf2), expression of Nrf2-dependent antioxidant enzymes, and DNA repair activity. Moreover, the protective effects of Pter were abolished by small interference RNA-mediated Nrf2 silencing. Furthermore, Pter was also found to induce the phosphorylation of Nrf2 and the known phosphatidylinositol-3-kinase (PI3K) phosphorylated kinase, Akt. The specific inhibitor of PI3K, LY294002, successfully abrogated Pter-induced Nrf2 phosphorylation, activation of Nrf2-antioxidant response element pathway, ROS scavenging ability, and DNA repair activity.

CONCLUSION: The present study indicated that Pter effectively protected against UVB-induced photodamage by increasing endogenous defense mechanisms, scavenging UVB-induced ROS, and aiding in damaged DNA repair through a PI3K-dependent activation of Nrf2/ARE pathway.

KEYWORDS: Nrf2; Pterostilbene; antioxidants; photoprotection; ultraviolet

PMID: 28532341 DOI: 10.1080/13510002.2017.1329917

Pterostilbene inhibits inflammation and ROS production in chondrocytes by activating Nrf2 pathway.

Xue EX1, Lin JP2, Zhang Y1, Sheng SR1, Liu HX1, Zhou YL1, Xu H1.

Author information

Abstract

Pterostilbene has been reported as a potential drug to inhibit oxidative stress and inflammation. However, the effect of pterostilbene on chondrocytes and osteoarthritis remains to be elucidated. We sought to investigate whether pterostilbene could protect chondrocytes from inflammation and ROS production through factor erythroid 2-related factor 2 (Nrf2) activation. The pterostilbene toxicity on chondrocytes collected from cartilages of Sprague-Dawley rats was assessed by CCK-8 test. Immunofluorescence and Western blotting explored the nuclear translocation of Nrf2. Nrf2 expression was silenced by siRNA to evaluate the involvement of Nrf2 in the effect of pterostilbene on chondrocytes. Finally, osteoarthritis model was established by the transection of anterior cruciate ligament and partial medial meniscectomy in rats, and then these rats received pterostilbene 30 mg/kg, daily, p.o. for 8 weeks. Histology and immunohistochemistry were used to assess histopathological change and Nrf2 expression in cartilage. Nuclear translocation of Nrf2 was stimulated by pterostilbene without cellular toxicity. Pterostilbene inhibited the level of COX-2, iNOS, PGE2, and NO, as well as the mitochondrial and total intracellular ROS production induced by IL-1β in chondrocytes, partially reversed by the Nrf2 silencing. Pterostilbene prevented cartilage degeneration and promoted the nuclear translocation of Nrf2 in cartilage. These results suggest that pterostilbene could inhibit the IL-1β-induced inflammation and ROS production in chondrocytes by stimulating the nuclear translocation of Nrf2.

KEYWORDS:
chondrocyte; inflammation; nuclear factor erythroid 2-related factor 2; pterostilbene; reactive oxygen species

PMID: 28410217 PMCID: PMC5522043 DOI: 10.18632/oncotarget.16716


Role of pterostilbene in attenuating immune mediated devastation of pancreatic beta cells via Nrf2 signaling cascade.

Sireesh D1, Ganesh MR2, Dhamodharan U1, Sakthivadivel M3, Sivasubramanian S3, Gunasekaran P3, Ramkumar KM4.
Nrf2 (nuclear factor erythroid 2-related factor-2) is a transcription factor that regulates oxidative/xenobiotic stress response and also suppress inflammation. Nrf2 signaling is associated with an increased susceptibility to various kinds of stress. Nrf2 has been shown as a promising therapeutic target in various human diseases including diabetes. Our earlier studies showed Pterostilbene (PTS) as a potent Nrf2 activator, and it protects the pancreatic β-cells against oxidative stress. In this study, we investigated PTS confer protection against cytokine-induced β-cell apoptosis and its role on insulin secretion in streptozotocin (STZ)-induced diabetic mice. The Nrf2 activation potential of PTS was assessed by dissociation of the Nrf2-Keap1 complex and by expression of ARE-driven downstream target genes in MIN6 cells. Further, the nuclear Nrf2 translocation and blockage of apoptotic signaling as demonstrated by the reduction of BAX/Bcl-2 ratio, Annexin-V positive cells and caspase-3 activity conferred the cyto-protection of PTS against cytokine-induced cellular damage. In addition, PTS treatment markedly improved glucose homeostasis and abated inflammatory response evidenced by the reduction of proinflammatory cytokines in diabetic mice. The inhibition of β-cell apoptosis by PTS as assessed by BAX/Bcl-2 ratio and caspase-3 activity in the pancreas was associated with the activation of Nrf2 and the expression of its downstream target genes. PTS also inhibited the activation of iNOS and decreased nitric oxide (NO) formation in the pancreas of diabetic animals. The results obtained from both in vitro and in vivo experiments showed that PTS improves β-cell function and survival against cytokine stress and also prevents STZ-induced diabetes.

KEYWORDS:
Cytokine cocktail; Diabetes; MIN6; Nrf2; Streptozotocin

PMID: 28343084 DOI: 10.1016/j.jnutbio.2017.02.015


Pterostilbene attenuates high glucose-induced oxidative injury in hippocampal neuronal cells by activating nuclear factor erythroid 2-related factor 2.

In the present study, neuroblastoma (SH-SY5Y) cells were used to investigate the mechanisms mediating the potential protective effects of pterostilbene (PTE) against mitochondrial metabolic impairment and oxidative stress induced by hyperglycemia for mimicking the diabetic encephalopathy. High glucose medium (100mM) decreased cellular viability after 24h incubation which was evidenced by: (i) reduced mitochondrial complex I and III activities; (ii) reduced mitochondrial cytochrome C; (iii) increased reactive oxygen species (ROS) generation; (iv) decreased mitochondrial membrane potential (ΔΨm); and (v) increased lactate dehydrogenase (LDH) levels. PTE (2.5, 5, and 10μM for 24h) was nontoxic and induced the nuclear transition of Nrf2. Pretreatment of PTE (2.5, 5, and 10μM for 2h) displayed a dose-dependently neuroprotective effect, as indicated by significantly prevented high glucose-induced loss of cellular viability, generation of ROS, reduced mitochondrial complex I and III activities, reduced mitochondrial cytochrome C, decreased ΔΨm, and increased LDH levels. Moreover, the levels of nuclear factor erythroid 2-related factor 2 (Nrf2), heme oxygenase-1 (HO-1) and glutathione S-transferase (GST) were elevated after PTE treatment. In addition, the elevation of nuclear Nrf2 by PTE treatment (10μM for 2h) was abolished by Nrf2 siRNA. Importantly, Nrf2 siRNA induced the opposite changes in mitochondrial complex I and III activities, mitochondrial cytochrome C, reactive species generation, ΔΨm, and LDH. Overall, the present findings were the first to show that pterostilbene attenuated high glucose-induced central nervous system injury in vitro through the activation of Nrf2 signaling, displaying protective effects against mitochondrial dysfunction-derived oxidative stress.

KEYWORDS:
High glucose; Neuroprotection; Nuclear factor erythroid 2-related factor 2 signaling; Oxidative stress; Pterostilbene

PMID: 28089584 DOI: 10.1016/j.bbadis.2017.01.005


The resveratrol derivatives trans-3,5-dimethoxy-4-fluoro-4'-hydroxystilbene and trans-2,4',5-trihydroxystilbene decrease oxidative stress and prolong lifespan in Caenorhabditis elegans.

Fischer N1, Büchter C1, Koch K1, Albert S2, Csuk R2, Wätjen W1.

Author information

Abstract

OBJECTIVES:
Resveratrol (trans-3,4’,5-trihydroxystilbene (1)) was previously shown to extend the lifespan of different model organisms. However, its pharmacological efficiency is controversially discussed. Therefore, the bioactivity of four newly synthesized stilbenes (trans-3,5-dimethoxy-4-fluoro-4’-
hydroxystilbene (3), trans-4’-hydroxy-3,4,5-trifluorostilbene (4), trans-2,5-dimethoxy-4’
hydroxystilbene (5), trans-2,4’,5-trihydroxystilbene (6)) was compared to (1) and pterostilbene
(trans-3,5-dimethoxy-4’-hydroxystilbene (2)) in the established model organism Caenorhabditis
elegans.

METHODS:
Trolox equivalent antioxidant capacity (TEAC), 2’,7’-dichlorofluorescein (DCF),
thermotolerance assays, C. elegans lifespan analyses.

KEY FINDINGS:
All compounds exert a strong in-vitro radical scavenging activity (6 > 1 > 5 > 2 = 3 = 4), but in
vivo, only (3) and (6) reduce reactive oxygen species (ROS) accumulation. Furthermore, (3) and
(6) increased the mobility of aged nematodes and prolonged their mean lifespans, while these
compounds decreased the thermal stress resistance. Using daf-16 (FoxO), skn-1 (Nrf2) and sir-
2.1 (sirtuin) loss-of-function mutant strains, the in vivo antioxidant effects of compounds (3) and
(6) were abolished, showing the necessity of these evolutionary highly conserved factors.
However, short-time treatment with stilbenes (3) and (6) did not modulate the cellular
localization of the transcription factors DAF-16 and SKN-1.

CONCLUSION:
In contrast to resveratrol, the synthetic stilbene derivatives (3) and (6) increase the lifespan of C.
elegans, rendering them promising candidates for pharmacological anti-ageing purposes.
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KEYWORDS:
Nrf2; ageing; insulin-signalling; oxidative stress; secondary plant compounds

PMID: 27882602 DOI: 10.1111/jphp.12657

27.

Promising therapeutic potential of pterostilbene and its
mechanistic insight based on preclinical evidence.

Kosuru R1, Rai U1, Prakash S1, Singh A2, Singh S3.

Author information

Abstract

Pterostilbene (PS) is a well-recognized antioxidant that primarily exists in blueberries,
grapevines and heartwood of red sandalwood. Interest in this compound has been renewed in
recent years, and studies have found that PS possesses an array of pharmacological properties,
including chemopreventive, antiinflammatory, antidiabetic, antidyslipidemic, antiatherosclerotic
and neuroprotective effects. However, the greater in vivo bioavailability of PS, as compared to resveratrol, is an added advantage for its efficacy. This review provides a summary regarding the sources, pharmacokinetic aspects and pharmacodynamics of PS, with a focus on the molecular mechanisms underlying its protective effects against cancer, brain injuries and heart disease. Studies regarding the safety profile of PS have also been included. Based on the presently available evidence, we conclude that PS represents an active phytonutrient and a potential drug with pleiotropic health applications.

KEYWORDS:
AMPK; Cardiovascular disease; HO-1; NF-κB; Nrf2; Pterostilbene

PMID: 27475678 DOI: 10.1016/j.ejphar.2016.07.046


Pterostilbene-mediated Nrf2 activation: Mechanistic insights on Keap1:Nrf2 interface.

Bhakkiyalakshmi E1, Dineshkumar K2, Karthik S1, Sireesh D3, Hopper W2, Paulmurugan R4, Ramkumar KM5.

Author information

Abstract

The discovery of Keap1-Nrf2 protein-protein interaction (PPI) inhibitors has become a promising strategy to develop novel lead molecules against variety of stress. Hence, Keap1-Nrf2 system plays an important role in oxidative/electrophilic stress associated disorders. Our earlier studies identified pterostilbene (PTS), a natural analogue of resveratrol, as a potent Nrf2 activator and Keap1-Nrf2 PPI inhibitor as assessed by luciferase complementation assay. In this study, we further identified the potential of PTS in Nrf2 activation and ARE-driven downstream target genes expression by nuclear translocation experiments and ARE-luciferase reporter assay, respectively. Further, the luciferase complementation assay identified that PTS inhibits Keap1-Nrf2 PPI in both dose and time-dependent manner. Computational studies using molecular docking and dynamic simulation revealed that PTS directly interacts with the basic amino acids of kelch domain of Keap1 and perturb Keap1-Nrf2 interaction pattern. This manuscript not only shows the binding determinants of Keap1-Nrf2 proteins but also provides mechanistic insights on Nrf2 activation potential of PTS.

KEYWORDS:
ARE; Keap1; Molecular docking; Molecular dynamic simulation; Nrf2; Pterostilbene

PMID: 27312421 DOI: 10.1016/j.bmc.2016.05.011

Neuroprotective effects of pterostilbene against oxidative stress injury: Involvement of nuclear factor erythroid 2-related factor 2 pathway.

Wang B1, Liu H1, Yue L1, Li X1, Zhao L1, Yang X1, Wang X1, Yang Y2, Qu Y3.

Author information

Abstract

Nuclear factor erythroid 2 (NF-E2)-related factor 2 (Nrf2) regulates multiple anti-oxidative enzymes and has neuroprotective effects. Pterostilbene (PTE) is a natural anti-oxidant found in blueberries. Its non-metabolized form exhibits high distribution in the brain after dietary administration. In this study, we aimed to explore the potential of PTE in protecting murine hippocampal neuronal HT22 cells against glutamate-induced oxidative stress injury and possible underlying mechanisms. PTE was nontoxic and induced the nuclear translocation of Nrf2 when HT22 cell cultures were incubated with different concentrations of PTE. Further, PTE displayed a dose-dependent neuroprotective effect, as indicated by increased cell viability and a reduction in lactate dehydrogenase (LDH) release after glutamate treatment. Nrf2 siRNA treatment inhibited PTE-induced neuroprotective effects. Moreover, the levels of nuclear Nrf2 and downstream heme oxygenase-1 (HO-1) and NAD(P)H:quinone oxidoreductase 1 (NQO1) were elevated after PTE treatment. The PTE-induced elevation of nuclear Nrf2, as well as the increases in HO-1 and NQO1 levels, was abolished by Nrf2 siRNA. PTE treatment reduced the production of reactive oxygen species (ROS) and significantly enhanced the activities of the cellular anti-oxidants glutathione (GSH) and superoxide dismutase (SOD), indicating an attenuation of glutamate-induced oxidative stress. These changes in ROS and GSH and SOD activity were reversed by Nrf2 siRNA. Our results indicate that PTE treatment attenuates glutamate-induced oxidative stress injury in neuronal cells via the Nrf2 signaling pathway.

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KEYWORDS:
Glutamate; Neuroprotection; Nuclear factor erythroid 2 (NF-E2)-related factor 2 signaling; Oxidative stress; Pterostilbene

PMID: 27107941 DOI: 10.1016/j.brainres.2016.04.048

A comparative assessment of the cytotoxicity and nitric oxide reducing ability of resveratrol, pterostilbene and piceatannol in transformed and normal mouse macrophages.

Adiabouah Achy-Brou CA1, Billack B1.

Author information

Abstract

The present study investigated the pharmacological effects of three stilbenoids, resveratrol (RES), pterostilbene (PTR) and piceatannol (PIC), in transformed and normal macrophages. Our first aim was to comparatively assess the cytotoxicity of RES, PTR and PIC in unstimulated transformed mouse macrophages (RAW 264.7 cells) and primary peritoneal macrophages (PMs) harvested from both wild type and Nrf2 (nuclear factor erythroid 2-related factor 2)-deficient female mice. Our second aim was to investigate whether the inhibitory effect of RES, PTR and PIC on nitric oxide (NO) release from stimulated PMs depends on the status of the transcription factor Nrf2. The rationale for investigating Nrf2 status was based upon recent reports showing that certain compounds (sulforaphane and linalool) suppress LPS-induced inflammation in an Nrf2-dependent manner. Cell viability studies confirmed our prior work in unstimulated RAW 264.7 cells, with cytotoxic potency decreasing in the order of PTR > PIC > RES. Unstimulated PMs, regardless of Nrf2 status, were less sensitive to stilbenes, requiring at least a threefold higher stilbene concentration to inhibit cell viability, with cytotoxic potency again decreasing in the order of PTR > PIC > RES. In studies focused on our second aim, IC50 values for NO inhibition (measured as [Formula: see text]) in wild type PMs were similar for all three stilbenes (∼10 μM). In Nrf2-deficient PMs, the IC50 for NO inhibition by PIC did not change; however, a rightward shift in the concentration effect curve was observed for both RES and PTR, indicating a role for Nrf2 in the suppression of LPS-induced [Formula: see text] accumulation by these particular stilbenes.

KEYWORDS: Nrf2; Resveratrol; anti-inflammatory effect of stilbenes; macrophages; piceatannol; pterostilbene; stilbenoids

PMID: 27079867 DOI: 10.3109/01480545.2016.1169542


Anti-hyperlipidemic and anti-peroxidative role of pterostilbene via Nrf2 signaling in experimental diabetes.

Bhakkivalakshmi E1, Sireesh D1, Sakthivadivel M2, Sivasubramanian S2, Gunasekaran P2, Ramkumar KM3.
Author information

Abstract

Nuclear factor erythroid 2-related factor 2 (Nrf2), a key transcription factor triggers the expression of antioxidant and detoxification genes thereby providing cellular protective functions against oxidative stress-mediated disorders. Recent research has identified that pharmacological activation of Nrf2 also regulates the largest cluster of genes associated with lipid metabolism. With this background, this paper highlights the anti-hyperlipidemic and anti-oxidative role of pterostilbene (PTS), an Nrf2 activator, in streptozotocin (STZ)-induced diabetic model. PTS administration to diabetic mice for 5 weeks significantly regulated blood glucose levels through the elevation of insulin secretion. The circulatory and liver lipid profiles of total cholesterol (TC), triglycerides (TG) and non-esterified fatty acids (NEFA) were maintained to normal levels upon PTS treatment. Moreover, PTS administration also normalized the circulatory levels of very low-, low- and high density lipoprotein cholesterol (VLDL-, LDL-, HDL-C) and also reduced lipid peroxidation in STZ-induced diabetic mice. In addition, Nrf2 and its downstream targets, superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx) enzyme activities and glutathione (GSH) levels were significantly elevated in liver tissues of diabetic mice upon PTS administration. Further, H&E staining of diabetic mouse liver showed collapse in hepatic microvesicles due to altered lipid metabolism. Both structural and functional alterations were attenuated by PTS indicating its role in diabetic dyslipidemia through Nrf2-mediated mechanism that could be considered as a promising therapeutic agent.

KEYWORDS:
Diabetes; Dyslipidemia; Lipids; Nrf2; Pterostilbene; Streptozotocin

PMID: 26921755 DOI: 10.1016/j.ejphar.2016.02.054


Pterostilbene Ameliorates Streptozotocin-Induced Diabetes through Enhancing Antioxidant Signaling Pathways Mediated by Nrf2.

Elango B, Dornadula S, Paulmurugan R1, Ramkumar KM.

Author information

Abstract

Nuclear factor erythroid 2-related factor 2 (Nrf2) remains a master regulator of cytoprotective and antioxidant genes. In this study, we investigated the antidiabetic role of pterostilbene (PTS) in streptozotocin (STZ)-induced diabetic model through Nrf2-mediated antioxidant mechanisms. The ability of PTS to activate Nrf2 in MIN6 cells was assessed by dissociation of the Nrf2-

103
Keap1 complex at different time points and by expression of ARE-driven downstream target genes of Nrf2. Immunoblot experiments examining Nrf2 activation and phosphorylation indicated that it conferred cytoprotection against STZ-induced cellular damage. In STZ-induced diabetic mice, PTS administration significantly decreased blood glucose levels through the improvement of insulin secretion. In addition, we also observed insulin-positive cells with recovered islet architecture in the pancreas of STZ-induced diabetic mice after treatment with PTS. The activation of Nrf2 and expression of its downstream target genes were observed upon PTS treatment, thereby reducing oxidative damage to pancreas. Furthermore, PTS treatment significantly reverted the abundance of key glucose metabolism enzymes, such as hexokinase, glucose-6-phosphatase, glucose-6-phosphate dehydrogenase, and fructose-1,6-bisphosphatase, to near-normal levels in liver tissue of STZ-induced diabetic mice. These results clearly indicate that PTS maintains glucose homeostasis, suggesting the possibility that it is a future candidate for use in diabetes management.

PMID: 26700463 DOI: 10.1021/acs.chemrestox.5b00378


Pterostilbene Decreases the Antioxidant Defenses of Aggressive Cancer Cells In Vivo: A Physiological Glucocorticoids- and Nrf2-Dependent Mechanism.


Author information

Abstract

AIMS:
Polyphenolic phytochemicals have anticancer properties. However, in mechanistic studies, lack of correlation with the bioavailable concentrations is a critical issue. Some reports had suggested that these molecules downregulate the stress response, which may affect growth and the antioxidant protection of malignant cells. Initially, we studied this potential underlying mechanism using different human melanomas (with genetic backgrounds correlating with most melanomas), growing in nude mice as xenografts, and pterostilbene (Pter, a natural dimethoxylated analog of resveratrol).

RESULTS:
Intravenous administration of Pter decreased human melanoma growth in vivo. However, Pter, at levels measured within the tumors, did not affect melanoma growth in vitro. Pter inhibited pituitary production of the adrenocorticotropic hormone (ACTH), decreased plasma levels of corticosterone, and thereby downregulated the glucocorticoid receptor- and nuclear factor (erythroid-derived 2)-like 2 (Nrf2)-dependent antioxidant defense system in growing melanomas.
Exogenous corticosterone or genetically induced Nrf2 overexpression in melanoma cells prevented the inhibition of tumor growth and decreased antioxidant defenses in these malignant cells. These effects and mechanisms were also found in mice bearing different human pancreatic cancers. Glutathione depletion (selected as an antimelanoma strategy) facilitated the complete elimination by chemotherapy of melanoma cells isolated from mice treated with Pter.

**INNOVATION:**
Although bioavailability-related limitations may preclude direct anticancer effects in vivo, natural polyphenols may also interfere with the growth and defense of cancer cells by downregulating the pituitary gland-dependent ACTH synthesis.

**CONCLUSIONS:**
Pter downregulates glucocorticoid production, thus decreasing the glucocorticoid receptor and Nrf2-dependent signaling/transcription and the antioxidant protection of melanoma and pancreatic cancer cells. Antioxid. Redox Signal. 24, 974-990.

PMID: 26651028 PMCID: PMC4921902 DOI: 10.1089/ars.2015.6437


**Topical treatment with pterostilbene, a natural phytoalexin, effectively protects hairless mice against UVB radiation-induced skin damage and carcinogenesis.**

Sirerol JA1, Feddi F2, Mena S1, Rodriguez ML1, Sirera P1, Aupí M1, Pérez S1, Asensi M3, Ortega A3, Estrela JM4.

**Author information**

Abstract

The aim of our study was to investigate in the SKH-1 hairless mouse model the effect of pterostilbene (Pter), a natural dimethoxy analog of resveratrol (Resv), against procarcinogenic ultraviolet B radiation (UVB)-induced skin damage. Pter prevented acute UVB (360 mJ/cm(2))-induced increase in skin fold, thickness, and redness, as well as photaging-associated skin wrinkling and hyperplasia. Pter, but not Resv, effectively prevented chronic UVB (180 mJ/cm(2), three doses/week for 6 months)-induced skin carcinogenesis (90% of Pter-treated mice did not develop skin carcinomas, whereas a large number of tumors were observed in all controls). This anticarcinogenic effect was associated with (a) maintenance of skin antioxidant defenses (i.e., glutathione (GSH) levels, catalase, superoxide, and GSH peroxidase activities) close to control values (untreated mice) and (b) an inhibition of UVB-induced oxidative damage (using as biomarkers 8-hydroxy-2'-deoxyguanosine, protein carbonyls, and isoprostanes). The molecular mechanism underlying the photoprotective effect elicited by Pter was further
evaluated using HaCaT immortalized human keratinocytes and was shown to involve potential modulation of the Nrf2-dependent antioxidant response.

**KEYWORDS:**
Free radicals; Oxidative stress; Photocarcinogenesis; Phytochemicals; Polyphenols; Pterostilbene; Resveratrol; Skin damage; Stilbenes; UV radiation

PMID: 25845487 DOI: 10.1016/j.freeradbiomed.2015.03.027


**The emerging role of redox-sensitive Nrf2-Keap1 pathway in diabetes.**

Bhakkiyalakshmi E1, Sireesh D2, Rajaguru P3, Paulmurugan R4, Ramkumar KM5.

**Author information**

**Abstract**

The pathogenic processes involving in the development of diabetes range from autoimmune destruction of pancreatic β-cells with consequent insulin deficiency to abnormalities that result in resistance to insulin action. The major contributing factor for excessive β-cell death includes oxidative stress-mediated mitochondrial damage, which creates an imbalance in redox homeostasis. Yet, β-cells have evolved adaptive mechanisms to endure a wide range of stress conditions to safeguard its potential functions. These include 'Nrf2/Keap1' pathway, a key cellular defense mechanism, to combat oxidative stress by regulating phase II detoxifying and antioxidant genes. During diabetes, redox imbalance provokes defective Nrf2-dependent signaling and compromise antioxidant capacity of the pancreas which turnout β-cells to become highly vulnerable against various insults. Hence, identification of small molecule activators of Nrf2/Keap1 pathway remains significant to enhance cellular defense to overcome the burden of oxidative stress related disturbances. This review summarizes the molecular mechanism behind Nrf2 activation and the impact of Nrf2 activators in diabetes and its complications.

**KEYWORDS:**
Antioxidants; Bardoxolone methyl (PubChem CID: 400769); Cinnamaldehyde (PubChem CID: 637511); Curcumin (PubChem CID: 969516); Diabetes; Epigallocatechin gallate (PubChem CID: 65064); MG-132 (PubChem CID: 462382); Magnesium Lithospermate B (PubChem CID: 6438135); Nrf2 activators; Nrf2–Keap1 pathway; Oxidative stress; Pterostilbene (PubChem CID: 5281727); Resveratrol (PubChem CID: 445154); Sulforaphane (PubChem CID: 5350); tert-Butylhydroquinone (PubChem CID: 16043)

PMID: 25447793 DOI: 10.1016/j.phrs.2014.10.004

Involvement of the Nrf2 pathway in the regulation of pterostilbene-induced apoptosis in HeLa cells via ER stress.

Zhang B1, Wang XQ, Chen HY, Liu BH.

Abstract

Among the various cancer cell lines, HeLa cells were found to be sensitive to pterostilbene (Pte), a compound that is enriched in small fruits such as grapes and berries. However, the mechanism involved in the cytotoxicity of Pte has not been fully characterized. Using biochemical and free radical biological experiments in vitro, we identified the pro-apoptotic profiles of Pte and evaluated the level of redox stress-triggered ER stress during HeLa cell apoptosis. The data showed a strong dose-response relationship between Pte exposure and the characteristics of HeLa apoptosis in terms of changes in apoptotic morphology, DNA fragmentation, and activated caspases in the intrinsic apoptotic pathway. During drug exposure, alterations in the intracellular redox homeostasis that favor oxidation were necessary to cause ER stress-related apoptosis, as demonstrated by enzymatic and non-enzymatic redox modulators. A statistically significant and dose-dependent increase (P < 0.05) was found with regard to the unique expression levels of Nrf2/ARE downstream target genes in HeLa cells undergoing late apoptosis, levels that were restored with anti-oxidant application with the Pte treatment. Our research demonstrated that Pte triggered ER stress by redox homeostasis imbalance, which was negatively regulated by a following activation of Nrf2.

PMID: 25341683


The berry constituents quercetin, kaempferol, and pterostilbene synergistically attenuate reactive oxygen species: involvement of the Nrf2-ARE signaling pathway.

Saw CL1, Guo Y2, Yang AY2, Paredes-Gonzalez X2, Ramirez C3, Pung D4, Kong AN5.

Abstract

Quercetin, kaempferol, and pterostilbene are abundant in berries. The anti-oxidative properties of these constituents may contribute to cancer chemoprevention. However, their precise mechanisms of action and their combinatorial effects are not completely understood. Nuclear factor (erythroid-derived 2)-like 2 (Nrf2) regulates anti-oxidative stress enzymes and Phase II drug metabolizing/detoxifying enzymes by binding to antioxidant response element (ARE). This
study aimed to investigate the anti-oxidative stress activities of quercetin, kaempferol, and pterostilbene individually and in combination, as well as the involvement of the Nrf2-ARE signaling pathway. Quercetin, kaempferol, and pterostilbene all exhibited strong free-radical scavenging activity in the DPPH assay. The MTS assay revealed that low concentration combinations we tested were relatively non-toxic to HepG2-C8 cells. The results of the DCFH-DA assay and combination index (CI) indicated that quercetin, kaempferol, and pterostilbene attenuated intracellular reactive oxygen species (ROS) levels when pretreated individually and had synergistic effects when used in combination. In addition, the combination treatment significantly induced ARE and increased the mRNA and protein expression of Nrf2-regulated genes. Collectively, our study demonstrated that the berry constituents quercetin, kaempferol, and pterostilbene activated the Nrf2-ARE signaling pathway and exhibited synergistic anti-oxidative stress activity at appropriate concentrations.

KEYWORDS:
Antioxidant response element (ARE); Kaempferol; Nuclear factor (erythroid-derived 2)-like 2 (Nrf2); Pterostilbene; Quercetin; Reactive oxygen species

PMID: 25111660 DOI: 10.1016/j.fct.2014.07.038


Therapeutic potential of pterostilbene against pancreatic beta-cell apoptosis mediated through Nrf2.

Bhakkiyalakshmi E1, Shalini D, Sekar TV, Rajaguru P, Paulmurugan R, Ramkumar KM.

Author information

Abstract

BACKGROUND AND PURPOSE:
Nuclear factor erythroid 2-related factor 2 (Nrf2) is considered to be a 'master regulator' of the antioxidant response as it regulates the expression of several genes including phase II metabolic and antioxidant enzymes and thus plays an important role in preventing oxidative stress-mediated disorders, including diabetes. In this study, for the first time, we investigated the protective properties of a naturally available antioxidant, pterostilbene (PTS), against pancreatic beta-cell apoptosis and the involvement of Nrf2 in its mechanism of action.

EXPERIMENTAL APPROACH:
Immunoblotting and quantitative reverse transcriptase (qRT)-PCR analysis were performed to identify PTS-mediated nuclear translocation of Nrf2 protein and the following activation of target gene expression, respectively, in INS-1E cells. In addition, an annexin-V binding assay was carried out to identify the apoptotic status of PTS-treated INS-1E cells, while confirming the anti-apoptotic potential of Nrf2 by qRT-PCR analysis of the expressions of both pro- and anti-apoptotic genes.
KEY RESULTS:
PTS induced significant activation of Nrf2, in dose- and time-dependent manner, in streptozotocin-treated INS-1E rat pancreatic beta-cells. Furthermore, PTS increased the expression of target genes downstream of Nrf2, such as heme oxygenase 1 (HO1), superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx), that confer cellular protection. PTS also up-regulated the expression of anti-apoptotic gene, Bcl-2, with a concomitant reduction in pro-apoptotic Bax and caspase-3 expression.

CONCLUSION AND IMPLICATIONS:
Collectively, our findings indicate the therapeutic potential of Nrf2 activation by PTS as a promising approach to safeguard pancreatic beta-cells against oxidative damage in diabetes. © 2014 The British Pharmacological Society.

KEYWORDS:
Nrf2; apoptosis; diabetes; pancreatic beta cells; pterostilbene; streptozotocin

PMID: 24417315 PMCID: PMC3966753 DOI: 10.1111/bph.12577


Reporter protein complementation imaging assay to screen and study Nrf2 activators in cells and living animals.

Ramkumar KM1, Sekar TV, Foygel K, Elango B, Paulmurugan R.

Author information

Abstract

NF-E2-related factor-2 (Nrf2) activators promote cellular defense mechanism and facilitate disease prevention associated with oxidative stress. In the present study, Nrf2 activators were identified using cell-based luciferase enzyme fragment complementation (EFC) assay, and the mechanism of Nrf2 activation was studied by molecular imaging. Among the various Nrf2 activators tested, pterostilbene (PTS) showed effective Nrf2 activation, as seen by luminometric screening, and validation in a high throughput-intact cell-imaging platform. Further, PTS increased the expression of Nrf2 downstream target genes, which was confirmed using luciferase reporter driven by ARE-NQO1 and ARE-GST1 promoters. Daily administration of PTS disturbed Nrf2/Keap1 interaction and reduced complemented luciferase signals in HEK293TNKS mouse tumor xenografts. This study reveals the potentials of Nrf2 activators as chemosensitizing agents' for therapeutic intervention in cancer treatment. Hence, the validated assay can be used to evaluate the identified activators preclinically in small animal models by noninvasive molecular imaging approach.

PMID: 23826874 PMCID: PMC3759980 DOI: 10.1021/ac401569j
Pterostilbene is more potent than resveratrol in preventing azoxymethane (AOM)-induced colon tumorigenesis via activation of the NF-E2-related factor 2 (Nrf2)-mediated antioxidant signaling pathway.

Chiou YS1, Tsai ML, Nagabhushanam K, Wang YJ, Wu CH, Ho CT, Pan MH.

Author information

Abstract

Inflammatory bowel diseases have been a risk factor of colorectal cancer (CRC). The reactive oxygen species (ROS) generated by inflammatory cells create oxidative stress and contribute to neoplastic transformation, proliferation, and even metastasis. Previously, resveratrol (RS) and pterostilbene (PS) had been reported to prevent chemical-induced colon carcinogenesis by anti-inflammatory and pro-apoptotic properties. In this study, we investigated whether RS and PS could prevent the azoxymethane (AOM)-induced colon tumorigenesis via antioxidant action and to explore possible molecular mechanisms. Male BALB/c mice were injected with AOM (5 mg/kg of body weight) with or without RS or PS, and at the end of the protocol, all of the mice were euthanized and colons were analyzed. Administrations of PS can be more effective than RS in reducing AOM-induced formation of aberrant crypt foci (ACF), lymphoid nodules (LN), and tumors. We also find that PS is functioning more effectively than RS to reduce nuclear factor-κB (NF-κB) activation by inhibiting the phosphorylation of protein kinase C-β2 (PKC-β2) and decreasing downstream target gene expression, including inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), and aldose reductase (AR) in mouse colon stimulated by AOM. Moreover, administration of RS and PS for 6 weeks significantly enhanced expression of antioxidant enzymes, such as heme oxygenase-1 (HO-1) and glutathione reductase (GR), via activation of NF-E2-related factor 2 (Nrf2) signaling. When the above findings are taken together, they suggest that both stilbenes block cellular inflammation and oxidative stress through induction of HO-1 and GR, thereby preventing AOM-induced colon carcinogenesis. In comparison, PS was a more potent chemopreventive agent than RS for the prevention of colon cancer. This is also the first study to demonstrate that PS is a Nrf2 inducer and AR inhibitor in the AOM-treated colon carcinogenesis model.

PMID: 21355597 DOI: 10.1021/jf2000103
Resveratrol, pterostilbene, and dementia.

Lange KW1, Li S2.

Author information

Abstract

Resveratrol is a natural phytoestrogen with neuroprotective properties. Polyphenolic compounds including resveratrol exert in vitro antioxidant, anti-inflammatory, and anti-amyloid effects. Resveratrol and its derivative pterostilbene are able to cross the blood-brain barrier and to influence brain activity. The present short review summarizes the available evidence regarding the effects of these polyphenols on pathology and cognition in animal models and human subjects with dementia. Numerous investigations in cellular and mammalian models have associated resveratrol and pterostilbene with protection against dementia syndromes such as Alzheimer's disease (AD) and vascular dementia. The neuroprotective activity of resveratrol and pterostilbene demonstrated in in vitro and in vivo studies suggests a promising role for these compounds in the prevention and treatment of dementia. In comparison to resveratrol, pterostilbene appears to be more effective in combatting brain changes associated with aging. This may be attributed to the more lipophilic nature of pterostilbene with its two methoxyl groups compared with the two hydroxyl groups of resveratrol. The findings of available intervention trials of resveratrol in individuals with mild cognitive impairment or AD do not provide evidence of neuroprotective or therapeutic effects. Future clinical trials should be conducted with long-term exposure to preparations of resveratrol and pterostilbene with high bioavailability.


KEYWORDS:
cognition; dementia; polyphenols; pterostilbene; resveratrol

PMID: 29168580 DOI: 10.1002/biof.1396


Pterostilbene ameliorates intracerebroventricular streptozotocin induced memory decline in rats.
Naik B1, Nirwane A1, Majumdar A1.

**Author information**

**Abstract**

There is strong evidence that mitochondrial dysfunction mediated oxidative stress results in aging and energy metabolism deficits thus playing a prime role in pathogenesis of Alzheimer’s disease, neuronal death and cognitive dysfunction. Evidences accrued in empirical studies suggest the antioxidant, anticancer and anti-inflammatory activities of the phytochemical pterostilbene (PTS). PTS also exhibits favourable pharmacokinetic attributes compared to other stilbenes. Hence, in the present study, we explored the neuroprotective role of PTS in ameliorating the intracerebroventricular administered streptozotocin (STZ) induced memory decline in rats. PTS at doses of 10, 30 and 50 mg/kg, was administered orally to STZ administered Sprague-Dawley (SD) rats. The learning and memory tests, Morris water maze test and novel object recognition test were performed which revealed improved cognition on PTS treatment. Further, there was an overall improvement in brain antioxidant parameters like elevated catalase and superoxide dismutase activities, GSH levels, lowered levels of nitrites, lipid peroxides and carbonylated proteins. There was improved cholinergic transmission as evident by decreased acetylcholinesterase activities. The action of ATPases (Na+ K+, Ca2+ and Mg2+) indicating the maintenance of cell membrane potential was also augmented. mRNA expression of battery of genes involved in cellular mitochondrial biogenesis and inflammation showed variations which extrapolate to hike in mitochondrial biogenesis and abated inflammation. The histological findings corroborated the effective role of PTS in countering STZ induced structural aberrations in brain.

**KEYWORDS:**
AChE; ATPases; Brain; Fenofibrate; IL-6; Inflammation; Learning and memory; PGC1α; PPARα; Protein carbonylation; Pterostilbene; Rats; Streptozotocin; TNF-α


**Design, synthesis and evaluation of some N-methylenebenzenamine derivatives as selective acetylcholinesterase (AChE) inhibitor and antioxidant to enhance learning and memory.**

Shrivastava SK1, Srivastava P2, Upendra TVR2, Tripathi PN2, Sinha SK3.

**Author information**
Abstract

Series of some 3,5-dimethoxy-N-methylenebenzenamine and 4-(methyleneamino)benzoic acid derivatives comprising of N-methylenebenzenamine nucleus were designed, synthesized, characterized, and assessed for their acetylcholinesterase (AChE), butyrylcholinesterase (BChE) inhibitory, and antioxidant activity thereby improving learning and memory in rats. The IC50 values of all the compound along with standard were determined on AChE and BChE enzyme. The free radical scavenging activity was also assessed by in vitro DPPH (2,2-diphenyl-1-picrylhydrazyl) and hydrogen peroxide radical scavenging assay. The selective inhibitions of all compounds were observed against AChE in comparison with standard donepezil. The enzyme kinetic study of the most active compound 4 indicated uncompetitive AChE inhibition. The docking studies of compound 4 exhibited the worthy interaction on active-site gorge residues Phe330 and Trp279 responsible for its high affinity towards AChE, whereas lacking of the BChE inhibition was observed due to a wider gorge binding site and absence of important aromatic amino acids interactions. The ex vivo study confirmed AChE inhibition abilities of compound 4 at brain site. Further, a considerable decrease in escape latency period of the compound was observed in comparison with standard donepezil through in vivo Spatial Reference Memory (SRM) and Spatial Working Memory (SWM) models which showed the cognition-enhancing potential of compound 4. The in vivo reduced glutathione (GSH) estimation on rat brain tissue homogenate was also performed to evaluate free radical scavenging activity substantiated the antioxidant activity in learning and memory.

KEYWORDS:
Acetylcholinesterase inhibitor; Antioxidant; Learning and memory; Pterostilbene; Schiff base

PMID: 28126439 DOI: 10.1016/j.bmc.2017.01.010


Effects of pterostilbene and resveratrol on brain and behavior.

Poulose SM1, Thangthaeng N1, Miller MG1, Shukitt-Hale B2.

Author information

Abstract

Age is the greatest universal risk factor for neurodegenerative diseases. During aging, these conditions progress from minor loss of function to major disruptions in daily life, loss of independence and ultimately death. Because approximately 25% of the world population is expected to be older than age 65 by 2050, and no treatments exist to halt or reverse ongoing neurodegeneration, the need for effective prevention strategies is more pressing that ever before. A growing body of research supports the role of diet in healthy aging, particularly diets rich in bioactive phytochemical compounds. Recently, stilbenes such as resveratrol (3, 5, 4'-trans-trihydroxystilbene) and its analogue, pterostilbene, have gained a significant amount of attention
for their potent antioxidant, anti-inflammatory, and anticarcinogenic properties. However, evidence for the beneficial effects of stilbenes on cerebral function is just beginning to emerge. In this review, we summarize the current knowledge on the role of resveratrol and pterostilbene in improving brain health during aging, with specific focus on antioxidant and anti-inflammatory signaling and behavioral outcomes.

KEYWORDS:
Aging; Brain-signaling; Inflammation; Polyphenols; Pterostilbene; Resveratrol

PMID: 26212523 DOI: 10.1016/j.neuint.2015.07.017


Pterostilbene: Biomedical applications.

Estrela JM1, Ortega A, Mena S, Rodriguez ML, Asensi M.

Author information

Abstract

Resveratrol and its naturally dimethylated analog, pterostilbene, show similar biological activities. However, the higher in vivo bioavailability of pterostilbene represents a fundamental advantage. The main focus of this review is on biomedical applications of pterostilbene. The metabolism and pharmacokinetics of this stilbene in inflammatory dermatoses and photoprotection, cancer prevention and therapy, insulin sensitivity, blood glycemia and lipid levels, cardiovascular diseases, aging, and memory and cognition are addressed. Safety and toxicity, as well as recommendations for future research and biomedical uses, are discussed. This review includes comparisons between pterostilbene and other polyphenols, with particular emphasis on resveratrol. Potential benefits of using combinations of different polyphenols are considered. Based on present evidences we conclude that pterostilbene is an active phytonutrient and also a potential drug with multiple biomedical applications.

PMID: 23808710 DOI: 10.3109/10408363.2013.805182


A berry thought-provoking idea: the potential role of plant polyphenols in the treatment of age-related cognitive disorders.

Cherniack EP1.

Author information
Abstract

Today, tens of millions of elderly individuals worldwide suffer from dementia. While the pathogenesis of dementia is complex and incompletely understood, it may be, at least to a certain extent, the consequence of systemic vascular pathology. The metabolic syndrome and its individual components induce a proinflammatory state that damages blood vessels. This condition of chronic inflammation may damage the vasculature of the brain or be directly neurotoxic. Associations have been established between the metabolic syndrome, its constituents and dementia. A relationship has also been observed between certain dietary factors, such as constituents of the 'Mediterranean diet', and the metabolic syndrome; similar associations have been noted between these dietary factors and dementia. Fruit juices and extracts are under investigation as treatments for cognitive impairment. Blueberry, strawberry, blackberry, grape and plum juices or extracts have been successfully tested in cognitively impaired rodents. Published trials of the benefits of grape and blueberry juice in the treatment of small numbers of cognitively impaired persons have recently appeared. The benefits of fruit products are thought to be a result of its polyphenol content. A grape polyphenol found in grapes, resveratrol, now being studied in humans, and one in grapes and blueberries, pterostilbene, have been found to improve cognition in rodents. In the design of future human trials, one ought to consider the poor bioavailability of these products, the possible need to initiate the experimental therapy long before the onset of symptoms, and currently limited knowledge about the appropriate form (e.g. juice, powder or individual polyphenol) of treatment.

PMID: 22475317 DOI: 10.1017/S0007114512000669


Cellular and behavioral effects of stilbene resveratrol analogues: implications for reducing the deleterious effects of aging.

Joseph JA1, Fisher DR, Cheng V, Rimando AM, Shukitt-Hale B.

Author information

Abstract

Research suggests that polyphenolic compounds contained in fruits and vegetables that are rich in color may have potent antioxidant and anti-inflammatory activities. The present studies determined if stilbene (e.g., resveratrol) compounds would be efficacious in reversing the deleterious effects of aging in 19 month old Fischer 344 rats. Experiment I utilized resveratrol and six resveratrol analogues and examined their efficacies in preventing dopamine-induced decrements in calcium clearance following oxotremorine-induced depolarization in COS-7 cells transfected with M1 muscarinic receptors (MACHR) that we have shown previously to be sensitive to oxidative stressors. Experiment II utilized the most efficacious analogue
(pterostilbene) from experiment I and fed aged rats a diet with a low (0.004%) or a high (0.016%) concentration of pterostilbene. Results indicated that pterostilbene was effective in reversing cognitive behavioral deficits, as well as dopamine release, and working memory was correlated with pterostilbene levels in the hippocampus.

PMID: 18954071 DOI: 10.1021/jf802279h


**Low-dose pterostilbene, but not resveratrol, is a potent neuromodulator in aging and Alzheimer's disease.**


**Author information**

**Abstract**

Recent studies have implicated resveratrol and pterostilbene, a resveratrol derivative, in the protection against age-related diseases including Alzheimer's disease (AD). However, the mechanism for the favorable effects of resveratrol in the brain remains unclear and information about direct cross-comparisons between these analogs is rare. As such, the purpose of this study was to compare the effectiveness of diet-achievable supplementation of resveratrol to that of pterostilbene at improving functional deficits and AD pathology in the SAMP8 mouse, a model of accelerated aging that is increasingly being validated as a model of sporadic and age-related AD. Furthermore we sought to determine the mechanism of action responsible for functional improvements observed by studying cellular stress, inflammation, and pathology markers known to be altered in AD. Two months of pterostilbene diet but not resveratrol significantly improved radial arm water maze function in SAMP8 compared with control-fed animals. Neither resveratrol nor pterostilbene increased sirtuin 1 (SIRT1) expression or downstream markers of sirtuin 1 activation. Importantly, markers of cellular stress, inflammation, and AD pathology were positively modulated by pterostilbene but not resveratrol and were associated with upregulation of peroxisome proliferator-activated receptor (PPAR) alpha expression. Taken together our findings indicate that at equivalent and diet-achievable doses pterostilbene is a more potent modulator of cognition and cellular stress than resveratrol, likely driven by increased peroxisome proliferator-activated receptor alpha expression and increased lipophilicity due to substitution of hydroxy with methoxy group in pterostilbene.

PMID: 21982274 DOI: 10.1016/j.neurobiolaging.2011.08.015
Antioxidant Activity

A review of pterostilbene antioxidant activity and disease modification.

McCormack D1, McFadden D.

Author information

Abstract

Pterostilbene (trans-3,5-dimethoxy-4-hydroxystilbene) is a natural dietary compound and the primary antioxidant component of blueberries. It has increased bioavailability in comparison to other stilbene compounds, which may enhance its dietary benefit and possibly contribute to a valuable clinical effect. Multiple studies have demonstrated the antioxidant activity of pterostilbene in both in vitro and in vivo models illustrating both preventative and therapeutic benefits. The antioxidant activity of pterostilbene has been implicated in anticarcinogenesis, modulation of neurological disease, anti-inflammation, attenuation of vascular disease, and amelioration of diabetes. In this review, we explore the antioxidant properties of pterostilbene and its relationship to common disease pathways and give a summary of the clinical potential of pterostilbene in the prevention and treatment of various medical conditions.

PMID: 23691264 PMCID: PMC3649683 DOI: 10.1155/2013/575482

Estrogen receptor-α36 is involved in pterostilbene-induced apoptosis and anti-proliferation in in vitro and in vivo breast cancer.

Pan C1, Hu Y2, Li J3, Wang Z4, Huang J5, Zhang S1, Ding L5.

Author information

Abstract

Pterostilbene (trans-3,5-dimethoxy-4'-hydroxystilbene) is an antioxidant primarily found in blueberries. It also inhibits breast cancer regardless of conventional estrogen receptor (ER-α66) status by inducing both caspase-dependent and caspase-independent apoptosis. However, the
pterostilbene-induced apoptosis rate in ER-α66-negative breast cancer cells is much higher than that in ER-α66-positive breast cancer cells. ER-α36, a variant of ER-α66, is widely expressed in ER-α66-negative breast cancer, and its high expression mediates the resistance of ER-α66-positive breast cancer patients to tamoxifen therapy. The aim of the present study is to determine the relationship between the antiproliferation activity of pterostilbene and ER-α36 expression in breast cancer cells. Methyl-thiazolyl-tetrazolium (MTT) assay, apoptosis analysis, and an orthotopic xenograft mouse model were used to examine the effects of pterostilbene on breast cancer cells. The expressions of ER-α36 and caspase 3, the activation of ERK and Akt were also studied through RT-PCR, western blot analysis, and immunohistochemical (IHC) staining. ER-α36 knockdown was found to desensitize ER-α66-negative breast cancer cells to pterostilbene treatment both in vitro and in vivo, and high ER-α36 expression promotes pterostilbene-induced apoptosis in breast cancer cells. Western blot analysis data indicate that MAPK/ERK and PI3K/Akt signaling in breast cancer cells with high ER-α36 expression are mediated by ER-α36, and are inhibited by pterostilbene. These results suggest that ER-α36 is a therapeutic target in ER-α36-positive breast cancer, and pterostilbene is an inhibitor that targets ER-α36 in the personalized therapy against ER-α36-positive breast cancer.

PMID: 25127034 PMCID: PMC4134202 DOI: 10.1371/journal.pone.0104459


Pterostilbene impact on retinal endothelial cells under high glucose environment.

Shen H1, Rong H2.

Author information

Abstract

Diabetic retinopathy (DR) has complicated pathogenic factors. Studies showed that DR belongs to chronic inflammatory disease, and retinal endothelial cells oxidation by free radicals is one of its mechanisms. Pterostilbene, as the homologous derivative of resveratrol, has obvious antioxidant effect. Its influence on the DR has not been studied. This study intended to investigate the effect and mechanism of pterostilbene on human retinal endothelial cells (hRECs) under high glucose environment to illustrate pterostilbene impact on DR and provide basis for DR clinical treatment. hRECs cultured in high glucose environment were treated by 1.0 mmol/L pterostilbene. MTT assay was applied to test cell proliferation. ELISA was used to detect inflammatory factor TNF-α and IL-1β content. Real time PCR and Western blot were performed to examine NF-κB mRNA and protein expression. ROS and SOD activities were analyzed. Under high glucose environment, hRECs proliferation increased, TNF-α and IL-1β expression elevated, and NF-κB protein level upregulated significantly. On the other side, ROS production increased and SOD activity decreased obviously (P < 0.05). Pterostilbene can suppress hRECs over proliferation, decrease TNF-α and IL-1β, inhibit NF-κB protein expression, reduce ROS production, and increase SOD activity markedly compared with high glucose group (P < 0.05).
Pterostilbene may delay DR progress through alleviating inflammation and antioxidation to suppress hRECs over proliferation.

**KEYWORDS:**
Diabetic retinopathy; inflammatory factor; pterostilbene; retinal endothelial cell

PMID: 26722449 PMCID: PMC4680394


**Pterostilbene induce autophagy on human oral cancer cells through modulation of Akt and mitogen-activated protein kinase pathway.**

Ko CP1, Lin CW2, Chen MK3, Yang SF4, Chiou HL5, Hsieh MJ6.

**Author information**

**Abstract**

**OBJECTIVES:**
Extensive research supports the administration of herbal medicines or natural foods during cancer therapy. Pterostilbene, a naturally occurring phytoalexin, has various pharmacological activities, including antioxidant activity, cancer prevention activity, and cytotoxicity to many cancers. However, the effect of pterostilbene on the autophagy of tumor cells has not been clarified.

**MATERIALS AND METHODS:**
In this study, the unique effects of pterostilbene on the autophagy of human oral cancer cells were investigated.

**RESULTS:**
The results of this study showed that pterostilbene effectively inhibited the growth of human oral cancer cells by inducing cell cycle arrest and apoptosis. In addition, the formation of acidic vesicular organelles and LC3-II production also demonstrated that pterostilbene induced autophagy. Administering 3-methylamphetatine (3-MA) and bafilomycin A1 (BafA1) exerted differing effects on the pterostilbene-induced death of human oral cancer cells. Pterostilbene-induced autophagy was triggered by activation of JNK1/2 and inhibition of Akt, ERK1/2, and p38.

**CONCLUSION:**
In conclusion, this study demonstrated that pterostilbene caused autophagy and apoptosis in human oral cancer cells, suggesting that pterostilbene could serve as a new and promising agent for treating human oral cancer.
Molecular targets of the natural antioxidant pterostilbene: effect on protein kinase C, caspase-3 and apoptosis in human neutrophils in vitro.


Abstract

OBJECTIVE: Pterostilbene, a naturally occurring phenolic derivative, exhibits various pharmacological effects, e.g. anti-cancerous, antioxidant, anti-inflammatory and anti-diabetic. Based on our previous study, we assessed the cellular and molecular effects of pterostilbene on human neutrophils and in cell free systems. Experimental and theoretical molecular descriptors of stilbene derivatives were also determined.

METHODS: We assessed the antioxidant properties of pterostilbene using cell free system and computational methods. The effect of pterostilbene on protein kinase C activation/phosphorylation was detected by special anti-phospho protein kinase C antibodies. Membrane associated changes determining the life span of neutrophils and human recombinant caspase-3 assay were examined.

RESULTS: Pterostilbene possessed comparable antioxidant properties as resveratrol in cell free system. Computational methods were used to establish the molecular characteristics of stilbene derivatives. The values of electronic parameters suggest a slight enhancement of electron donor properties of pterostilbene compared to resveratrol. Phosphorylation and thus activation of protein kinase C alpha/beta II in activated neutrophils was not decreased by pterostilbene. Pterostilbene in concentrations of 10-100 μM was found to inhibit the activity of human caspase-3 purified enzyme and did not influence cell viability significantly.

CONCLUSION:
Pterostilbene, an analog of resveratrol, was identified as a good natural antioxidant compound. However, reducing the oxidative burst of human neutrophils during their activation in vitro with pterostilbene does not include protein kinase C phosphorylation pathway. Pterostilbene showed dose dependent activation/inhibition of caspase-3 enzyme activity.

PMID: 21187824


The berry constituents quercetin, kaempferol, and pterostilbene synergistically attenuate reactive oxygen species: involvement of the Nrf2-ARE signaling pathway.

Saw CL, Guo Y, Yang AY, Paredes-Gonzalez X, Ramirez C, Pung D, Kong AN.

Author information

Abstract

Quercetin, kaempferol, and pterostilbene are abundant in berries. The anti-oxidative properties of these constituents may contribute to cancer chemoprevention. However, their precise mechanisms of action and their combinatorial effects are not completely understood. Nuclear factor (erythroid-derived 2)-like 2 (Nrf2) regulates anti-oxidative stress enzymes and Phase II drug metabolizing/detoxifying enzymes by binding to antioxidant response element (ARE). This study aimed to investigate the anti-oxidative stress activities of quercetin, kaempferol, and pterostilbene individually and in combination, as well as the involvement of the Nrf2-ARE signaling pathway. Quercetin, kaempferol, and pterostilbene all exhibited strong free-radical scavenging activity in the DPPH assay. The MTS assay revealed that low concentration combinations we tested were relatively non-toxic to HepG2-C8 cells. The results of the DCFH-DA assay and combination index (CI) indicated that quercetin, kaempferol, and pterostilbene attenuated intracellular reactive oxygen species (ROS) levels when pretreated individually and had synergistic effects when used in combination. In addition, the combination treatment significantly induced ARE and increased the mRNA and protein expression of Nrf2-regulated genes. Collectively, our study demonstrated that the berry constituents quercetin, kaempferol, and pterostilbene activated the Nrf2-ARE signaling pathway and exhibited synergistic anti-oxidative stress activity at appropriate concentrations.

KEYWORDS:
Antioxidant response element (ARE); Kaempferol; Nuclear factor (erythroid-derived 2)-like 2 (Nrf2); Pterostilbene; Quercetin; Reactive oxygen species

PMID: 25111660 DOI: 10.1016/j.fct.2014.07.038

Pterostilbene suppresses oral cancer cell invasion by inhibiting MMP-2 expression.

Lin CW1, Chou YE, Chiou HL, Chen MK, Yang WE, Hsieh MJ, Yang SF.

Author information

Abstract

OBJECTIVE: Polyphenol compounds, present in a wide variety of natural plants, exhibit antioxidant and free radical scavenging ability and induce apoptosis in various cancer cells. However, the effect of pterostilbene on oral cancer cell metastasis has not been clarified.

RESEARCH DESIGN AND METHODS: The present study aimed to examine the anti-metastatic properties of pterostilbene in human oral squamous cell carcinoma (SCC)-9 cells.

RESULTS: In this study, pterostilbene treatment significantly inhibited migration/invasion capacities of SCC-9 cells in vitro. The results of zymography and western blotting revealed that the activities and protein levels of the MMP-2 and urokinase-type plasminogen activator (u-PA) was inhibited by pterostilbene. Western blot analysis also showed that pterostilbene inhibits the phosphorylation of Akt, extracellular signal-regulated kinase 1/2 and p38. Determinations of the mRNA levels, real-time polymerase chain reaction and promoter assays were conducted to evaluate the inhibitory effects of pterostilbene on MMP-2 and u-PA expression in SCC-9 cells. Such inhibitory effects were associated with the upregulation of tissue inhibitor of metalloproteinase-2, plasminogen activator inhibitor-1 and the downregulation of the transcription factors of NF-κB, SP-1 and CREB signaling pathways.

CONCLUSIONS: Pterostilbene may have potential use as a chemopreventive agent against oral cancer metastasis.

KEYWORDS: MMP-2; migration; oral cancer; pterostilbene; urokinase-type plasminogen activator

PMID: 25109417 DOI: 10.1517/14728222.2014.947962


Pterostilbene induces mitochondrially derived apoptosis in breast cancer cells in vitro.
Moon D1, McCormack D, McDonald D, McFadden D.

**Author information**

**Abstract**

**BACKGROUND:**
The ability of a breast cancer cell to evade apoptosis has a key role in tumor progression and sensitivity to treatment. High levels of Bcl-2-associated X protein (Bax) in tumor cells have been found to promote apoptosis and sensitize cells to anti-cancer therapies. Bcl-2-associated X protein redistribution to the mitochondrial membrane results in the release of proapoptotic factors including cytochrome C, second-mitochondrial-derived activator of caspase/direct inhibitor of apoptosis-binding protein with low PI (Smac/DIABLO), and Ca(2+). We aimed to explore this pathway in cancerous breast cell lines treated with the naturally occurring antioxidant 3,5-dimethoxy-4-hydroxystilbene (pterostilbene).

**METHODS:**
We used whole cell lysates +/- Bax SiRNA from the cell lines MCF-7 and MDA-MB-231 in an enzyme-linked immunosorbent assay to quantify Bax, cytochrome C, Smac/DIABLO expression, and manganese superoxide dismutase (MnSOD) activity after treatment with pterostilbene. We quantified cell death using histone-related DNA complexes from cytosolic and mitochondrial fractions and used methylthiazol tetrazolium assay to analyze cell proliferation, in the presence of Bax-silencing or scrambled RNA. We measured changes in cytosolic calcium using the ratiometric calcium-sensitive dye fura-2-AM using an inverted ratiometric monochromator microscope.

**RESULTS:**
Treatment of MCF-7 and MDA-MB-231 (MDA) cells with pterostilbene caused concentration-dependent increases in intracellular Bax at all doses tested. RNA silencing of Bax resulted in reduced rates of apoptosis in both cells types and increased cell survival when treated with pterostilbene. We observed an increase in cytochrome C in MDA cells after treatment with pterostilbene. The MCF-7 cells showed a net increase in cytosolic cytochrome C, with a corresponding reduction in mitochondrial cytochrome C after treatment with 50 and 75 μmol/L pterostilbene. We observed this again in Smac/DIABLO expression in both cell types. In MCF-7 cells, pterostilbene treatment caused an increase in cytosolic but a decrease in mitochondrial Smac/DIABLO protein concentrations. Pterostilbene significantly increase MnSOD activity in MDA-MB-231 cells. Finally, pterostilbene resulted in significant increases in cytosolic calcium concentrations.

**CONCLUSIONS:**
The natural dietary compound pterostilbene has an anti-proliferative effect and induces apoptosis in breast cancer cells in vitro via Bax activation and overexpression, resulting in increased MnSOD, Smac/DIABLO, and cytochrome C activity and cytosolic Ca(2+) overload.

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Synthesis and pharmacological evaluation of glycosides of resveratrol, pterostilbene, and piceatannol.


Abstract

To enhance their water solubility and pharmacological activities, the stilbenes resveratrol, pterostilbene, and piceatannol were glycosylated to their monoglucosides (β-glucosides) and diglycosides (β-maltosides) by cultured cells and cyclodextrin glucanotransferase (CGTase). Cultured cells of Phytolacca americana and glucosyltransferase (PaGT) were capable of glucosylation of resveratrol to its 3- and 4'-β-glucosides. Pterostilbene was slightly transformed into its 4'-β-glucoside by P. americana cells. Piceatannol was readily converted into piceatannol 4'-β-glucoside, with the highest yield among the three substrates. The 3- and 4'-β-glucosides of resveratrol were subjected to further glycosylation by CGTase to give 3- and 4'-β-maltoside derivatives. The inhibitory action of resveratrol and pterostilbene toward histamine release induced with compound 48/80 from rat peritoneal mast cells was improved by β-glucosylation and/or β-maltosylation (i.e., the inhibitory activity for histamine release of the 3- and 4'-β-glucosides of resveratrol, the 3- and 4'-β-maltosides of resveratrol, and the 4'-β-glucoside of pterostilbene was higher than that of the corresponding aglycones, resveratrol and pterostilbene, respectively). In addition, the phosphodiesterase (PDE) inhibitory activity of resveratrol and pterostilbene was enhanced by β-glucosylation and/or β-maltosylation (i.e., the PDE inhibitory activities of the 3- and 4'-β-glucosides of resveratrol, the 4'-β-maltoside of resveratrol, and the 4'-β-glucoside of pterostilbene were higher than those of the corresponding aglycones, resveratrol and pterostilbene, respectively).

KEYWORDS:
glycoside; pharmacological activity; piceatannol; pterostilbene; resveratrol; synthesis


Mikstacka R1, Rimando AM, Ignatowicz E.
Author information

Abstract

There is evidence that a diet rich in fruit and vegetables may reduce the risk of cancer and other degenerative diseases. However, potential health impact of bioactive phytochemicals is limited by their low amount and relatively poor bioavailability. It has been suggested that the health benefits associated with fruit and red wine consumption could be due to the whole antioxidant pool of the diet microcomponents. In this study, the antioxidant activities of trans-resveratrol, pterostilbene and quercetin, and the effect of their combination were investigated in human erythrocytes in vitro. H(2)O(2)-induced lipid peroxidation was assessed by measuring the amount of thiobarbituric acid reactive species. Quercetin and pterostilbene protected erythrocyte membranes against lipid peroxidation (IC(50) values = 64 +/- 8.7 microM and 44.5 +/- 7.8 microM, respectively). Resveratrol was significantly less effective. However, the three compounds protected the erythrocytes against hemolysis and GSH (reduced glutathione) depletion to the same extent. Combinations consisting of two compounds (molar ratio 1:1) influenced lipid peroxidation in a concentration-dependent manner. At lower concentrations, resveratrol with quercetin or pterostilbene inhibited synergistically the oxidative injury of membrane lipids At higher concentrations, an additive effect was observed. These protective effects may partially explain the health benefit of these bioactive microcomponents when together in the diet.

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Synthesis of glycosides of resveratrol, pterostilbene, and piceatannol, and their anti-oxidant, anti-allergic, and neuroprotective activities.


Author information

Abstract

Resveratrol was glucosylated to its 3- and 4'-β-glucosides by cultured cells of Phytolacca americana. On the other hand, cultured P. americana cells glucosylated pterostilbene to its 4'-β-glucoside. P. americana cells converted piceatannol into its 4'-β-glucoside. The 3- and 4'-β-glucosides of resveratrol were further glucosylated to 3- and 4'-β-maltosides of resveratrol, 4'-β-maltoside of which is a new compound, by cyclodextrin glucanotransferase. Resveratrol 3-β-glucoside and 3-β-maltoside showed low 2,2-diphenyl-1-picrylhydrazyl free-radical-scavenging
activity, whereas other glucosides had no radical-scavenging activity. Piceatannol 4’-β-glucoside showed the strongest inhibitory activity among the stilbene glycosides towards histamine release from rat peritoneal mast cells. Pterostilbene 4’-β-glucoside showed high phosphodiesterase inhibitory activity.

**KEYWORDS:**
glycoside; piceatannol; pterostilbene; resveratrol

PMID: 25229845 DOI: 10.1080/09168451.2014.921551


**A combination of pterostilbene with autophagy inhibitors exerts efficient apoptotic characteristics in both chemosensitive and chemoresistant lung cancer cells.**

Hsieh MJ, Lin CW, Yang SF, Sheu GT, Yu YY, Chen MK, Chiou HL.

**Author information**

**Abstract**

The emergence of multidrug resistance (MDR), meaning that cancer cells develop simultaneous resistance to different drugs, has limited the clinical efficacy and application of chemotherapy. Pterostilbene, a naturally occurring phytoalexin exerts a variety of pharmacologic activities, including cancer prevention, cytotoxicity, and antioxidant activity. In this study, results proved the capability of pterostilbene to effectively inhibit the cell viability of docetaxel-induced MDR human lung cancer cell lines through cell cycle arrest and apoptosis. Meanwhile, the observation of LC3-II production and formation of acidic vesicular organelles revealed an induction of autophagy at an early stage by pterostilbene, which was triggered by an inhibition of the AKT and JNK pathways and activation of ERK1/2. Furthermore, pretreatment with the autophagy inhibitors 3-methyladenine and bafilomycin A1 or with beclin-1 small interfering RNA was able to enhance pterostilbene-triggered apoptosis. In conclusion, this study demonstrated that pterostilbene causes autophagy and apoptosis in lung cancer cells. Furthermore, pterostilbene in combination with autophagy inhibitors may strengthen the efficiency of chemotherapeutic strategies in both chemosensitive and chemoresistant lung cancer cells, which may be of immense value for the clinical management of lung cancer patients with MDR.

**KEYWORDS:**
apoptosis; autophagy.; multidrug resistance; pterostilbene

PMID: 24154491 DOI: 10.1093/toxsci/kft238

Pharmacometrics of pterostilbene: preclinical pharmacokinetics and metabolism, anticancer, antiinflammatory, antioxidant and analgesic activity.

Remsberg CM1, Yáñez JA, Ohgami Y, Vega-Villa KR, Rimando AM, Davies NM.

Author information

Abstract

The present study evaluated the preclinical pharmacokinetics and pharmacodynamics of trans-pterostilbene, a constituent of some plants. Right jugular vein cannulated male Sprague-Dawley rats were dosed i.v. with 20 mg/kg of pterostilbene and samples were analysed by the reverse phase HPLC method. Serum AUC, serum t(1/2), urine t(1/2), Cl(total) and Vd(beta) were 17.5 +/- 6.6 microg/h/mL, 1.73 +/- 0.78 h, 17.3 +/- 5.6 h, 0.960 +/- 0.025 L/h/kg and 2.41 +/- 1.13 L/kg (mean +/- SEM), respectively. A pterostilbene glucuronidated metabolite was detected in both serum and urine. The in vitro metabolism in rat liver microsomes furthermore suggests phase II metabolism of pterostilbene. Pterostilbene demonstrated concentration-dependent anticancer activity in five cancer cell lines (1-100 microg/mL). An in vitro colitis model showed concentration-dependent suppression of PGE(2) production in the media of HT-29 cells. Antiinflammatory activity was examined by inducing inflammation in canine chondrocytes followed by treatment with pterostilbene (1-100 microg/mL). The results showed decreased levels of MMP-3, sGAG and TNF-alpha compared with control levels. Pterostilbene exhibited concentration-dependent antioxidant capacity measured by the ABTS method. Pterostilbene increased the latency period to response in both tail-flick and hot-plate analgesic tests.

PMID: 17726731 DOI: 10.1002/ptr.2277


The stilbenes resveratrol, pterostilbene and piceid affect growth and stress resistance in mammalian cells via a mechanism requiring estrogen receptor beta and the induction of Mn-superoxide dismutase.

Robb EL1, Stuart JA2.

Author information

Abstract
The mitochondrial antioxidant enzyme, Mn superoxide dismutase (MnSOD), has been shown to confer cytoprotection and to regulate cell cycle progression. Resveratrol, a phytoestrogen found in red wines and other foods, has been previously reported to increase MnSOD protein levels and activity both in vitro and in vivo. Numerous structural analogues of resveratrol produced via the same stilbene synthesis pathway (e.g. pterostilbene and piceid) and also present in foods and red wine may be capable of eliciting the same effects. Furthermore, in humans resveratrol is rapidly metabolized to resveratrol-4'-sulfate, resveratrol-3-glucuronide and other metabolites in vivo. Although these metabolites may accumulate to relatively high levels in plasma and tissues, little is known about their biological activities. Here the activities were compared of these stilbenes and stilbene metabolites in mammalian cells. Two key cellular activities associated with resveratrol were examined: inhibition of proliferative growth and increased stress resistance (important anti-cancer and cell protective activities, respectively). While resveratrol-4'-sulfate and resveratrol-3-glucuronide had no effect on either cell growth or stress resistance, both pterostilbene and piceid were at least as effective as resveratrol. Using pharmacological and genetic approaches, it was found that the effects of pterostilbene and piceid required an induction of the mitochondrial enzyme MnSOD and intact mitochondrial respiration. In addition, using estrogen receptor beta (ERbeta) knockout mouse myoblasts, it was demonstrated that the effects of stilbene compounds on cell growth and stress resistance all require ERbeta. Taken together, these results indicate that resveratrol, pterostilbene and piceid all activate the same mitochondrial response in mammalian cells, and therefore these latter two molecules might be as effective as resveratrol in eliciting positive health outcomes in vivo.

**KEYWORDS:**
Cell growth; Estrogen receptor beta; Mitochondria; Reactive oxygen species; Stilbene; Stress resistance; Superoxide dismutase

PMID: 24361291 DOI: 10.1016/j.phytochem.2013.11.019


**Protective effects of pterostilbene against acetaminophen-induced hepatotoxicity in rats.**

*El-Sayed el-SM1, Mansour AM, Nady ME.*

**Author information**

**Abstract**

The present study was undertaken to evaluate the protective effect of pterostilbene against acetaminophen-induced hepatotoxicity. Silymarin was used as a standard hepatoprotective agent. A single dose of acetaminophen (800 mg/kg i.p.), injected to male rats, caused significant increases in serum levels of alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, bilirubin, total cholesterol, triglycerides, tumor necrosis factor alpha, and hepatic contents of malondialdehyde, nitric oxide, caspase-3, hydroxyproline, with significant decreases in serum HDL-cholesterol, total proteins, albumin, and hepatic activities of reduced glutathione,
superoxide dismutase and catalase as compared with the control group. On the other hand, administration of each of pterostilbene (50 mg/kg, p.o.) and silymarin (100 mg/kg, p.o.) for 15 days before acetaminophen ameliorated liver function and oxidative stress parameters. Histopathological evidence confirmed the protection offered by pterostilbene from the tissue damage caused by acetaminophen. In conclusion, pterostilbene possesses multimechanistic hepatoprotective activity that can be attributed to its antioxidant, anti-inflammatory, and antiapoptotic actions.

KEYWORDS:
Acetaminophen; Antioxidant; Hepatotoxicity; Pterostilbene; Silymarin

PMID: 25201704 DOI: 10.1002/jbt.21604


Pterostilbene inhibits dimethylnitrosamine-induced liver fibrosis in rats.

Lee MF1, Liu ML, Cheng AC, Tsai ML, Ho CT, Liou WS, Pan MH.

Author information

Abstract

Pterostilbene, found in grapes and berries, exhibits pleiotropic effects, including anti-inflammatory, antioxidant, and anti-proliferative activities. This study was conducted to investigate the effect of pterostilbene on liver fibrosis and the potential underlying mechanism for such effect. Sprague-Dawley rats were intraperitoneally given dimethyl n-nitrosamine (DMN) (10mg/kg) 3 days per week for 4 weeks. Pterostilbene (10 or 20mg/kg) was administered by oral gavage daily. Liver function, morphology, histochemistry, and fibrotic parameters were examined. Pterostilbene supplementation alleviated the DMN-induced changes in the serum levels of alanine transaminase and aspartate transaminase (p<0.05). Fibrotic status and the activation of hepatic stellate cells were improved upon pterostilbene supplementation as evidenced by histopathological examination as well as the expression of α-smooth muscle actin (α-SMA), transforming growth factor-β1 (TGF-β1), and matrix metalloproteinase 2 (MMP2). These data demonstrated that pterostilbene exhibited hepatoprotective effects on experimental fibrosis, potentially by inhibiting the TGF-β1/Smad signaling.

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Genomic analysis of pterostilbene predicts its antiproliferative effects against pancreatic cancer in vitro and in vivo.

McCormack DE1, Mannal P, McDonald D, Tighe S, Hanson J, McFadden D.

Author information

Abstract

BACKGROUND:
To investigate the inhibitory role of pterostilbene in pancreatic cancer, we conducted a genomic analysis of pterostilbene-treated pancreatic cancer cells. We also investigated the effect of pterostilbene upon the carcinogenic markers, manganese superoxide dismutase, cytochrome C, Smac/DIABLO, and STAT3 phosphorylation in vitro. The antiproliferative effects of pterostilbene were further evaluated in an in vivo model.

METHODS:
Pancreatic cancer cells were treated with pterostilbene and evaluated with DNA microarray analysis. Pterostilbene-treated cells were analyzed for cytochrome C, Smac/DIABLO, manganese superoxide dismutase (MnSOD)/antioxidant activity, and STAT3 phosphorylation using ELISA. Data were statistically analyzed using ANOVA. Pterostilbene was then administered to nude mice for 8 weeks, and tumor growth rates were recorded and statistically analyzed.

RESULTS:
Microarray analysis of pterostilbene-treated cells revealed upregulation of pro-apoptosis genes. In vitro, pterostilbene treatment altered levels of phosphorylated STAT3, MnSOD/antioxidant activity, cytochrome C, and Smac/DIABLO. In nude mice, oral pterostilbene inhibited tumor growth rates.

CONCLUSION:
Pterostilbene alters gene expression in pancreatic cancer and increases the antiproliferative markers cytochrome C, Smac/DIABLO, and MnSOD/antioxidant activity. It was also shown to inhibit phosphorylated STAT3, a marker of accelerated tumorigenesis, and decrease pancreatic tumor growth in vivo. Further studies are warranted to elucidate the effects of pterostilbene in humans.

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Pterostilbene and allopurinol reduce fructose-induced podocyte oxidative stress and inflammation via microRNA-377.

Wang W1, Ding XQ1, Gu TT1, Song L1, Li JM1, Xue QC1, Kong LD2.

Author information

Abstract

High dietary fructose is an important causative factor in the development of metabolic syndrome-associated glomerular podocyte oxidative stress and injury. Here, we identified microRNA-377 (miR-377) as a biomarker of oxidative stress in renal cortex of fructose-fed rats, which correlated with podocyte injury and albuminuria in metabolic syndrome. Fructose feeding increased miR-377 expression, decreased superoxide dismutase (SOD) expression and activity, and caused O2(-) and H2O2 overproduction in kidney cortex or glomeruli of rats. This reactive oxygen species induction increased p38 MAPK phosphorylation and thioredoxin-interacting protein (TXNIP) expression and activated the NOD-like receptor pyrin domain-containing 3 (NLRP3) inflammasome to produce interleukin-1β in kidney glomeruli of fructose-fed rats. These pathological processes were further evaluated in cultured differentiated podocytes exposed to 5mM fructose, or transfected with miR-377 mimic/inhibitor and TXNIP siRNA, or co-incubated with p38 MAPK inhibitor, demonstrating that miR-377 overexpression activates the O2(-)/p38 MAPK/TXNIP/NLRP3 inflammasome pathway to promote oxidative stress and inflammation in fructose-induced podocyte injury. Antioxidants pterostilbene and allopurinol were found to ameliorate fructose-induced hyperuricemia, podocyte injury, and albuminuria in rats. More importantly, pterostilbene and allopurinol inhibited podocyte miR-377 overexpression to increase SOD1 and SOD2 levels and suppress the O2(-)/p38 MAPK/TXNIP/NLRP3 inflammasome pathway activation in vivo and in vitro, consistent with the reduction of oxidative stress and inflammation. These findings suggest that miR-377 plays an important role in glomerular podocyte oxidative stress, inflammation, and injury driven by high fructose. Inhibition of miR-377 by antioxidants may be a promising therapeutic strategy for the prevention of metabolic syndrome-associated glomerular podocyte injury.

KEYWORDS:
Allopurinol; Free radicals; Fructose; MiR-377; NLRP3 inflammasome; Oxidative stress; Podocyte injury; Pterostilbene; TXNIP

PMID: 25746774 DOI: 10.1016/j.freeradbiomed.2015.02.029


Pterostilbene induces apoptosis and cell cycle arrest in diffuse large B-cell lymphoma cells.
Kong Y1, Chen G1, Xu Z2, Yang G1, Li B2, Wu X1, Xiao W1, Xie B1, Hu L1, Sun X1, Chang G1, Gao M1, Gao L1, Dai B3, Tao Y1, Zhu W2, Shi J1.

Author information

Abstract

Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma (NHL). Pterostilbene, a natural dimethylated analog of resveratrol, has been shown to possess diverse pharmacological activities, including anti-inflammatory, antioxidant and anticancer properties. However, to the best of our knowledge, there has been no study of the effects of pterostilbene upon hematological malignancies. Herein, we report the antitumor activity and mechanism of pterostilbene against DLBCL cells both in vitro and in vivo. We found that pterostilbene treatment resulted in a dose-dependent inhibition of cell viability. In addition, pterostilbene exhibited a strong cytotoxic effect, as evidenced not only by reductions of mitochondrial membrane potential (MMP) but also by increases in cellular apoptotic index and reactive oxygen species (ROS) levels, leading to arrest in the S-phase of the cell cycle. Furthermore, pterostilbene treatment directly up-regulated p-p38MAPK and down-regulated p-ERK1/2. In vivo, intravenous administration of pterostilbene inhibited tumor development in xenograft mouse models. Overall, the results suggested that pterostilbene is a potential anticancer pharmaceutical against human DLBCL by a mechanism involving the suppression of ERK1/2 and activation of p38MAPK signaling pathways.

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Cytotoxic and antioxidant effects of methoxylated stilbene analogues on HepG2 hepatoma and Chang liver cells: Implications for structure activity relationship.

Hasiah AH1, Ghazali AR, Weber JF, Velu S, Thomas NF, Inayat Hussain SH.

Author information

Abstract

Stilbenes possess a variety of biological activities including chemopreventive activity. This study was conducted to evaluate the structural activity relationships of six methoxylated stilbene analogues with respect to their cytotoxic effects and antioxidant activities on HepG2 hepatoma and Chang liver cells. The cytotoxic and total antioxidant activities of six stilbene analogues were determined by MTT and Ferric Reducing Antioxidant Power (FRAP) assays, respectively. We found that the cis-methoxylated stilbene: (Z)-3,4,4’-trimethoxystilbene was the most potent and selective antiproliferative agent (IC₅₀ 89 µM) in HepG2 cells. For the total antioxidant
activity, compounds possessing hydroxyl groups at the 4' position namely (E)-3-methoxy-4'-hydroxy-stilbene, (E)-3,5-dimethoxy-4'-hydroxy-stilbene (pterostilbene), (E)-4-methoxy-4'-hydroxy-stilbene showed the highest antioxidant activity. Structure activity relationship studies of these compounds demonstrated that the cytotoxic effect and antioxidant activities of the tested compounds in this study were structurally dependent.

PMID: 20385705 DOI: 10.1177/0960327110368739


Protective effect of Pterostilbene against free radical mediated oxidative damage.

Acharya JD1, Ghaskadbi SS.

Author information

Abstract

BACKGROUND:
Pterostilbene, a methoxylated analog of Resveratrol, is gradually gaining more importance as a therapeutic drug owing to its higher lipophilicity, bioavailability and biological activity than Resveratrol. This study was undertaken to characterize its ability to scavenge free radicals such as superoxide, hydroxyl and hydrogen peroxide and to protect bio-molecules within a cell against oxidative insult.

METHODS:
Anti-oxidant activity of Pterostilbene was evaluated extensively by employing several in vitro radical scavenging/inhibiting assays and pulse radiolysis study. In addition, its ability to protect rat liver mitochondria against tertiary-butyl hydroperoxide (TBHP) and hydroxyl radical generated oxidative damage was determined by measuring the damage markers such as protein carbonyls, protein sulphydryls, lipid hydroperoxides, lipid peroxides and 8-hydroxy-2'-deoxyguanosine. Pterostilbene was also evaluated for its ability to inhibit •OH radical induced single strand breaks in pBR322 DNA.

RESULT:
Pterostilbene exhibited strong anti-oxidant activity against various free radicals such as DPPH, ABTS, hydroxyl, superoxide and hydrogen peroxide in a concentration dependent manner. Pterostilbene conferred protection to proteins, lipids and DNA in isolated mitochondrial fractions against TBHP and hydroxyl radical induced oxidative damage. It also protected pBR322 DNA against oxidative assault.

CONCLUSIONS:
Thus, present study provides an evidence for the strong anti-oxidant property of Pterostilbene, methoxylated analog of Resveratrol, thereby potentiating its role as an anti-oxidant.
Pterostilbene inhibits breast cancer in vitro through mitochondrial depolarization and induction of caspase-dependent apoptosis.

Alosi JA1, McDonald DE, Schneider JS, Privette AR, McFadden DW.

Author information

Abstract

BACKGROUND:
Epidemiologic studies suggest that diets high in fruits and vegetables reduce cancer risk. Resveratrol, a compound present in grapes, has been shown to inhibit a variety of primary tumors. Pterostilbene, an analogue of resveratrol found in blueberries, has both antioxidant and antiproliferative properties. We hypothesized that pterostilbene would induce apoptosis and inhibit breast cancer cell growth in vitro.

METHODS:
Breast cancer cells were treated with graduated doses of pterostilbene. Cell viability was measured by MTT assay. Apoptosis was evaluated via DNA fragmentation assay and TUNEL assay. Apo-ONE caspase-3/7 assay was used to evaluate caspase activity. Flow cytometry was used to evaluate mitochondrial depolarization, superoxide formation, and cell cycle. Student’s t-test and two-way ANOVA with Bonferroni posttests were utilized for statistical analysis.

RESULTS:
Pterostilbene decreased breast cancer cell viability in a concentration- and time-dependent manner. Pterostilbene treatment increased caspase-3/7 activity and apoptosis in both cell lines. Caspase-3/7 inhibitors completely reversed pterostilbene's effects on cell viability. Pterostilbene treatment triggered mitochondrial depolarization, increased superoxide anion, and caused alteration in cell cycle.

CONCLUSIONS:
Pterostilbene treatment inhibits the growth of breast cancer in vitro through caspase-dependent apoptosis. Mitochondrial membrane depolarization and increased superoxide anion may contribute to the activation downstream effector caspases. Caspase inhibition leads to complete reversal of pterostilbene's effect on cell viability. Further in vitro mechanistic studies and in vivo experiments are warranted to determine its potential for the treatment of breast cancer.

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Cancer chemopreventive and antioxidant activities of pterostilbene, a naturally occurring analogue of resveratrol.

Rimando AM1, Cuendet M, Desmarchelier C, Mehta RG, Pezzuto JM, Duke SO.

Abstract

Pterostilbene, a natural methoxylated analogue of resveratrol, was evaluated for antioxidative potential. The peroxyl-radical scavenging activity of pterostilbene was the same as that of resveratrol, having total reactive antioxidant potentials of 237 +/- 58 and 253 +/- 53 microM, respectively. Both compounds were found to be more effective than Trolox as free radical scavengers. Using a plant system, pterostilbene also was shown to be as effective as resveratrol in inhibiting electrolyte leakage caused by herbicide-induced oxidative damage, and both compounds had the same activity as alpha-tocopherol. Pterostilbene showed moderate inhibition (IC50 = 19.8 microM) of cyclooxygenase (COX)-1, and was weakly active (IC50 = 83.9 microM) against COX-2, whereas resveratrol strongly inhibited both isoforms of the enzyme with IC50 values of approximately 1 microM. Using a mouse mammary organ culture model, carcinogen-induced preneoplastic lesions were, similarly to resveratrol, significantly inhibited by pterostilbene (ED50 = 4.8 microM), suggesting antioxidant activity plays an important role in this process.

PMID: 12033810

Pterostilbene inhibits lung cancer through induction of apoptosis.

Schneider JG1, Alosi JA, McDonald DE, McFadden DW.

Abstract

BACKGROUND:
Lung cancer remains the leading cause of cancer mortality in the United States. Resveratrol is a potent antioxidant found in grapes that inhibits several types of cancer, including lung cancer. Herein, we investigated the effects of pterostilbene, an analog of resveratrol found in blueberries, on lung cancer, in vitro. We hypothesized that pterostilbene would inhibit lung cancer cell growth in vitro by a pro-apoptotic mechanism.
METHODS:
Two lung cancer cell lines (NCI-H460 and SK-MES-1) were cultured using standard techniques. Cells were treated with increasing doses of pterostilbene (10-100 microM). Cell viability was measured at 24, 48, and 72h using a MTT assay. Apo-ONE Caspase-3/7 assay was used to evaluate caspase activity. T-test and two-way ANOVA were used for statistical analysis.

RESULTS:
Pterostilbene significantly decreased cell viability in lung cancer cells in a concentration- and time-dependent manner (P<0.001). Concentrations greater than 20 microM of pterostilbene produced significant growth inhibition by 72h (P<0.001). Apoptosis and caspase-3/7 activity were significantly increased by pterostilbene treatment (P<0.05).

CONCLUSIONS:
Pterostilbene inhibits growth via apoptosis induction in vitro. Further in vitro mechanistic studies and in vivo experiments are warranted to determine the potential role for pterostilbene in lung cancer treatment or prevention.

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The antioxidant role of pterostilbene in streptozotocin-nicotinamide-induced type 2 diabetes mellitus in Wistar rats.

Amarnath Satheesh M1, Pari L.

Author information

Abstract

The antioxidant effect of pterostilbene on streptozotocin-nicotinamide-induced diabetic rats has been assessed. The activity of superoxide dismutase, catalase, glutathione peroxidase, glutathione-S-transferase and reduced glutathione was significantly decreased in liver and kidney of diabetic animals when compared with normal control. There were significant improvements in these activities after treatment with pterostilbene at a dose of 40 mg kg(-1) for six weeks. The increased levels of lipid peroxidation measured as thiobarbituric acid reactive substances (TBARS) in liver and kidney of diabetic rats were also normalized by treatment with pterostilbene. Chronic treatment of pterostilbene remarkably reduced the pathological changes observed in liver and kidney of diabetic rats. These results indicated the antioxidant property of pterostilbene.

PMID: 17132211 DOI: 10.1211/jpp.58.11.0009

**Inhibitory effects of (-)-epigallocatechin-3-gallate and pterostilbene on pancreatic cancer growth in vitro.**

Kostin SF1, McDonald DE, McFadden DW.

**Author information**

**Abstract**

**BACKGROUND:**
It has been previously shown that the naturally occurring antioxidant (-)-epigallocatechin-3-gallate (EGCG), found in green tea, and pterostilbene, a stilbenoid derived from blueberries, inhibit pancreatic cancer in vitro when used individually. We hypothesized that the combination of EGCG and pterostilbene would reveal additive effects in vitro.

**METHODS:**
Using the pancreatic cancer cell lines MIA PaCa-2 and PANC-1, efficacy and synergism were evaluated for cell proliferation and viability (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assays, cell cycle analysis) and mitochondrial apoptosis (mitochondrial depolarization, cytochrome C release, caspase-3/7 activity, cell death detection using enzyme-linked immunosorbent assay).

**RESULTS:**
Cell proliferation assays revealed significant additive antiproliferative effects with pterostilbene and EGCG in both cell lines at the later, 72-h, point (P < 0.05). MIA underwent S-phase arrest with the combination (10-12% increase); however, cell cycle arrest was not observed in PANC. The combination induced mitochondrial depolarization and upregulated cytochrome C (P < 0.05) in MIA, but these effects were not observed in PANC. EGCG increased caspase-3/7 in MIA; however, the combination did not significantly increase the activity in either cell line (P < 0.05). Apoptosis was only observed in PANC (P < 0.05). The reduction in proliferation in MIA in the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assays with the combination indicated that cell death occurs, possibly through another mechanism.

**CONCLUSIONS:**
Our results are encouraging regarding the future use of EGCG and pterostilbene to improve traditional pancreatic cancer therapies. In conclusion, EGCG and pterostilbene have additive, antiproliferative effects in vitro and alter the apoptotic mechanisms in both cell lines by modulation at different points in the mechanism.

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In vitro evaluation of the cytotoxic, anti-proliferative and anti-oxidant properties of pterostilbene isolated from Pterocarpus marsupium.

Chakraborty A1, Gupta N, Ghosh K, Roy P.

Author information

Abstract

Pterostilbene, a dimethyl ester derivative of resveratrol, may act as an cytotoxic and hence as an anti-cancer agent. The present study was conducted to test the anti-cancer activity of pterostilbene purified from Pterocarpus marsupium on breast (MCF-7) and prostate (PC3) cancer cell lines. The purified pterostilbene was found to cause apoptosis in both the cell lines, which was marked by DNA fragmentation, formation of apoptotic bodies and membrane distortions. Apoptosis probably was due to the production of reactive oxygen species in MCF-7 and nitric oxide over production in PC3 cells. Even the drug detoxifying anti-oxidant enzymes could not nullify the effect of pterostilbene as required by the cancer cells for survival. Pterostilbene was found to inhibit the cell proliferating factors like Akt, Bcl-2 and induced the mitochondrial apoptotic signals like Bax, and the series of caspases. It also inhibited Matrix metalloproteinase 9 (MMP9) and alpha-methylacyl-CoA recemase (AMACR), two very well known metastasis inducers. In conclusion, pterostilbene has multiple target sites to induce apoptosis. Hence, after proper validation it can be used as a potential agent for the cure of breast and prostate cancer.

PMID: 20152895 DOI: 10.1016/j.tiv.2010.02.007


Pharmacokinetics, oral bioavailability, and metabolic profile of resveratrol and its dimethylether analog, pterostilbene, in rats.

Kapetanovic IM1, Muzzio M, Huang Z, Thompson TN, McCormick DL.

Author information

Abstract

PURPOSE:
Resveratrol (3,5,4'-trihydroxy-trans-stilbene) is a naturally occurring polyphenol with a broad range of possible health benefits, including anti-cancer activity. However, the biological activity of resveratrol may be limited by poor absorption and first-pass metabolism: only low plasma concentrations of resveratrol are seen following oral administration, and metabolism to
glucuronide and sulfate conjugates is rapid. Methylated polyphenol analogs (such as pterostilbene [3,5-dimethoxy-4'-hydroxy-trans-stilbene], the dimethylether analog of resveratrol) may overcome these limitations to pharmacologic efficacy. The present study was designed to compare the bioavailability, pharmacokinetics, and metabolism of resveratrol and pterostilbene following equimolar oral dosing in rats.

METHODS:
The agents were administered orally via gavage for 14 consecutive days at 50 or 150 mg/kg/day for resveratrol and 56 or 168 mg/kg/day for pterostilbene. Two additional groups were dosed once intravenously with 10 and 11.2 mg/kg for resveratrol and pterostilbene, respectively. Plasma concentrations of agents and metabolites were measured using a high-pressure liquid chromatograph-tandem mass spectrometer system. Noncompartmental analysis was used to derive pharmacokinetic parameters.

RESULTS:
Resveratrol and pterostilbene were approximately 20 and 80% bioavailable, respectively. Following oral dosing, plasma levels of pterostilbene and pterostilbene sulfate were markedly greater than were plasma levels of resveratrol and resveratrol sulfate. Although plasma levels of resveratrol glucuronide exceeded those of pterostilbene glucuronide, those differences were smaller than those of the parent drugs and sulfate metabolites.

CONCLUSIONS:
When administered orally, pterostilbene demonstrates greater bioavailability and total plasma levels of both the parent compound and metabolites than does resveratrol. These differences in agent pharmacokinetics suggest that the in vivo biological activity of equimolar doses of pterostilbene may be greater than that of resveratrol.

PMID: 21116625 PMCID: PMC3090701 DOI: 10.1007/s00280-010-1525-4


Topical treatment with pterostilbene, a natural phytoalexin, effectively protects hairless mice against UVB radiation-induced skin damage and carcinogenesis.

Sirerol JA1, Feddi F2, Mena S1, Rodriguez ML1, Sirera P1, Aupí M1, Pérez S1, Asensi M3, Ortega A3, Estrela JM4.

Author information

Abstract

The aim of our study was to investigate in the SKH-1 hairless mouse model the effect of pterostilbene (Pter), a natural dimethoxy analog of resveratrol (Resv), against procarcinogenic
ultraviolet B radiation (UVB)-induced skin damage. Pter prevented acute UVB (360 mJ/cm²)-induced increase in skin fold, thickness, and redness, as well as photoaging-associated skin wrinkling and hyperplasia. Pter, but not Resv, effectively prevented chronic UVB (180 mJ/cm², three doses/week for 6 months)-induced skin carcinogenesis (90% of Pter-treated mice did not develop skin carcinomas, whereas a large number of tumors were observed in all controls). This anticarcinogenic effect was associated with (a) maintenance of skin antioxidant defenses (i.e., glutathione (GSH) levels, catalase, superoxide, and GSH peroxidase activities) close to control values (untreated mice) and (b) an inhibition of UVB-induced oxidative damage (using as biomarkers 8-hydroxy-2'-deoxyguanosine, protein carbonyls, and isoprostanes). The molecular mechanism underlying the photoprotective effect elicited by Pter was further evaluated using HaCaT immortalized human keratinocytes and was shown to involve potential modulation of the Nrf2-dependent antioxidant response.

**KEYWORDS:**
Free radicals; Oxidative stress; Photocarcinogenesis; Phytochemicals; Polyphenols; Pterostilbene; Resveratrol; Skin damage; Stilbenes; UV radiation

PMID: 25845487 DOI: 10.1016/j.freeradbiomed.2015.03.027


**Pterostilbene as treatment for severe acute pancreatitis.**

Lin YJ1, Ding Y2, Wu J1, Ning BT3.

**Author information**

**Abstract**

Acute pancreatitis (AP) has a fast onset and progression, which lead to an unfavorable prognosis. Therefore, the development of novel drugs for its treatment is critical. As a homologous derivative of resveratrol, pterostilbene exerts a variety of effects including anti-inflammatory, antioxidant, and antitumor effects. This study investigated the potential of pterostilbene for treatment of severe AP (SAP) and related mechanisms. Effects of pterostilbene were evaluated in a Wistar rat model of AP. Serum levels of amylase (AMY), creatinine (Cr), and alanine aminotransferase (ALT) were quantified. Furthermore, serum levels of tumor necrosis factor (TNF)-a and interleukin (IL)-1b were quantified using enzyme-linked immunosorbent assay. Nuclear factor (NF)-kB expression in pancreatic tissues was quantified by real-time PCR and western blotting. The production of reactive oxygen species (ROS) was determined using a spectrometer, while superoxide dismutase (SOD) activity was assayed. In the AP rat model, the expression of inflammatory markers TNF-a and IL-1b, expression of NF-kB, and serum indices (AMY, Cr, and ALT) increased compared to the corresponding levels in the control group (P < 0.05). Pterostilbene reduced serum levels of TNF-a and IL-1b; decreased NF-kB gene expression, serum indices, and ROS generation; and increased SOD activity in a dose-dependent manner. In conclusion, pterostilbene can alleviate SAP-induced tissue damage by decreasing the
inflammatory response and by promoting antioxidation leading to the protection of pancreatic tissues.

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Pterostilbene-O-acetamidoalkylbenzylamines derivatives as novel dual inhibitors of cholinesterase with anti-β-amyloid aggregation and antioxidant properties for the treatment of Alzheimer's disease.

Li Y1, Qiang X1, Li Y1, Yang X1, Luo L1, Xiao G1, Cao Z1, Tan Z2, Deng Y3.

Author information

Abstract

A series of pterostilbene-O-acetamidoalkylbenzylamines were designed, synthesized and evaluated as dual inhibitors of AChE and BuChE. To further explore the multifunctional properties of the new derivatives, their antioxidant activities and inhibitory effects on self-induced Aβ1-42 aggregation and HuAChE-induced Aβ1-40 aggregation were also tested. The results showed that most of these compounds could effectively inhibit AChE and BuChE. Particularly, compound 21d exhibited the best AChE inhibitory activity (IC50=0.06 μM) and good inhibition of BuChE (IC50=28.04 μM). Both the inhibition kinetic analysis and molecular modeling study revealed that these compounds showed mixed-type inhibition, binding simultaneously to the CAS and PAS of AChE. In addition to cholinesterase inhibitory activities, these compounds showed different levels of antioxidant activity. However, the inhibitory activities against self-induced and HuAChE-induced Aβ aggregation of these new derivatives were unsatisfied. Taking into account the results of the biological evaluation, further modifications will be designed in order to increase the potency on the different targets. The results displayed in this Letter can be a new starting point for further development of multifunctional agents for Alzheimer's disease.

KEYWORDS:
Alzheimer’s disease; Antioxidant; Aβ aggregation inhibitors; Dual cholinesterase inhibitors; Pterostilbene-O-acetamidoalkylbenzylamines

PMID: 26947607 DOI: 10.1016/j.bmcl.2016.02.079

Pterostilbene inhibits colorectal aberrant crypt foci (ACF) and colon carcinogenesis via suppression of multiple signal transduction pathways in azoxymethane-treated mice.

Chiou YS1, Tsai ML, Wang YJ, Cheng AC, Lai WM, Badmaev V, Ho CT, Pan MH.

Author information

Abstract

Pterostilbene (PS), a natural dimethylated analogue of resveratrol, is known to have diverse pharmacologic activities including anticancer, anti-inflammation, antioxidant, apoptosis, antiproliferation, and analgesic potential. This paper reports the inhibitory effect of dietary administration of pterostilbene against the formation of azoxymethane (AOM)-induced colonic aberrant crypt foci (ACF) preneoplastic lesions and adenomas in male ICR mice and delineates its possible molecular mechanisms. ICR mice were given two AOM injections intraperitoneal and continuously fed a 50 or 250 ppm pterostilbene diet for 6 or 23 weeks. It was found that the dietary administration of pterostilbene effectively reduced AOM-induced formation of ACF and adenomas and inhibited the transcriptional activation of iNOS and COX-2 mRNA and proteins in mouse colon stimulated by AOM. Treatment with pterostilbene resulted in the induction of apoptosis in mouse colon. Moreover, administration of pterostilbene for 23 weeks significantly suppressed AOM-induced GSK3beta phosphorylation and Wnt/beta-catenin signaling. It was also found that pterostilbene significantly inhibited AOM-induced expression of VEGF, cyclin D1, and MMPs in mouse colon. Furthermore, pterostilbene markedly inhibited AOM-induced activation of Ras, phosphatidylinositol 3 kinase/Akt, and EGFR signaling pathways. All of these results revealed that pterostilbene is an effective antitumor agent as well as its inhibitory effect through the down-regulation of inflammatory iNOS and COX-2 gene expression and up-regulation of apoptosis in mouse colon, suggesting that pterostilbene is a novel functional agent capable of preventing inflammation-associated colon tumorigenesis.

PMID: 20681671 DOI: 10.1021/jf101571z


Pterostilbene induces apoptosis through caspase activation in ovarian cancer cells.

Dong J, Guo H, Chen Y.

Author information

Abstract

AIM:
Pterostilbene, an analog of resveratrol increasing bioavailability has shown to offer antioxidant and anticancer properties in vitro and in vivo. Dietary compounds with anti-oxidant properties have been shown to gain importance due to therapeutic applications. In addition, compounds with higher bioavailability levels show great interest in present scenario. Thus, the present study aimed at investigating the cytotoxic role of pterostilbene and its mechanism of cell death in ovarian cancer cells line.

MATERIALS AND METHODS:
The effect of pterostilbene was determined on SKOV-3 cells, by cytotoxicity assays, oxidative stress levels, [Ca2+]i levels, mitochondrial depolarization, cell cycle analysis and caspase 3, 8, and 9 activities.

RESULTS:
The study revealed that pterostilbene offered cytotoxic effect at a concentration of IC50-55 uM. Further, pterostilbene induced reactive oxygen species (ROS) mediated intrinsic pathway of apoptosis through enhancing oxidative stress, [Ca2+]i levels, mitochondrial depolarization, Sub G1 accumulation, and activation of caspase 3 and 9.

CONCLUSION:
The study demonstrates for the first time the cytotoxic potential of pterostilbene against ovarian cancer cells.

PMID: 27352561


Pterostilbene inhibited tumor invasion via suppressing multiple signal transduction pathways in human hepatocellular carcinoma cells.

Pan MH, Chiou YS, Chen WJ, Wang JM, Badmaev V, Ho CT.

Author information

Abstract

Pterostilbene, a natural dimethylated analog of resveratrol, is known to have diverse pharmacologic activities including anticancer, anti-inflammation, antioxidant, apoptosis, anti-proliferation and analgesic potential. However, the effects of pterostilbene in preventing invasion of cancer cells have not been studied. Here, we report our finding that pterostilbene significantly suppressed 12-O-tetradecanoylphorbol 13-acetate (TPA)-induced invasion, migration and metastasis of human hepatoma cells (HepG(2) cells). Increase in the enzyme activity, protein and messenger RNA levels of matrix metalloproteinase (MMP)-9 were observed in TPA-treated HepG(2) cells, and these were blocked by pterostilbene. In addition, pterostilbene can inhibit TPA-induced expression of vascular endothelial growth factor, epidermal growth factor and
epidermal growth factor receptor. Transient transfection experiments also showed that pterostilbene strongly inhibited TPA-stimulated nuclear factor kappa B (NF-kappaB) and activator protein-1 (AP-1)-dependent transcriptional activity in HepG(2) cells. Moreover, pterostilbene can suppress TPA-induced activation of extracellular signal-regulated kinase 1/2, p38 mitogen-activated protein kinase, c-Jun N-terminal kinases 1/2 and phosphatidylinositol 3-kinase/Akt and protein kinase C that are upstream of NF-kappaB and AP-1. Significant therapeutic effects were further demonstrated in vivo by treating nude mice with pterostilbene (50 and 250 mg/kg intraperitoneally) after inoculation with HepG(2) cells into the tail vein. Presented data reveal that pterostilbene is a novel, effective, anti-metastatic agent that functions by downregulating MMP-9 gene expression.

PMID: 19447859 DOI: 10.1093/carcin/bgp121


**Pterostilbene, a natural dimethylated analog of resveratrol, inhibits rat aortic vascular smooth muscle cell proliferation by blocking Akt-dependent pathway.**

Park ES1, Lim Y, Hong JT, Yoo HS, Lee CK, Pyo MY, Yun YP.

**Author information**

**Abstract**

Vascular smooth muscle cells (VSMCs) are the main cellular component in the arterial wall, and abnormal proliferation of VSMCs plays a central role in the pathogenesis of atherosclerosis and restenosis after angioplasty, and possibly in the development of hypertension. Pterostilbene, a natural dimethylated analog of resveratrol, is known to have diverse pharmacological activities including anti-cancer, anti-inflammatory and anti-oxidant activities. The present study was designed to investigate the effects of pterostilbene on platelet-derived growth factor (PDGF)-BB-induced VSMCs proliferation as well as the molecular mechanisms of the antiproliferative effects. The cell growth of VSMCs was determined by cell counting and [(3)H]thymidine incorporation assays. Pterostilbene significantly inhibited the DNA synthesis and proliferation of PDGF-BB-stimulated VSMCs in a concentration-dependent manner. The inhibition percentages of pterostilbene at 1, 3 and 5microM to VSMCs proliferation were 68.5, 80.7 and 94.6%, respectively. The DNA synthesis of pterostilbene at 1, 3 and 5microM in VSMCs was inhibited by 47.4, 76.7 and 100%, respectively. Pterostilbene inhibited the PDGF-BB-stimulated phosphorylation of Akt kinase. However, pterostilbene did not change the expression of extracellular signal-related kinase (ERK) 1/2, PLCgamma1, phosphatidylinositol (PI)3 kinase and PDGF-Rbeta phosphorylation. In addition, pterostilbene down-regulated the cell cycle-related proteins including the expression of cyclin-dependent kinase (CDK) 2, cyclin E, CDK4, cyclin D1, retinoblastoma (Rb) proteins and proliferative cell nuclear antigen (PCNA). These findings suggest that the inhibition of pterostilbene to the cell proliferation and DNA synthesis of
PDGF-BB-stimulated VSMCs may be mediated by the suppression of Akt kinase. Furthermore, pterostilbene may be a potential anti-proliferative agent for the treatment of atherosclerosis and angioplasty restenosis.

PMID: 20398797 DOI: 10.1016/j.vph.2010.04.001


**Understanding the mode of action of a pterostilbene derivative as anti-inflammatory agent.**

Nikhil K1, Sharan S1, Palla SR2, Sondhi SM2, Peddinti RK2, Roy P3.

**Author information**

**Abstract**

Inflammatory response plays an important role not only in the normal physiology, but also in the pathology of certain diseases such as cancers. In our previous study, we found a novel derivative of pterostilbene (PTER), to be an effective inducer of apoptosis in human breast and prostate cancer cells affecting various cellular targets. Herein, we further attempted to investigate its anti-inflammatory potential followed by its probable mode of action. The newly developed compound was tested for its anti-inflammatory actions in lipopolysaccharide (LPS) stimulated RAW264.7 macrophages and carrageenan induced rat paw edema models. Our data showed that the derivative inhibited the expression of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) as well as the downstream products like nitric oxide (NO) and PGE2, at much lower doses as compared to PTER. This effect was found to be associated with the inhibition of phosphorylation/degradation of IκB-α and nuclear translocation of the p-NFκB p65. Moreover, inhibition of mitogen-activated protein kinases (MAPKs) and activator protein-1 (AP-1) was also observed. In addition, the newly developed compound also reduced the paw edema, the tissue content of NO, PGE2 and expression of iNOS and COX-2 proteins within the tissues after λ-carrageenan stimulation. Taken together, our findings provide the possibility that the PTER derivative might have enhanced cancer chemopreventive potential based on its stronger anti-NFκB and anti-inflammatory activities as compared to its natural counterpart, i.e., PTER. Thus, this compound can be used towards the development of an effective anti-inflammatory agent.

**KEYWORDS:**
Anti-inflammatory; Carrageenan; Lipopolysaccharide; NFκB; Pterostilbene derivative; RAW 264.7 macrophage

PMID: 25981112 DOI: 10.1016/j.intimp.2015.05.003

Plant stilbenes induce endoplasmic reticulum stress and their anti-cancer activity can be enhanced by inhibitors of autophagy.

Papandreou I1, Verras M2, McNeil B3, Koong AC4, Denko NC5.

Author information

Abstract

BACKGROUND:
Environmental conditions or chemical agents can interfere with the function of the endoplasmic reticulum, and the resulting endoplasmic reticulum (ER) stress can be toxic to the cell if it is not relieved. The classical compensatory response to ER stress is the unfolded protein response (UPR) that reduces protein load in the ER. However, autophagy may also compensate by removing large insoluble protein aggregates. Agents that stress the ER can have anti-cancer activity, and novel applications of ER stress inducing agents are being investigated. Plant stilbenes are a class of stress responsive molecules that includes resveratrol, which are being investigated as potential therapeutics in humans for conditions such as aging or cancer.

RESULTS:
We performed a screen of 1726 small, drug like molecules to identify those that could activate an ER-stress responsive luciferase gene. After secondary screening, we determined that the plant stilbenes pterostilbene and piceatannol were the most potent inducers of ER stress from this group. ER stress can be particularly toxic to cells with high ER load, so we examined their effect on cells expressing the Wnt family of secreted glycoprotein growth factors. Molecular analysis determined that these ER stress-inducing stilbenes could block Wnt processing and also induce autophagy in acute lymphoblastic leukemia cells expressing Wnt16. Combining pterostilbene (to induce ER stress) with chloroquine (to inhibit autophagy) lead to significant cellular toxicity in cells from aggressive acute lymphoblastic leukemia.

CONCLUSIONS:
Plant stilbenes are potent inducers of ER stress. However, their toxicity is more pronounced in cancer cells expressing Wnt growth factors. The toxicity of stilbenes in these ALL cells can be potentiated by the addition of autophagy inhibitors, suggesting a possible therapeutic application.

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KEYWORDS:
High throughput screen; Stilbenes; Stress responses; Unfolded Protein Response; Wnt growth factors

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In vivo effect of pinosylvin and pterostilbene in the animal model of adjuvant arthritis.

Macickova T1, Drabikova K, Nosal R, Bauerova K, Mihalova D, Harmatha J, Pecivova J.

Author information

Abstract

OBJECTIVE:
The aim of this study was to evaluate the effects of pinosylvin (PIN) and pterostilbene (PTE), natural substances from the stilbenoid group, on the development of adjuvant arthritis in rats.

METHODS:
Adjuvant arthritis (AA) was induced by a single intradermal injection of Mycobacterium butyricum in incomplete Freund's adjuvant in male Lewis rats. Our experiments included healthy intact animals as reference controls, arthritic animals without any drug administration, and arthritic animals with administration of PIN and PTE in the oral daily dose of 30 mg/kg b.w. The treatment involved administration of the substances tested from day 0, i.e. the day of immunization, to the experimental day 28. The following parameters were monitored: change of the hind paw volume (HPV) on day 14, 21 and 28, luminol-enhanced chemiluminescence (CL) of the joint and myeloperoxidase (MPO) activity in hind paw joint homogenates (day 28).

RESULTS:
Arthritic animals treated with PIN showed a decrease in HPV, significantly on days 14 and 28. PIN decreased CL of the joint as well as MPO activity of the joint homogenate, in comparison with untreated animals. PTE had no effect on HPV and MPO activity in hind paw joint homogenates and exerted only a partial effect on luminol-enhanced CL.

CONCLUSIONS:
On the basis of our results we conclude that the effect of PTE on CL was only partial. PIN, on the other hand, had a beneficial anti-inflammatory and antioxidant effect on oxidative stress induced biochemical changes occurring in AA, as determined by all three functional parameters.

PMID: 21187826


HO-1 Signaling Activation by Pterostilbene Treatment Attenuates Mitochondrial Oxidative Damage Induced by Cerebral Ischemia Reperfusion Injury.

Yang Y1,2, Wang J1, Li Y3, Fan C4, Jiang S1, Zhao L1, Di S4, Xin Z1, Wang B1, Wu G1, Li X1, Li Z5, Gao X5, Dong Y6, Qu Y7.
Ischemia reperfusion (IR) injury (IRI) is harmful to the cerebral system and causes mitochondrial oxidative stress. The antioxidant response element (ARE)-mediated antioxidant pathway plays an important role in maintaining the redox status of the brain. Heme oxygenase-1 (HO-1), combined with potent AREs in the promoter of HO-1, is a highly effective therapeutic target for protection against cerebral IRI. Pterostilbene (PTE), a natural dimethylated analog of resveratrol from blueberries, is a strong natural antioxidant. PTE has been shown to be beneficial for some nervous system diseases and may regulate HO-1 signaling. This study was designed to investigate the protective effects of PTE on cerebral IRI and to elucidate potential mechanisms underlying those effects. Mouse brains and cultured HT22 neuron cells were subjected to IRI. Prior to this procedure, the brains or cells were exposed to PTE in the absence or presence of the HO-1 inhibitor ZnPP or HO-1 small interfering RNA (siRNA). PTE conferred a cerebral protective effect, as shown by increased neurological scores, viable neurons and decreased brain edema as well as a decreased ion content and apoptotic ratio in vivo. PTE also increased the cell viability and decreased the lactate dehydrogenase (LDH) leakage and apoptotic ratio in vitro. ZnPP and HO-1 siRNA both blocked PTE-mediated cerebral protection by inhibiting HO-1 signaling and further inhibited two HO-1 signaling-related antioxidant molecules: NAD(P)H: quinone oxidoreductase 1 (NQO1) and glutathione S-transferases (GSTs), which are induced by PTE. PTE also promoted a well-preserved mitochondrial membrane potential (MMP), mitochondria complex I activity, and mitochondria complex IV activity, increased the mitochondrial cytochrome c level, and decreased the cytosolic cytochrome c level. However, this PTE-elevated mitochondrial function was reversed by ZnPP or HO-1 siRNA treatment. In summary, our results demonstrate that PTE treatment attenuates cerebral IRI by reducing IR-induced mitochondrial oxidative damage through the activation of HO-1 signaling.

**KEYWORDS:**
Cerebral protection; HO-1 signaling; Ischemia reperfusion; Mitochondrial oxidative damage; Pterostilbene

PMID: 25983033 DOI: 10.1007/s12035-015-9194-2


**Effect of tannic acid, resveratrol and its derivatives, on oxidative damage and apoptosis in human neutrophils.**

Zielińska-Przyjemska M1, Ignatowicz E1, Krajka-Kuźniak V1, Baer-Dubowska W2.

**Author information**
Abstract

In this study we compared the antioxidant and DNA protective activity of tannic acid and stilbene derivatives, resveratrol, 3,5,4(')-trimethoxystilbene (TMS) and pterostilbene in human neutrophils stimulated to oxidative burst by 12-O-tetradecanoyl-phorbol-13-acetate (TPA) in relation to apoptosis induction. All polyphenols within the concentration range 1-100 μM reduced the intracellular ROS and H2O2 production in the TPA-stimulated cells. Tannic acid was the most effective polyphenol in protection against DNA damage induced by TPA. In the resting neutrophils resveratrol and to lesser extent other polyphenols increased DNA damage and increased the level of p53. Pretreatment of the TPA-stimulated cells with tannic acid or stilbenes led to the induction of apoptosis. The most significant effect was observed as a result of treatment with TMS and resveratrol. These compounds appeared the most effective inducers of p53 in the TPA-challenged neutrophils, what may suggest that pro-apoptotic activity of these stilbenes might be related to p53 activation. Overall, the results of our present study demonstrate that tannic acid and stilbenes modulate the ROS production, ultimately leading to cell apoptosis in human neutrophils stimulated to oxidative burst. In resting neutrophils they exhibit pro-oxidant activity, which is accompanied by p53 induction.

KEYWORDS:
Apoptosis; DNA damage; Neutrophils; Stilbene derivatives; Tannic acid

PMID: 26231140 DOI: 10.1016/j.fct.2015.07.013


Pterostilbene, a new agonist for the peroxisome proliferator-activated receptor alpha-isoform, lowers plasma lipoproteins and cholesterol in hypercholesterolemic hamsters.

Rimando AM1, Nagmani R, Feller DR, Yokoyama W.

Author information

Abstract

Resveratrol, a stilbenoid antioxidant found in grapes, wine, peanuts and other berries, has been reported to have hypolipidemic properties. We investigated whether resveratrol and its three analogues (pterostilbene, piceatannol, and resveratrol trimethyl ether) would activate the peroxisome proliferator-activated receptor alpha (PPARalpha) isoform. This nuclear receptor is proposed to mediate the activity of lipid-lowering drugs such as the fibrates. The four stilbenes were evaluated at 1, 10, 100, and 300 microM along with ciprofibrate (positive control), for the activation of endogenous PPARalpha in H4IIEC3 cells. Cells were transfected with a peroxisome proliferator response element-AB (rat fatty acyl CoA beta-oxidase response element)-luciferase gene reporter construct. Pterostilbene demonstrated the highest induction of PPARalpha showing 8- and 14-fold increases in luciferase activity at 100 and 300 microM, respectively, relative to the control. The maximal luciferase activity responses to pterostilbene
were higher than those obtained with the hypolipidemic drug, ciprofibrate (33910 and 19460 relative luciferase units, respectively), at 100 microM. Hypercholesterolemic hamsters fed with pterostilbene at 25 ppm of the diet showed 29% lower plasma low density lipoprotein (LDL) cholesterol, 7% higher plasma high density lipoprotein (HDL) cholesterol, and 14% lower plasma glucose as compared to the control group. The LDL/HDL ratio was also statistically significantly lower for pterostilbene, as compared to results for the control animals, at this diet concentration. Results from in vitro studies showed that pterostilbene acts as a PPARalpha agonist and may be a more effective PPARalpha agonist and hypolipidemic agent than resveratrol. In vivo studies demonstrate that pterostilbene possesses lipid and glucose lowering effects.

PMID: 15853379 DOI: 10.1021/jf0580364


Scavenging of hydroxyl radical by resveratrol and related natural stilbenes after hydrogen peroxide attack on DNA.

Rossi M1, Caruso F, Antonioletti R, Viglianti A, Traversi G, Leone S, Basso E, Cozzi R.

Author information

Abstract

Resveratrol (3,5,4'-trihydroxystilbene) is of interest due to its role in prevention and therapy of degenerative diseases as cancer and aging. However, depending on its concentration and cell type studied, resveratrol activity appears conflicting. It exerts antioxidant action, as a scavenger of free radicals and as promoter of antioxidant enzyme activity, but resveratrol acts also as a pro-oxidant. Here we present experimental and theoretical studies for resveratrol and two methoxy-derivatives found in plants, pterostilbene and 3,5,4'-trimethoxystilbene. We show that both methoxy-derivatives induce less DNA damage than resveratrol. The protective effects of the three molecules against oxidative DNA damage induced by hydrogen peroxide treatment were analyzed on mammalian cells in vitro. Our data show for the first time that methoxylated derivatives of resveratrol are very efficient in reducing DNA damage: using the same concentration of the three molecules we obtain a relative reduction of 85.5% (pterostilbene), 43.7% (trimethoxystilbene) and 21.1% (resveratrol). Analysis of the crystal structures of pterostilbene and 3,5,4'-trimethoxystilbene, compared to resveratrol, show fewer intermolecular interactions and a lack of planarity, due to packing forces, which is confirmed by density functional theory (DFT) calculations. We also describe the results of DFT calculations (including water solvent effects) in which the three stilbene species scavenge the hydroxyl radical (associated with the H2O2 insult).

KEYWORDS:
DNA protection; Hydrogen peroxide; Hydroxyl radical; Pterostilbene; Resveratrol
Stilbenoids from Rheum undulatum Protect Hepatocytes Against Oxidative Stress Through AMPK Activation.

Dong GZ1, Lee YI1, Jeong JH1, Zhao HY1, Jeon R1, Lee HJ2, Ryu JH1.

Abstract

Oxidative stress promotes several diseases, including liver disease. We have isolated several stilbenoids from Rheum undulatum to investigate their hepatoprotective activities and mechanism. Stilbenoids from R. undulatum protects hepatocytes against arachidonic acid + iron (AA + Fe) induced oxidative stress. Pterostilbene (compound 5) shows stronger activity than the others. Trimethoxystilbenoid (compound 6) shows best activity on protection of HepG2 cells from AA + Fe-induced oxidative stress, and trans-stilbenoid (compound 7) shows weak activity. These stilbenoids suppress ROS generation in AA + Fe-treated HepG2 cells and also suppress AA + Fe-induced MMP disruption. Their protective effects on AA + Fe-induced MMP disruption were abrogated by treatment of AMP-activated protein kinase (AMPK) inhibitor, compound C or transfection of dominant negative form of AMPK. Taken together, stilbenoids from R. undulatum protect hepatocytes against AA + Fe-induced oxidative stress through AMPK activation. And the methoxy groups in the aryl groups are important for their cytoprotective activity.

KEYWORDS:
AMPK; Rheum undulatum; antioxidant; hepatocyte protection; stilbenoid

Biological activity of peanut (Arachis hypogaea) phytoalexins and selected natural and synthetic Stilbenoids.

Sobolev VS1, Khan SI, Tabanca N, Wedge DE, Manly SP, Cutler SJ, Coy MR, Becnel JJ, Neff SA, Gloer JB.

Abstract
The peanut plant (Arachis hypogaea L.), when infected by a microbial pathogen, is capable of producing stilbene-derived compounds that are considered antifungal phytoalexins. In addition, the potential health benefits of other stilbenoids from peanuts, including resveratrol and pterostilbene, have been acknowledged by several investigators. Despite considerable progress in peanut research, relatively little is known about the biological activity of the stilbenoid phytoalexins. This study investigated the activities of some of these compounds in a broad spectrum of biological assays. Since peanut stilbenoids appear to play roles in plant defense mechanisms, they were evaluated for their effects on economically important plant pathogenic fungi of the genera Colletotrichum, Botrytis, Fusarium, and Phomopsis. We further investigated these peanut phytoalexins, together with some related natural and synthetic stilbenoids (a total of 24 compounds) in a panel of bioassays to determine their anti-inflammatory, cytotoxic, and antioxidant activities in mammalian cells. Several of these compounds were also evaluated as mammalian opioid receptor competitive antagonists. Assays for adult mosquito and larvae toxicity were also performed. The results of these studies reveal that peanut stilbenoids, as well as related natural and synthetic stilbene derivatives, display a diverse range of biological activities.

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**Pterostilbene induces autophagy and apoptosis in sensitive and chemoresistant human bladder cancer cells.**

Chen RJ1, Ho CT, Wang YJ.

**Author information**

Abstract

**SCOPE:**
Bladder cancer is one of the most common malignancies in the world. The majority of bladder cancer deaths are due to unresectable lesions that are resistant to chemotherapy. Pterostilbene (PT), a naturally occurring phytoalexin, possesses a variety of pharmacologic activities, including antioxidant, cancer prevention activity and cytotoxicity to many cancers. We found that PT effectively inhibits the growth of sensitive and chemoresistant human bladder cancer cells by inducing cell cycle arrest, autophagy and apoptosis. Down-regulations of Cyclin A, B and D1 and pRB are the results of PT-induced cell cycle arrest.

**METHODS AND RESULTS:**
Autophagy occurred at an early stage and was observed through the formation of acidic vesicular organelles (the marker for autophagy) and microtubule-associated protein 1 light chain 3-II production. Apoptosis occurred at a later stage and was detected by Annexin V and 4',6-diamidino-2-phenylindole staining. PT-induced autophagy was triggered by the inhibition of active human protein kinase/the mammalian TOR/p70S6K pathway and activation of extracellular signal-regulated kinase pathway. Inhibition of autophagy by pretreatment with 3-
methyladenine, bafilomycin A1, Beclin 1 or extracellular signal-regulated kinase short hairpin RNA enhanced PT-triggered apoptosis.

CONCLUSION:
This is the first study to demonstrate that PT causes autophagy in cancer cells and suggests that PT could serve as a new and promising agent for the treatment of sensitive and chemoresistant bladder cancer cells.

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Blueberry Component Pterostilbene Protects Corneal Epithelial Cells from Inflammation via Anti-oxidative Pathway.

Li J1,2, Ruzhi Deng1,2, Hua X2,3, Zhang L2, Lu F1, Coursey TG2, Pflugfelder SC2, Li DQ2.

Author information

Abstract

Blueberries have been recognized to possess protective properties from inflammation and various diseases, but not for eye and ocular disorders. This study explores potential benefits of pterostilbene (PS), a natural component of blueberries, in preventing ocular surface inflammation using an in vitro culture model of human corneal epithelial cells (HCECs) exposed to hyperosmotic medium at 450 mOsM. Gene expression was detected by RT-qPCR, and protein production or activity was determined by ELISA, zymography, Western blotting and immunofluorescent staining. Reactive oxygen species (ROS) production was measured using DCFDA kit. The addition of PS significantly reduced the expression of pro-inflammatory mediators, TNF-α, IL-1β, IL-6, MMP-2 and MMP-9 in HCECs exposed to hyperosmotic medium. Pre-treatment with PS (5 to 20 μM) suppressed ROS overproduction in a dose-dependent manner. Additionally, PS significantly decreased the levels of oxidative damage biomarkers, malondialdehyde (MDA), 4-hydroxynonenal (4-HNE), aconitase-2 and 8-hydroxydeoxyguanosine (8-OHdG). Importantly, PS was found to rebalance homeostasis between oxygenases and anti-oxidative enzymes by decreasing cyclooxygenase 2 (COX2) expression and restoring the activity of antioxidant enzymes, superoxide dismutase 1 (SOD1) and peroxiredoxin-4 (PRDX4) during hyperosmotic stress. Our findings demonstrate that PS protects human cornea from hyperosmolarity-induced inflammation and oxidative stress, suggesting protective effects of PS on dry eye.

PMID: 26762881 PMCID: PMC4725955 DOI: 10.1038/srep19408
Antioxidant activity of hydroxystilbene derivatives in homogeneous solution.

Amorati R1, Lucarini M, Mugnaini V, Pedulli GF, Roberti M, Pizzirani D.

Abstract

The antioxidant activity of the cis and trans isomers of several analogues of resveratrol and pterostilbene has been investigated, especially with regard to the effect of the stereochemistry about the olefinic double bond. The antioxidant power of these compounds was estimated by measuring the rate constants for their reactions with peroxyl radicals and, with two of them, the bond dissociation enthalpy (BDE) of the phenolic O-H bond which is cleaved in the inhibition reaction. The present data show that in homogeneous solution the various hydroxystilbenes investigated behave as mild antioxidants with the notable exceptions of the trans isomer of 4 and 6, whose activities are only slightly lower than that of alpha-tocopherol (vitamin E). The rate constants of the inhibition reaction show that the antioxidant activity of the cis-hydroxystilbene is in all the examined cases worse, by a factor ranging between 2 and 6, than that of the corresponding trans isomers. This lower reactivity depends on enthalpy factors as it can be inferred by the experimental values of the O-H bond dissociation enthalpy in the two geometric isomers of 3',5'-di-tert-butyl-4'-hydroxy-3,5-dimethoxystilbene showing that the strength of the O-H bond in the cis isomer is larger by 1.8 kcal/mol. DFT calculations provide a rationalization of this result, indicating that, although the cis geometry implies a destabilization with respect to the trans species of both phenoxy radical and parent hydroxystilbene, the destabilization of the radical is larger because the folding of the structure strongly reduces the delocalization of the unpaired electron on the styryl group. A comparison of these results with previously reported data on the proapoptotic activity of these stilbenoids suggests that these two properties are not correlated.

PMID: 15471458 DOI: 10.1021/jo0497860

Pterostilbene protects vascular endothelial cells against oxidized low-density lipoprotein-induced apoptosis in vitro and in vivo.

Zhang L1, Zhou G, Song W, Tan X, Guo Y, Zhou B, Jing H, Zhao S, Chen L.
Abstract

Vascular endothelial cell (VEC) apoptosis is the main event occurring during the development of atherosclerosis. Pterostilbene (PT), a natural dimethylated analog of resveratrol, has been the subject of intense research in cancer and inflammation. However, the protective effects of PT against oxidized low-density lipoprotein (oxLDL)-induced apoptosis in VECs have not been clarified. We investigated the anti-apoptotic effects of PT in vitro and in vivo in mice. PT at 0.1-5 μM possessed antioxidant properties comparable to that of trolox in a cell-free system. Exposure of human umbilical vein VECs (HUVECs) to oxLDL (200 μg/ml) induced cell shrinkage, chromatin condensation, nuclear fragmentation, and cell apoptosis, but PT protected against such injuries. In addition, PT injection strongly decreased the number of TUNEL-positive cells in the endothelium of atherosclerotic plaque from apoE(-/-) mice. OxLDL increased reactive oxygen species (ROS) levels, NF-κB activation, p53 accumulation, apoptotic protein levels and caspases-9 and -3 activities and decreased mitochondrial membrane potential (MMP) and cytochrome c release in HUVECs. These alterations were attenuated by pretreatment with PT. PT inhibited the expression of lectin-like oxLDL receptor-1 (LOX-1) expression in vitro and in vivo. Cotreatment with PT and siRNA of LOX-1 synergistically reduced oxLDL-induced apoptosis in HUVECs. Overexpression of LOX-1 attenuated the protection by PT and suppressed the effects of PT on oxLDL-induced oxidative stress. PT may protect HUVECs against oxLDL-induced apoptosis by downregulating LOX-1-mediated activation through a pathway involving oxidative stress, p53, mitochondria, cytochrome c and caspase protease. PT might be a potential natural anti-apoptotic agent for the treatment of atherosclerosis.

PMID: 21928089 DOI: 10.1007/s10495-011-0653-6


Perecko T1, Jancinova V, Drabikova K, Nosal R, Harmatha J.

Author information

Abstract

OBJECTIVES:
Oxidative stress is related to a number of autoimmune diseases, e.g. rheumatoid arthritis, cancer, etc. The main source of pathologically working reactive oxygen species (ROS) are activated polymorphonuclear leukocytes (PMNL).

OBJECTIVE:
There are some papers comparing structure - pharmacological efficiency relationship of vegetal substances from the stilbenoid group. We compared the effect of trans-resveratrol, which is well-known by its antioxidative activity, with the effect of pinosylvin and pterostilbene.

METHODS:
Luminol-enhanced chemiluminescence (CL) was used to study the antioxidative action. The effect was observed in whole blood and in isolated PMNL. The concentrations of substances tested were 0.01-100 microM. Due to the different abilities of luminol and isoluminol to pass through the cell membrane, we studied the effect of the substances tested on intracellular and extracellular ROS. To stimulate the production of ROS we used phorbol-myristate-acetate (PMA), which activates PMNL via protein kinase C.

RESULTS:
Resveratrol, pinosylvin and pterostilbene inhibited significantly the CL of whole blood and extra- and intracellular CL of isolated PMNL in a dosedependent manner. Depending on different functional groups of the stilbene molecule, resveratrol inhibited CL of whole blood and isolated PMNL, whereas pinosylvin influenced mainly intracellular CL and pterostilbene extracellular CL.

CONCLUSION:
The presence of different functional groups in the molecules of stilbenoids influence their antioxidative effect. Modification of these functional groups may result in derivatives with required antioxidative properties, targeting mainly extracellular ROS which are responsible for tissue damage during chronic inflammation.

PMID: 18987580


Neuroprotective actions of pterostilbene on hypoxic-ischemic brain damage in neonatal rats through upregulation of heme oxygenase-1.

Li D1, Song T1, Yang L2, Wang X1, Yang C1, Jiang Y1.

Author information

Abstract

Neonatal hypoxic-ischemic (HI) brain damage causes acute mortality and morbidity in newborns and long-term neurological disorders in the survivors. Pterostilbene (PTE) is a natural compound possessing various biological and pharmacological activities. In the present study, we aimed to investigate the effect of PTE on neonatal HI brain damage in P7 rat model and to explore the possible mechanisms. Neonatal HI brain damage was induced in rat pups (P7). Prior to the induction of HI injury, PTE was injected with or without zinc protoporphyrin IX (ZnPP), an inhibitor of heme oxygenase-1 (HO-1). ZnPP was used to test whether abnormal changes of HO-1 expression were involved in the effect of PTE. The results showed that PTE exhibited excellent neuroprotective effects against neonatal HI brain injury, as evidenced by the decrease of brain infarct volume, brain edema, neurological score, and improvement in motor coordination motor
deficit and working memory deficit. PTE pretreatment decreased the expression of several proinflammatory cytokines, including TNFα, IL-1β, IL-6, and key transcription factor p65 NF-κB, and reduced the number of TUNEL-stained neurons, indicating the inhibition of inflammation and programmed cell death. Moreover, PTE pretreatment decreased thiobarbituric acid reactive substances content, increased superoxide dismutase activity and decreased reactive oxygen species level, indicating that PTE played an important antioxidant role. Furthermore, ZnPP was able to inhibit PTE-induced suppression of oxidative stress, programmed cell death, inflammation and brain damage. In conclusion, PTE pretreatment prevented HI-induced brain injury in newborns through HO-1-mediated reduction of oxidative stress, programmed cell death, and inflammation, and final improvement of histological and functional injury. Overall, the data that obtained in rat model provide novel insights into the pathogenesis of neonatal HI brain injury and may be translational to human clinical intervention for HI-associated brain injury in newborns.

KEYWORDS: Brain damage; HI; Heme oxygenase-1; Neonatal rat; Pterostilbene

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Ebselen reduces the toxicity of mechlorethamine in A-431 cells via inhibition of apoptosis.

Lulla A1, Pino MA, Pietka-Ottlik M, Młochowski J, Sparavalo O, Billack B.

Author information

Abstract

A series of test compounds were evaluated for an ability to reduce the toxicity of the nitrogen mustard mechlorethamine (HN2) in vitro. The test compounds included resveratrol, pterostilbene, vitamin C, ebselen, ebselen diselenide, and ebselen-sulfur. Among them, ebselen demonstrated the highest degree of protection against HN2 toxicity. To this end, pretreatment of the cells with ebselen offered protection against the toxicant whereas no protection was observed when cells were first incubated with HN2 and then treated with ebselen. Significant increases in caspase 3 and caspase 9 activities were observed in response to HN2, and ebselen was found to reduce these effects. Taken together, the data presented here indicate that ebselen is an effective countermeasure to nitrogen mustard in vitro, which is worthy of future investigation in vivo.

PMID: 23649643 DOI: 10.1002/jbt.21490

The Use of Stilbene Scaffold in Medicinal Chemistry and Multi-Target Drug Design.


Author information

Abstract

The stilbene scaffold is a basic element for a number of biologically active natural and synthetic compounds, and it is considered as a privileged structure. Stilbenes exemplified by resveratrol, combretastatin A-4 and pterostilbene are of significant interest for drug research and development because of their potential in therapeutic and preventive application. Resveratrol, present in grapes and other food products, plays a role in the prevention of several human pathological processes and has been suggested as an anticancer agent. Moreover, recent evidence has revealed its potential effect on the aging process, diabetes and neurological dysfunction. Combretastatin A-4, from the bark of South African bush willow Combretum caffrum, also shows significant antitumor activity. Pterostilbene is closely related to resveratrol, sharing the same unique therapeutic potential as anti-inflammatory, antineoplastic and antioxidant agent. Therefore, research and development of stilbene-based medicinal chemistry have become rapidly evolving and increasingly active topics covering almost the whole range of therapeutic fields. In the present review, we provide an overview of the role of stilbenes in medicinal chemistry. In this context, we highlight the chemical methodologies adopted for the synthesis of stilbene derivatives, and outline the successful design of novel stilbene based hybrids in the field of cancer, Alzheimer's and other relevant diseases. This information may be useful in further design of stilbene-based molecules as new leads for the development of novel agents with clinical potential or as effective chemical probes to dissect biological processes.

PMID: 27183980


Anti-hyperlipidemic and anti-oxidative role of pterostilbene via Nrf2 signaling in experimental diabetes.

Bhakkiyalakshmi E1, Sireesh D1, Sakthivadivel M2, Sivasubramanian S2, Gunasekaran P2, Ramkumar KM3.

Author information

Abstract

Nuclear factor erythroid 2-related factor (Nrf2), a key transcription factor triggers the expression of antioxidant and detoxification genes thereby providing cellular protective functions against oxidative stress-mediated disorders. Recent research has identified that pharmacological
activation of Nrf2 also regulates the largest cluster of genes associated with lipid metabolism. With this background, this paper highlights the anti-hyperlipidemic and anti-peroxidative role of pterostilbene (PTS), an Nrf2 activator, in streptozotocin (STZ)-induced diabetic model. PTS administration to diabetic mice for 5 weeks significantly regulated blood glucose levels through the elevation of insulin secretion. The circulatory and liver lipid profiles of total cholesterol (TC), triglycerides (TG) and non-esterified fatty acids (NEFA) were maintained to normal levels upon PTS treatment. Moreover, PTS administration also normalized the circulatory levels of very low-, low- and high density lipoprotein cholesterol (VLDL-, LDL-, HDL-C) and also reduced lipid peroxidation in STZ-induced diabetic mice. In addition, Nrf2 and its downstream targets, superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx) enzyme activities and glutathione (GSH) levels were significantly elevated in liver tissues of diabetic mice upon PTS administration. Further, H&E staining of diabetic mouse liver showed collapse in hepatic microvesicles due to altered lipid metabolism. Both structural and functional alterations were attenuated by PTS indicating its role in diabetic dyslipidemia through Nrf2-mediated mechanism that could be considered as a promising therapeutic agent.

KEYWORDS:
Diabetes; Dyslipidemia; Lipids; Nrf2; Pterostilbene; Streptozotocin

PMID: 26921755 DOI: 10.1016/j.ejphar.2016.02.054


Suppression of Nitric Oxide Production and Cardiovascular Risk Factors in Healthy Seniors and Hypercholesterolemic Subjects by a Combination of Polyphenols and Vitamins.

Qureshi AA1, Khan DA, Mahjabeen W, Papasian CJ, Qureshi N.

Author information

Abstract

BACKGROUND:
Dysregulated immune function associated with ageing has been implicated in a variety of human diseases. We have demonstrated the anti-inflammatory properties of resveratrol, pterostilbene, morin hydrate, quercetin, δ-tocotrienol, riboflavin in a variety of experimental animal models, and determined that these compounds act by inhibiting proteasome activity.

AIMS:
To determine whether serum nitric oxide (NO) levels increase with age in humans, and whether the combined cholesterol-lowering and inflammation-reducing properties of resveratrol, pterostilbene, Morin hydrate, quercetin, δ-tocotrienol, riboflavin, and nicotinic acid would reduce cardiovascular risk factors in humans when used as nutritional supplements with, or without, other dietary changes.
METHODS:
Elderly human subjects were stratified into two groups based on total serum cholesterol levels. Initial total serum cholesterol levels were normal and elevated in Group 1 and 2 subjects, respectively. Baseline serum NO, C-reactive protein (CRP), γ-glutamyltransferase (γ-GT) activity, uric acid, total antioxidant status (TAS), total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglycerides levels were established over a four week period. Group 1 subjects subsequently received nutritional supplementation with one of two different combinations (NS-7 = 25 mg of each, resveratrol, pterostilbene, quercetin, δ-tocotrienol, nicotinic acid, morin hydrate or NS-6 = morin hydrate replaced with quercetin, 50 mg/capsule). Group 2 subjects also received these nutritional supplements (two capsules/d), but an AHA Step-1 diet was also implemented. After these interventions were administered for four weeks, the above parameters were re-measured and changes from baseline levels determined. Nitric acid (NO) levels in children, young adults, and seniors were also compared.

RESULTS:
The key results of the current study were: 1) that serum NO levels were significantly increased in seniors compared to both children (~80%) and young adults (~65%); 2) that the intake of two capsules/d of NS-7 or NS-6 for four weeks significantly (P < 0.05) decreased serum NO (39%, 24%), CRP (19%, 21%), uric acid (6%, 12%) levels, and γ-GT activity (8%, 6%), respectively in free-living healthy seniors; 3) that serum NO (36%, 29%), CRP (29%, 20%), uric acid (6%, 9%) γ-GT activity (9%, 18%), total cholesterol (8%, 11%), LDL-cholesterol (10%, 13%), and triglycerides (16%, 23%) levels were significantly (P < 0.02) decreased in hypercholesterolemic subjects restricted to AHA Step-1 diet plus intake of SN-7 or SN-6 (two capsules/d), respectively; 4) that TAS was increased (3%, 9%; P < 0.05) in free-living healthy seniors receiving NS-7 or NS-6 alone, and in hypercholesterolemic subjects plus AHA Step-1 diet (20%, 12%; P < 0.02) with either of the combinations tested.

CONCLUSIONS:
Serum NO levels are elevated in elderly humans compared to children or young adults. Diet supplementation with combinations of resveratrol, pterostilbene, morin hydrate, quercetin, δ-tocotrienol, riboflavin, and nicotinic acid reduce cardiovascular risk factors in humans when used as nutritional supplements with, or without, other dietary changes.

PMID: 23125945 PMCID: PMC3486425 DOI: 10.4172/2155-9880.S5-008


Resveratrol, pterostilbene, and piceatannol in vaccinium berries.

Rimando AM1, Kalt W, Magee JB, Dewey J, Ballington JR.

Author information
Abstract

A study was conducted to determine the presence of resveratrol, pterostilbene, and piceatannol in Vaccinium berries. Samples representing selections and cultivars of 10 species from Mississippi, North Carolina, Oregon, and Canada were analyzed by gas chromatography/mass spectrometry. Resveratrol was found in Vaccinium angustifolium (lowbush blueberry), Vaccinium arboretum (sparkleberry), Vaccinium ashei (rabbiteye blueberry), Vaccinium corymbosum (highbush blueberry), Vaccinium elliottii (Elliott's blueberry), Vaccinium macrocarpon (cranberry), Vaccinium myrtillus (bilberry), Vaccinium stamineum (deerberry), Vaccinium vitis-ideae var. vitis-ideae (lingonberry), and Vaccinium vitis-ideae var. minor (partridgeberry) at levels between 7 and 5884 ng/g dry sample. Lingonberry was found to have the highest content, 5884 ng/g dry sample, comparable to that found in grapes, 6471 ng/g dry sample. Pterostilbene was found in two cultivars of V. ashei and in V. stamineum at levels of 99-520 ng/g dry sample. Piceatannol was found in V. corymbosum and V. stamineum at levels of 138-422 ng/g dry sample. These naturally occurring stilbenes, known to be strong antioxidants and to have cancer chemopreventive activities, will add to the purported health benefits derived from the consumption of these small fruits.

PMID: 15264904 DOI: 10.1021/jf040095e


Neuroprotective effects of pterostilbene against oxidative stress injury: Involvement of nuclear factor erythroid 2-related factor 2 pathway.

Wang B1, Liu H1, Yue L1, Li X1, Zhao L1, Yang X1, Wang X1, Yang Y2, Qu Y3.

Author information

Abstract

Nuclear factor erythroid 2 (Nf-E2)-related factor 2 (Nrf2) regulates multiple anti-oxidative enzymes and has neuroprotective effects. Pterostilbene (PTE) is a natural anti-oxidant found in blueberries. Its non-metabolized form exhibits high distribution in the brain after dietary administration. In this study, we aimed to explore the potential of PTE in protecting murine hippocampal neuronal HT22 cells against glutamate-induced oxidative stress injury and possible underlying mechanisms. PTE was nontoxic and induced the nuclear translocation of Nrf2 when HT22 cell cultures were incubated with different concentrations of PTE. Further, PTE displayed a dose-dependent neuroprotective effect, as indicated by increased cell viability and a reduction in lactate dehydrogenase (LDH) release after glutamate treatment. Nrf2 siRNA treatment inhibited PTE-induced neuroprotective effects. Moreover, the levels of nuclear Nrf2 and downstream heme oxygenase-1 (HO-1) and

NAD(P)H:
quinone oxidoreductase 1 (NQO1) were elevated after PTE treatment. The PTE-induced elevation of nuclear Nrf2, as well as the increases in HO-1 and NQO1 levels, was abolished by Nrf2 siRNA. PTE treatment reduced the production of reactive oxygen species (ROS) and significantly enhanced the activities of the cellular anti-oxidants glutathione (GSH) and superoxide dismutase (SOD), indicating an attenuation of glutamate-induced oxidative stress. These changes in ROS and GSH and SOD activity were reversed by Nrf2 siRNA. Our results indicate that PTE treatment attenuates glutamate-induced oxidative stress injury in neuronal cells via the Nrf2 signaling pathway.

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KEYWORDS:
Glutamate; Neuroprotection; Nuclear factor erythroid 2 (NF-E2)-related factor 2 signaling; Oxidative stress; Pterostilbene

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Leishmanicidal Effect of Synthetic trans-Resveratrol Analogs.

Passos CL1, Ferreira C1, Soares DC1, Saraiva EM1.

Author information

Abstract

BACKGROUND:
Stilbene-based compounds show antitumoral, antioxidant, antihistaminic, anti-inflammatory and antimicrobial activities. Here, we evaluated the effect of the trans-resveratrol analogs, pterostilbene, piceatannol, polydatin and oxyresveratrol, against Leishmania amazonensis.

METHODOLOGY/PRINCIPAL FINDINGS:
Our results demonstrated a low murine macrophage cytotoxicity of all four analogs. Moreover, pterostilbene, piceatannol, polydatin and oxyresveratrol showed an anti-L. amazonensis activity with IC50 values of 18 μM, 65 μM, 95 μM and 65 μM for promastigotes, respectively. For intracellular amastigotes, the IC50 values of the analogs were 33.2 μM, 45 μM, 29 μM and 30.5 μM, respectively. Among the analogs assayed only piceatannol altered the cell cycle of the parasite, increasing 5-fold the cells in the Sub-G0 phase and decreasing 1.7-fold the cells in the G0-G1 phase. Piceatannol also changed the parasite mitochondrial membrane potential (ΔΨm) and increased the number of annexin-V positive promastigotes, which suggests incidental death.

CONCLUSION/SIGNIFICANCE:
Among the analogs tested, piceatannol, which is a metabolite of resveratrol, was the more promising candidate for future studies regarding treatment of leishmaniasis.
Effects of resveratrol and its derivatives on lipopolysaccharide-induced microglial activation and their structure-activity relationships.


Author information

Abstract

The inhibitory effects of 21 resveratrol derivatives on lipopolysaccharide (LPS)-induced nitric oxide (NO) production in microglia and their structure-activity relationships were studied. It was found, for the first time, that certain resveratrol derivatives that have 3,5-dimethoxyl groups in the A-ring, such as (E)-4-(3,5-dimethoxystyryl)phenol (pterostilbene, compound 2), or have substituted the B-ring of resveratrol with quinolyl, such as (E)-5-[2-(quinolin-4-yl)vinyl]benzene-1,3-diol (compound 18) and (E)-4-(3,5-dimethoxystyryl)quinoline (compound 19), strongly inhibited NO production. Compounds 2, 18, and 19 reduced LPS-induced protein and mRNA expression of inducible NO synthase (iNOS), but did not display direct NO-scavenging activity up to 30 microM in sodium nitroprusside (SNP) solution. Moreover, compounds 2, 18, and 19 could also significantly inhibit the production of TNF-alpha by LPS-activated microglia. Further studies revealed that compounds 2, 18, and 19 inhibited LPS-induced NO and TNF-alpha production in microglia by blocking IkappaBalpha phosphorylation and degradation. The potent inhibitory effects of compounds 2, 18, and 19 on microglial activation suggest their potential for treatment of neurodegenerative diseases accompanied by microglial activation.

Resveratrol and related stilbenes: their anti-aging and anti-angiogenic properties.

Kasiotis KM1, Pratsinis H, Kletsas D, Haroutounian SA.

Author information

Abstract
Dietary stilbenes comprise a class of natural compounds that display significant biological activities of medicinal interest. Among them, their antioxidant, anti-aging and anti-angiogenic properties are well established and subjects of numerous research endeavors. This mini-review aspires to account and present the literature reports published on research concerning various natural and synthetic stilbenes, such as trans-resveratrol. Special focus was given to most recent research findings, while the mechanisms underlying their anti-aging and anti-angiogenic effects as well as the respective signaling pathways involved were also presented and discussed.

KEYWORDS:
Aging; Angiogenesis; Lifespan; Polyphenol; Resveratrol; Stilbenes

PMID: 23567244 DOI: 10.1016/j.fct.2013.03.038


**Nutritional Supplement-5 with a Combination of Proteasome Inhibitors (Resveratrol, Quercetin, δ-Tocotrienol) Modulate Age-Associated Biomarkers and Cardiovascular Lipid Parameters in Human Subjects.**

Qureshi AA1, Khan DA, Mahjabeen W, Papasian CJ, Qureshi N.

**Author information**

**Abstract**

**BACKGROUND:**
Age-associated altered redox imbalances and dysregulated immune function, contribute to the development of a variety of age associated diseases. Inflammatory markers and lipid profiles are useful prognostic indicators of a variety of age-associated and cardiovascular diseases. We have previously studied the impact of several proteasome inhibitors on several markers of inflammation and lipid profiles in vitro, in vivo, in cell lines, animal models, and in human subjects. The current study represents an extension of this work. Our main hypothesis is that a combination of various naturally-occurring proteasome inhibitors, which inhibits nitric oxide (NO), and C-reactive protein (CRP) mediated inflammation, will have better efficacy in the prevention and treatment of age-associated disorders including cardiovascular disease.

**METHODS:**
Two double blind, randomized, placebo-controlled cross-over trials were conducted to determine the impact of a mixture of NS-5 (resveratrol, pterostilbene, quercetin, θ-tocotrienol, nicotinic acid) on serum NO, CRP, γ-glutamyl-transferase (γ-GT) activity, total antioxidant status (TAS), total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides levels. Healthy seniors (Group-1; n = 32) free-living (A, B; 16/group), and hypercholesterolemic (Group-2; n = 64) subjects on AHA-Step-1-diet were divided into two groups (C, D; 32/group). Baseline levels were established for parameters as mentioned above. Groups A, C were administered 4-
capsules/d of NS-5 and groups B, D, placebo (starch) for 6-weeks. Groups were crossed-over, followed by a 2-week wash-out period. Groups A, C were given 4-capsules/d of placebo and groups B, D, 4-capsules/d of NS-5 for 6-weeks. Groups C, D were continued on AHA-Step-1-diet.

RESULTS:
All the subjects completed each phase in both studies without any complaints. There were significant ($P < 0.01 - 0.05$) decreases in the serum levels of NO (30%, 26%), CRP (29%, 21%), $\gamma$-GT activity (14%, 17%), and blood pressure (systolic/diastolic, 3/6%, 3/3%) of Groups A and B, respectively, of free-living healthy seniors without affecting the total, HDL-, LDL-cholesterol or triglycerides compared to their respective baseline values. However, serum levels of NO (36%, 43%), CRP (31%, 48%), $\gamma$-GT (17%, 20%), total cholesterol (19%, 15%), LDL-cholesterol (28%, 20%), triglycerides (11%, 18%) of Groups C and D were significantly ($P < 0.01$-0.05) decreased with NS-5 treatment of hypercholesterolemic subjects compared to baseline values, without affecting the serum HDL-cholesterol levels. The serum levels of total antioxidant status (TAS) were increased (10%, 14%; $P < 0.05$) in Groups A and B, increased (19%, 24%; $P < 0.02$), and blood pressure (systolic/diastolic, 5/6%, 3/5%) in Groups C and D with NS-5 treatment, compared to respective baseline values.

CONCLUSIONS:
The consumption of NS-5 mixture decreased significantly serum NO, CRP and $\gamma$-GT levels, improved TAS and lipid profiles at risk cardiovascular and hold promise for delaying onset of age-associated diseases.

KEYWORDS:
Anti-inflammatory and anti-ageing agents; C-reactive protein (CRP); Nitric oxide (NO); Quercetin; Resveratrol; Total antioxidant status (TAS); $\gamma$-glutamyl-transferase ($\gamma$-GT); $\delta$-tocotrienol

PMID: 24319627 PMCID: PMC3851026 DOI: 10.4172/2155-9880.1000238

Dietary Phenolic Compounds Interfere with the Fate of Hydrogen Peroxide in Human Adipose Tissue but Do Not Directly Inhibit Primary Amine Oxidase Activity.

Carpéné C1, Hasnaoui M1, Balogh B2, Matyus P2, Fernández-Quintela A3, Rodríguez V3, Mercader J4, Portillo MP3.

Author information

Abstract
Resveratrol has been reported to inhibit monoamine oxidases (MAO). Many substrates or inhibitors of neuronal MAO interact also with other amine oxidases (AO) in peripheral organs, such as semicarbazide-sensitive AO (SSAO), known as primary amine oxidase, absent in neurones, but abundant in adipocytes. We asked whether phenolic compounds (resveratrol, pterostilbene, quercetin, and caffeic acid) behave as MAO and SSAO inhibitors. AO activity was determined in human adipose tissue. Computational docking and glucose uptake assays were performed in 3D models of human AO proteins and in adipocytes, respectively. Phenolic compounds fully inhibited the fluorescent detection of H2O2 generated during MAO and SSAO activation by tyramine and benzylamine. They also quenched H2O2-induced fluorescence in absence of biological material and were unable to abolish the oxidation of radiolabelled tyramine and benzylamine. Thus, phenolic compounds hampered H2O2 detection but did not block AO activity. Only resveratrol and quercetin partially impaired MAO-dependent [(14)C]-tyramine oxidation and behaved as MAO inhibitors. Phenolic compounds counteracted the H2O2-dependent benzylamine-stimulated glucose transport. This indicates that various phenolic compounds block downstream effects of H2O2 produced by biogenic or exogenous amine oxidation without directly inhibiting AO. Phenolic compounds remain of interest regarding their capacity to limit oxidative stress rather than inhibiting AO.


**Resveratrol and its methoxy-derivatives as modulators of DNA damage induced by ionising radiation.**

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**Author information**

**Abstract**

Various naturally occurring stilbene-like compounds that are related to resveratrol (RSV) possess some of the beneficial effects of the parent molecule and provide even further benefits. Therefore, a series of methoxylated analogues of RSV were prepared with the aim of increasing antitumour and proapoptotic activity. In a previous article, we studied two methoxy-derivatives, pterostilbene (PTERO) and trimethoxystilbene (TRIMETHOXY), in which the first was formed by the substitution of two hydroxyl groups with two methoxy groups (trans-3,5-dimethoxy-4'-hydroxystilbene) and the second was formed by the replacement of all three OH groups with methoxy groups (trans-3,5,4'-trimethoxystilbene). Both methoxy-derivatives showed stronger antioxidant activity when compared with RSV. In the present article, we focused on the analysis of the ability of RSV and its two methoxylated derivatives to protect proliferating non-tumoural cells from the damage induced by ionising radiation (IR). First we showed that the methoxy derivatives, contrary to their parental compound, are unable to affect topoisomerase enzyme and consequently are not clastogenic per se. Second we showed that both PTERO and TRIMETHOXY more efficiently reduce the chromosome damage induced by IR. Furthermore, TRIMETHOXY, but not PTERO, causes a delay in cell proliferation, particularly in mitosis.
progression increasing the number of cells in metaphase at the expense of prophases and ana/telophases.

PMID: 26819346 DOI: 10.1093/mutage/gew002


Utilization of adjuvant arthritis model for evaluation of new approaches in rheumatoid arthritis therapy focused on regulation of immune processes and oxidative stress.

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Author information

Abstract

As a number of disease-modifying anti-rheumatic drugs often have side effects at high doses and/or during long-term administration, increased efficacy without increased toxicity is expected for combination therapy of rheumatoid arthritis (RA). The safety of long-term therapy of RA is very important as patients with RA are usually treated for two or more decades. This experimental overview is focused on some promising substances and their combinations with the standard antirheumatic drug - methotrexate (Mtx) for treatment of rheumatoid arthritis. The adjuvant arthritis model in Lewis rats was used for evaluation of antiinflammatory efficacy of the substances evaluated. Mtx was administered in the oral dose of 0.3 mg/kg b.w. twice a week. Natural and synthetic antioxidants were administered in the daily oral dose of 20 mg/kg b.w for coenzyme Q(10) (CoQ(10)), 150 mg/kg b.w for carnosine (Carn), 15 mg/kg b.w. for stobadine dipalmitate (Stb) and its derivative SMe1.2HCl (SMe1), and 30 mg/kg b.w. for pinosylvin (Pin) or pterostilbene (Pte). Mtx in the oral dose of 0.4 mg/kg b.w. twice a week was combined with Pin in the oral daily dose of 50 mg/kg b.w. Clinical (hind paw volume - HPV), biochemical (activity of GGT in joint and level of TBARS in plasma), and immunological (IL-1 in plasma) parameters were assessed. Our results achieved with different antioxidants in monotherapies showed a reduction of oxidative stress in adjuvant arthritis independently of the chemical structure of the compounds. Pin was the most effective antioxidant tested in decreasing HPV. All combinations tested showed a higher efficacy in affecting biochemical or immunological parameters than Mtx administered in monotherapy. The findings showed the benefit of antioxidant compounds for their use in combination therapy with methotrexate.

KEYWORDS:
arthrits; carnosine; coenzyme Q10; combination therapy; methotrexate; oxidative stress; pyridoindoles; stilbenoids

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Resveratrol, pterostilbene, and dementia.

Lange KW1, Li S2.

Author information

Abstract

Resveratrol is a natural phytoestrogen with neuroprotective properties. Polyphenolic compounds including resveratrol exert in vitro antioxidant, anti-inflammatory, and antiamyloid effects. Resveratrol and its derivative pterostilbene are able to cross the blood-brain barrier and to influence brain activity. The present short review summarizes the available evidence regarding the effects of these polyphenols on pathology and cognition in animal models and human subjects with dementia. Numerous investigations in cellular and mammalian models have associated resveratrol and pterostilbene with protection against dementia syndromes such as Alzheimer's disease (AD) and vascular dementia. The neuroprotective activity of resveratrol and pterostilbene demonstrated in in vitro and in vivo studies suggests a promising role for these compounds in the prevention and treatment of dementia. In comparison to resveratrol, pterostilbene appears to be more effective in combatting brain changes associated with aging. This may be attributed to the more lipophilic nature of pterostilbene with its two methoxyl groups compared with the two hydroxyl groups of resveratrol. The findings of available intervention trials of resveratrol in individuals with mild cognitive impairment or AD do not provide evidence of neuroprotective or therapeutic effects. Future clinical trials should be conducted with long-term exposure to preparations of resveratrol and pterostilbene with high bioavailability.


KEYWORDS:
cognition; dementia; polyphenols; pterostilbene; resveratrol

PMID: 29168580 DOI: 10.1002/biof.1396


Biological/chemopreventive activity of stilbenes and their effect on colon cancer.

Rimando AM1, Suh N.

Author information

Abstract

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Colon cancer is one of the leading causes of cancer death in men and women in Western countries. Epidemiological studies have linked the consumption of fruits and vegetables to a reduced risk of colon cancer, and small fruits are particularly rich sources of many active phytochemical stilbenes, such as resveratrol and pterostilbene. Recent advances in the prevention of colon cancer have stimulated an interest in diet and lifestyle as an effective means of intervention. As constituents of small fruits such as grapes, berries and their products, stilbenes are under intense investigation as cancer chemopreventive agents. One of the best-characterized stilbenes, resveratrol, has been known as an antioxidant and an anti-aging compound as well as an anti-inflammatory agent. Stilbenes have diverse pharmacological activities, which include cancer prevention, a cholesterol-lowering effect, enhanced insulin sensitivity, and increased lifespan. This review summarizes results related to the potential use of various stilbenes as cancer chemopreventive agents, their mechanisms of action, as well as their pharmacokinetics and efficacy for the prevention of colon cancer in animals and humans.

PMID: 18843589 DOI: 10.1055/s-0028-1088301


Cellular and behavioral effects of stilbene resveratrol analogues: implications for reducing the deleterious effects of aging.

Joseph JA1, Fisher DR, Cheng V, Rimando AM, Shukitt-Hale B.

Author information

Abstract

Research suggests that polyphenolic compounds contained in fruits and vegetables that are rich in color may have potent antioxidant and anti-inflammatory activities. The present studies determined if stilbene (e.g., resveratrol) compounds would be efficacious in reversing the deleterious effects of aging in 19 month old Fischer 344 rats. Experiment I utilized resveratrol and six resveratrol analogues and examined their efficacies in preventing dopamine-induced decrements in calcium clearance following oxotremorine-induced depolarization in COS-7 cells transfected with M1 muscarinic receptors (MAChR) that we have shown previously to be sensitive to oxidative stressors. Experiment II utilized the most efficacious analogue (pterostilbene) from experiment I and fed aged rats a diet with a low (0.004%) or a high (0.016%) concentration of pterostilbene. Results indicated that pterostilbene was effective in reversing cognitive behavioral deficits, as well as dopamine release, and working memory was correlated with pterostilbene levels in the hippocampus.

PMID: 18954071 DOI: 10.1021/jf802279h

Anti-inflammatory activity of natural stilbenoids: A review.

Dvorakova M1, Landa P2.

Author information

Abstract

Resveratrol and other natural stilbenoids, including piceatannol, pterostilbene, and gnetol, are well-known anti-inflammatory compounds with indisputable activity in vitro as well as in vivo. Their molecular targets include inducible nitric oxide synthase, cyclooxygenases, leukotrienes, nuclear factor kappa B, tumor necrosis factor α, interleukins and many more. This anti-inflammatory activity together with their antioxidant activity is believed to stand behind their other positive health effects against cancer, cardiovascular and neurodegenerative diseases or diabetes. Thus, they are nowadays commercially marketed as nutraceuticals. Naturally, they are present in wine, grapes or berries. However, there is a rigorous debate about the real effect of these compounds on human health. It is argued that the concentration of stilbenoids in food and beverages is too low to have any therapeutic potential and this concentration is further reduced by their low bioavailability and extensive metabolism. Therefore, this review focuses on in vitro, in vivo, preclinical as well as clinical data available for various natural stilbenoids and summarizes the anti-inflammatory targets on molecular level, compares the relevance of the experimental studies, discusses the metabolism of stilbenoids and the potential activity of their metabolites and relates this knowledge to human health. Moreover, the ways to augment stilbenoids efficacy are suggested with special focus on multitargeted therapy and nanocarriers.

KEYWORDS:
Bioavailability; Encapsulation; Inflammation; Metabolites; Multi-targeted therapy; Natural stilbenes

PMID: 28803136 DOI: 10.1016/j.phrs.2017.08.002

Anti-adipogenesis mechanism of pterostilbene through the activation of heme oxygenase-1 in 3T3-L1 cells.

Seo YJ1, Kim KJ1, Koh EJ1, Choi J1, Lee BY2.

Author information

Abstract

BACKGROUND:
Pterostilbene is a stilbenoid and major compound and has diverse biological activities, such as antioxidant, anti-cancer, and anti-inflammatory. However, it has not been shown whether pterostilbene affects the mitotic clonal expansion during adipogenesis in 3T3-L1 cells.
PURPOSE:
In the present study, we aimed to demonstrate the detailed mechanism of pterostilbene on anti-adipogenesis in 3T3-L1 cells.

METHODS:
Preadipocytes were converted to adipocytes through treatment with MDI (IBMX; 3-isobutyl-1-methylxanthine, DEX; dexamethasone, insulin) in 3T3-L1 cells. Oil Red O staining was performed to measure intracellular lipid accumulation. Western blot analysis was conducted to analyze protein expressions.

RESULTS:
Our results showed that pterostilbene decreased the lipid accumulation compared to MDI-induced differentiation, using Oil Red O staining. Next, we found that pterostilbene suppressed the expression of C/EBPα, PPARγ, and aP2 as well as the mitotic clonal expansion-associated proteins CHOP10 and C/EBPβ, by western blot analysis. Our results indicated that pterostilbene may repress adipocyte differentiation through the activation of HO-1 expression prior to entering into the mitotic clonal expansion in 3T3-L1 cells. RNA interference was used to determine whether HO-1 acts as a regulator of CHOP10.

CONCLUSION:
Our results revealed that pterostilbene induced HO-1 expression which acts as a regulator of CHOP10. Together, we demonstrated that pterostilbene suppresses the initiation of mitotic clonal expansion via up-regulation of HO-1 expression during adipocyte differentiation of 3T3-L1 cells.

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KEYWORDS:
Adipocytes; Adipogenesis; CHOP10; Heme oxygenase-1; Pterostilbene

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Modulatory role of Pterocarpus santalinus against alcohol-induced liver oxidative/nitrosative damage in rats.

Bulle S1, Reddy VD1, Padmavathi P2, Maturu P3, N Ch V4.

Author information

Abstract

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Pterocarpus santalinus, a traditional medicinal plant has shown protective mechanisms against various complications. The aim of the present study is to evaluate therapeutic efficacy of P. santalinus heartwood methanolic extract (PSE) against alcohol-induced oxidative/nitrosative stress leading to hepatotoxicity. In-vitro studies revealed that PSE possess strong DPPH (1,1-diphenyl-2-picryl hydrazyl) and nitric oxide radical scavenging activity. For in vivo studies male albino Wistar rats were treated with 20% alcohol (5g/kg b.wt/day) and PSE (250mg/kg b.wt/day) for 60days. Results showed that alcohol administration significantly altered plasma lipid profile with marked increase in the levels of plasma transaminases (ALT and AST), alkaline phosphatase (ALP), lactate dehydrogenase (LDH) and gamma glutamyl transferase (γGT). Moreover, lipid peroxides, nitric oxide (NOx) levels in plasma and liver were increased with increased iNOS protein expression in liver was noticed in alcohol administered rats and these levels were significantly brought back close to normal level by PSE administration except iNOS protein expression. Alcohol administration also decreased the content of reduced glutathione (GSH) and activities of glutathione peroxidase (GPx), glutathione-s transferase (GST), glutathione reductase (GR), superoxide dismutase (SOD) and catalase (CAT) in liver, which were significantly enhanced by administration of PSE. The active compounds pterostilbene, lignan and lupeols present in PSE might have shown protection against alcohol-induced hepatic damage by possibly reducing the rate of lipid peroxidation, NOx levels and increasing the antioxidant defence mechanism in alcohol administered rats. Both biochemical and histopathological results in the alcohol-induced liver damage model emphasize beneficial action of PSE as a hepatoprotective agent.

KEYWORDS:
Alcohol; Hepatotoxicity; Nitrosative stress; Oxidative stress; P. santalinus

PMID: 27544549 DOI: 10.1016/j.biopharm.2016.08.031


Autophagy-inducing effect of pterostilbene: A prospective therapeutic/preventive option for skin diseases.

Chen RJ1, Lee YH1, Yeh YL1, Wu WS1, Ho CT2, Li CY3, Wang BJ4, Wang YJ5.

Author information

Abstract

Pterostilbene is a naturally occurring analog of resveratrol with many health benefits. These health benefits are associated with its antioxidant activity, anti-inflammatory effects, and chemopreventive effects attributed to its unique structure. The skin cancer chemopreventive potential of pterostilbene is supported by a variety of mechanistic studies confirming the anti-inflammatory effects in skin cancer models. Molecular biological studies have identified that pterostilbene targets pleotropic signaling pathways, including those involved in mitogenesis, cell cycle regulation, and apoptosis. Recently, pterostilbene has been reported to induce autophagy in cancer and normal cells. Through autophagy induction, the inflammatory-related skin diseases
can be attenuated. This finding suggests the potential use of pterostilbene in the treatment and prevention of skin disorders via alleviating inflammatory responses by autophagy induction. This review summarizes the protective and therapeutic benefits of pterostilbene in skin diseases from the viewpoint of its antioxidant, anti-inflammatory, and autophagy-inducing effects. Novel underlying mechanisms regarding these effects are discussed. We proposed that pterostilbene, a promising natural product, can be used as a preventive and therapeutic agent for inflammation-related skin disorders through induction of autophagy.

KEYWORDS:
autophagy; inflammation; pterostilbene; skin disorders

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Int Urol Nephrol. 2017 Nov 1. doi: 10.1007/s11255-017-1734-4. [Epub ahead of print]

Pterostilbene protects against uraemia serum-induced endothelial cell damage via activation of Keap1/Nrf2/HO-1 signaling.

Chen ZW1, Miu HF1, Wang HP2, Wu ZN2, Wang WJ1, Ling YJ2, Xu XH2, Sun HJ2, Jiang X3.

Author information

Abstract

Chronic kidney disease causes uremia-related endothelial cell dysfunction associated with high risk for cardiovascular diseases. The vascular endothelium is permanently exposed to uraemic toxins including indoxyl sulfate, which provokes endothelial damage in subjects with end-stage renal disease. Pterostilbene (PT) is identified to be homologous derivative of resveratrol and exerts antioxidant and anti-inflammatory actions. However, the effects of PT on uraemic serum-induced endothelial cell damage have not been elucidated. In this study, we investigated the effects and mechanisms of PT on uraemic serum (US)-mediated injury in human umbilical vein endothelial cells (HUVECs). Treatment of US obviously reduced cell viability, inhibited superoxide dismutase activity and catalase activity, suppressed phosphorylated endothelial nitric oxide synthase (eNOS) protein level and eNOS activity, whereas promoted lactate dehydrogenase leakage, increased malondialdehyde, hydrogen peroxide, superoxide anions levels and NAD(P)H activity accompanied with increased nitrative stress and inflammatory response in HUVECs, and these changes were reversed after PT treatment. Under US environment, PT downregulated Kelch-like ECH-associated protein 1 (Keap1) and upregulated nuclear factor erythroid-2-related factor 2 (Nrf2) and its downstream target heme oxygenase-1 (HO-1) protein levels. Of note, the level of HO-1 was decreased after the transfection of cells with Nrf2-siRNA, and HO-1 inhibitor Snpp abolished the protective effects of PT on HUVECs in response to US. Collectively, our study demonstrated that PT is effective in reducing US-evoked endothelial cell dysfunction via suppression of oxidative/nitrative stress and inflammatory response, which at least partly depended on Keap1/Nrf2/HO-1 signaling pathway.
Pterostilbene down-regulates hTERT at physiological concentrations in breast cancer cells: potentially through the inhibition of cMyc.

Daniel M1, Tollefsbol TO1,2,3,4,5.

Author information

Abstract

Human telomerase reverse transcriptase (hTERT) encodes the catalytic subunit of telomerase, which has been shown to be upregulated in many cancers. Pterostilbene is a naturally occurring stilbenoid and phytoalexin found primarily in blueberries that exhibits antioxidant activity and inhibits the growth of various cancer cell types. Therefore, the aim of this study was to determine whether treatment with pterostilbene, at physiologically achievable concentrations, can inhibit the proliferation of breast cancer cells and down-regulate the expression of hTERT. We found that pterostilbene inhibits the cellular proliferation of MCF-7 and MDA-MB-231 breast cancer cells in both a time- and dose-dependent manner, without significant toxicity to the MCF10A control cells. Pterostilbene was also shown to increase apoptosis in both breast cancer cell lines. Dose-dependent cell cycle arrest in G1 and G2/M phase was observed after treatment with pterostilbene in MCF-7 and MDA-231 cells, respectively. hTERT expression was down-regulated after treatment in both a time- and dose-dependent manner. Pterostilbene also reduced telomerase levels in both cell lines in a dose-dependent manner. Moreover, cMyc, a proposed target of the pterostilbene-mediated inhibition of hTERT, was down-regulated both transcriptionally and posttranscriptionally after treatment. Collectively, these findings highlight a promising use of pterostilbene as a natural, preventive and therapeutic agent against the development and progression of breast cancer. This article is protected by copyright. All rights reserved.

KEYWORDS:
Blueberries; Breast cancer; Cancer; Physiological concentrations; Pterostilbene; Telomerase; cMyc; hTERT

PMID: 29125889 DOI: 10.1002/jcb.26495

Pharmacometrics of stilbenes: seguing towards the clinic.
Roupe KA1, Remsberg CM, Yáñez JA, Davies NM.

Author information

Abstract

Stilbenes are small molecular weight (approximately 200-300 g/mol), naturally occurring compounds and are found in a wide range of plant sources, aromatherapy products, and dietary supplements. These molecules are synthesized via the phenylpropanoid pathway and share some structural similarities to estrogen. Upon environmental threat, the plant host activates the phenylpropanoid pathway and stilbene structures are produced and subsequently secreted. Stilbenes act as natural protective agents to defend the plant against viral and microbial attack, excessive ultraviolet exposure, and disease. One stilbene, resveratrol, has been extensively studied and has been shown to possess potent anti-cancer, anti-inflammatory and anti-oxidant activities. Found primarily in the skins of grapes, resveratrol is synthesized by Vitis vinifera grapevines in response to fungal infection or other environmental stressors. Considerable research showing resveratrol to be an attractive candidate in combating a wide variety of cancers and diseases has fueled interest in determining the disease-fighting capabilities of other structurally similar stilbene compounds. The purpose of this review is to describe four such structurally similar stilbene compounds, piceatannol, pinosylvin, raphontigenin, and pterostilbene and detail some current pharmaceutical research and highlight their potential clinical applications.

PMID: 18666380


Pterostilbene protects against UVB-induced photo-damage through a phosphatidylinositol-3-kinase-dependent Nrf2/ARE pathway in human keratinocytes.
Li H1, Jiang N1,2, Liang B1, Liu Q1,3, Zhang E1, Peng L1, Deng H1, Li R1, Li Z1, Zhu H1.

Author information

Abstract

OBJECTIVE:
Ultraviolet B (UVB) irradiation is the initial etiological factor for various skin disorders, including erythema, sunburn, photoaging, and photocarcinogenesis. Pterostilbene (Pter) displayed remarkable antioxidant, anti-inflammatory, and anticarcinogenic activities. This study
aimed to investigate the effective mechanism of Pter against UVB-induced photodamage in immortalized human keratinocytes.

METHODS:
Human keratinocytes were pretreated with Pter (5 and 10 μM) for 24 h prior to UVB irradiation (300 mJ/cm²). Harvested cells were analyzed by MTT, DCFH-DA, comet, western blotting, luciferase promoter, small interference RNA transfection, and quantitative real-time polymerase chain reaction assay.

RESULTS:
Pter significantly attenuated UVB-induced cell death and reactive oxygen species (ROS) generation, and effectively increased nuclear translocation of NF-E2-related factor-2 (Nrf2), expression of Nrf2-dependent antioxidant enzymes, and DNA repair activity. Moreover, the protective effects of Pter were abolished by small interference RNA-mediated Nrf2 silencing. Furthermore, Pter was also found to induce the phosphorylation of Nrf2 and the known phosphatidylinositol-3-kinase (PI3K) phosphorylated kinase, Akt. The specific inhibitor of PI3K, LY294002, successfully abrogated Pter-induced Nrf2 phosphorylation, activation of Nrf2-oxidant response element pathway, ROS scavenging ability, and DNA repair activity.

CONCLUSION:
The present study indicated that Pter effectively protected against UVB-induced photodamage by increasing endogenous defense mechanisms, scavenging UVB-induced ROS, and aiding in damaged DNA repair through a PI3K-dependent activation of Nrf2/ARE pathway.

KEYWORDS:
Nrf2; Pterostilbene; antioxidants; photoprotection; ultraviolet

PMID: 28532341 DOI: 10.1080/13510002.2017.1329917


Synthesis, oxygen radical absorbance capacity, and tyrosinase inhibitory activity of glycosides of resveratrol, pterostilbene, and pinostilbene.

Uesugi D1, Hamada H1, Shimoda K2, Kubota N2, Ozaki SI3, Nagatani N4.

Author information

Abstract

The stilbene compound resveratrol was glycosylated to give its 4′-O-β-D-glucoside as the major product in addition to its 3-O-β-D-glucoside by a plant glucosyltransferase from Phytolacca americana expressed in recombinant Escherichia coli. This enzyme transformed pterostilbene to
its 4'-O-β-D-glucoside, and converted pinostilbene to its 4'-O-β-D-glucoside as a major product and its 3-O-β-D-glucoside as a minor product. An analysis of antioxidant capacity showed that the above stilbene glycosides had lower oxygen radical absorbance capacity (ORAC) values than those of the corresponding stilbene aglycones. The 3-O-β-D-glucoside of resveratrol showed the highest ORAC value among the stilbene glycosides tested, and pinostilbene had the highest value among the stilbene compounds. The tyrosinase inhibitory activities of the stilbene aglycones were improved by glycosylation; the stilbene glycosides had higher activities than the stilbene aglycones. Resveratrol 3-O-β-D-glucoside had the highest tyrosinase inhibitory activity among the stilbene compounds tested.

**KEYWORDS:** glycoside; pinostilbene; pterostilbene; resveratrol

PMID: 27756183 DOI: 10.1080/09168451.2016.1240606


**Pterostilbene ameliorates intracerebroventricular streptozotocin induced memory decline in rats.**

Naik B1, Nirwane A1, Majumdar A1.

**Author information**

**Abstract**

There is strong evidence that mitochondrial dysfunction mediated oxidative stress results in aging and energy metabolism deficits thus playing a prime role in pathogenesis of Alzheimer's disease, neuronal death and cognitive dysfunction. Evidences accrued in empirical studies suggest the antioxidant, anticancer and anti-inflammatory activities of the phytochemical pterostilbene (PTS). PTS also exhibits favourable pharmacokinetic attributes compared to other stilbenes. Hence, in the present study, we explored the neuroprotective role of PTS in ameliorating the intracerebroventricular administered streptozotocin (STZ) induced memory decline in rats. PTS at doses of 10, 30 and 50 mg/kg, was administered orally to STZ administered Sprague-Dawley (SD) rats. The learning and memory tests, Morris water maze test and novel object recognition test were performed which revealed improved cognition on PTS treatment. Further, there was an overall improvement in brain antioxidant parameters like elevated catalase and superoxide dismutase activities, GSH levels, lowered levels of nitrites, lipid peroxides and carbonylated proteins. There was improved cholinergic transmission as evident by decreased acetylcholinesterase activities. The action of ATPases (Na+ K+, Ca2+ and Mg2+) indicating the maintenance of cell membrane potential was also augmented. mRNA expression of battery of genes involved in cellular mitochondrial biogenesis and inflammation showed variations which extrapolate to hike in mitochondrial biogenesis and abated inflammation. The histological findings corroborated the effective role of PTS in countering STZ induced structural aberrations in brain.

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**KEYWORDS:**
AChE; ATPases; Brain; Fenofibrate; IL-6; Inflammation; Learning and memory; PGC1α; PPARα; Protein carbonylation; Pterostilbene; Rats; Streptozotocin; TNF-α


**Design, synthesis and evaluation of some N-methylenebenzenamine derivatives as selective acetylcholinesterase (AChE) inhibitor and antioxidant to enhance learning and memory.**

Shrivastava SK1, Srivastava P2, Upendra TVR2, Tripathi PN2, Sinha SK3.

**Author information**

**Abstract**

Series of some 3,5-dimethoxy-N-methylenebenzenamine and 4-(methyleneamino)benzoic acid derivatives comprising of N-methylenebenzenamine nucleus were designed, synthesized, characterized, and assessed for their acetylcholinesterase (AChE), butyrylcholinesterase (BChE) inhibitory, and antioxidant activity thereby improving learning and memory in rats. The IC50 values of all the compound along with standard were determined on AChE and BChE enzyme. The free radical scavenging activity was also assessed by in vitro DPPH (2,2-diphenyl-1-picrylhydrazyl) and hydrogen peroxide radical scavenging assay. The selective inhibitions of all compounds were observed against AChE in comparison with standard donepezil. The enzyme kinetic study of the most active compound 4 indicated uncompetitive AChE inhibition. The docking studies of compound 4 exhibited the worthy interaction on active-site gorge residues Phe330 and Trp279 responsible for its high affinity towards AChE, whereas lacking of the BChE inhibition was observed due to a wider gorge binding site and absence of important aromatic amino acids interactions. The ex vivo study confirmed AChE inhibition abilities of compound 4 at brain site. Further, a considerable decrease in escape latency period of the compound was observed in comparison with standard donepezil through in vivo Spatial Reference Memory (SRM) and Spatial Working Memory (SWM) models which showed the cognition-enhancing potential of compound 4. The in vivo reduced glutathione (GSH) estimation on rat brain tissue homogenate was also performed to evaluate free radical scavenging activity substantiated the antioxidant activity in learning and memory.

**KEYWORDS:**
Acetylcholinesterase inhibitor; Antioxidant; Learning and memory; Pterostilbene; Schiff base
The resveratrol derivatives trans-3,5-dimethoxy-4-fluoro-4'-hydroxystilbene and trans-2,4',5-trihydroxystilbene decrease oxidative stress and prolong lifespan in Caenorhabditis elegans.

Fischer N1, Büchter C1, Koch K1, Albert S2, Csuk R2, Wätjen W1.

Author information

Abstract

OBJECTIVES:
Resveratrol (trans-3,4',5-trihydroxystilbene (1)) was previously shown to extend the lifespan of different model organisms. However, its pharmacological efficiency is controversially discussed. Therefore, the bioactivity of four newly synthesized stilbenes (trans-3,5-dimethoxy-4-fluoro-4'-hydroxystilbene (3), trans-4'-hydroxy-3,4,5-trifluorostilbene (4), trans-2,5-dimethoxy-4'-hydroxystilbene (5), trans-2,4',5-trihydroxystilbene (6)) was compared to (1) and pterostilbene (trans-3,5-dimethoxy-4'-hydroxystilbene (2)) in the established model organism Caenorhabditis elegans.

METHODS:
Trolox equivalent antioxidant capacity (TEAC), 2',7'-dichlorofluorescein (DCF), thermotolerance assays, C. elegans lifespan analyses.

KEY FINDINGS:
All compounds exert a strong in-vitro radical scavenging activity (6 > 1 > 5 > 2 = 4), but in vivo, only (3) and (6) reduce reactive oxygen species (ROS) accumulation. Furthermore, (3) and (6) increased the mobility of aged nematodes and prolonged their mean lifespans, while these compounds decreased the thermal stress resistance. Using daf-16 (FoxO), skn-1 (Nrf2) and sir-2.1 (sirtuin) loss-of-function mutant strains, the in vivo antioxidant effects of compounds (3) and (6) were abolished, showing the necessity of these evolutionary highly conserved factors. However, short-time treatment with stilbenes (3) and (6) did not modulate the cellular localization of the transcription factors DAF-16 and SKN-1.

CONCLUSION:
In contrast to resveratrol, the synthetic stilbene derivatives (3) and (6) increase the lifespan of C. elegans, rendering them promising candidates for pharmacological anti-ageing purposes.

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Pterostilbene: Biomedical applications.

Estrela JM, Ortega A, Mena S, Rodriguez ML, Asensi M.

Author information

Abstract

Resveratrol and its naturally dimethylated analog, pterostilbene, show similar biological activities. However, the higher in vivo bioavailability of pterostilbene represents a fundamental advantage. The main focus of this review is on biomedical applications of pterostilbene. The metabolism and pharmacokinetics of this stilbene in inflammatory dermatoses and photoprotection, cancer prevention and therapy, insulin sensitivity, blood glycemia and lipid levels, cardiovascular diseases, aging, and memory and cognition are addressed. Safety and toxicity, as well as recommendations for future research and biomedical uses, are discussed. This review includes comparisons between pterostilbene and other polyphenols, with particular emphasis on resveratrol. Potential benefits of using combinations of different polyphenols are considered. Based on present evidences we conclude that pterostilbene is an active phytonutrient and also a potential drug with multiple biomedical applications.

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Pterostilbene Inhibits Vascular Smooth Muscle Cells Migration and Matrix Metalloproteinase-2 through Modulation of MAPK Pathway.

Lin HC1,2,3, Hsieh MJ1,4, Peng CH5, Yang SF1,6, Huang CN1,7.

Author information

Abstract

Smooth muscle cells (SMCs) migration and matrix metalloproteinase-2 (MMP-2) activation are main roles in atherosclerosis. Pterostilbene (trans-3, 5-dimethoxy-4-hydroxystilbene) is known to have various pharmacologic effects such as anti-inflammatory and anticancerinogenic properties.
The present study aimed to investigate the anti-atherosclerotic property of pterostilbene in the rat smooth muscle cell (SMC) A7r9 cell lines and the underlying mechanisms. In this study, pterostilbene treatment significantly inhibited migration/invasion capacities of in A7r9 cell. Pterostilbene was also found to significantly decreased MMP-2 activity and expression by gelatin zymography and western blot assay in SMC. In the MAPK signaling pathway, western blot assay also indicated that pterostilbene up-regulated the phosphorylation of extracellular-signal-regulated kinase (Erk)1/2. Moreover, inhibition of Erk1/2 by specific inhibitors significantly abolished the pterostilbene-decreased expression of MMP-2 and migration/invasion capacities. These findings suggest that pterostilbene inhibited SMC migration and that MMP-2 activation could be mediated via Erk1/2 phosphorylation. It is further possible that pterostilbene could play a novel role in the treatment of atherosclerosis.

PRACTICAL APPLICATION:
Pterostilbene is a plant polyphenol compound that is principally found in blueberries. In this study, we found that pterostilbene could inhibit SMCs migration via down-regulation of MMP-2. Particularly, expression of MMP-2 was found to be strongly associated with the phosphorylation of Erk1/2.

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KEYWORDS:
matrix metalloproteinase-2; migration; pterostilbene; smooth muscle cells

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Orally administrated pterostilbene attenuates acute cerebral ischemia-reperfusion injury in a dose- and time-dependent manner in mice.

Zhou Y1, Zhang XM1, Ma A1, Zhang YL1, Chen YY1, Zhou H1, Li WJ1, Jin X2.

Author information

Abstract

Pterostilbene (3,5-dimethoxy-4-hydroxystilbene) is a component of blueberry. It has been reported that long-term treatment with blueberry has a neuroprotective effect. However, it has not been reported whether pterostilbene is effective in attenuating cerebral ischemia/reperfusion (I/R) injury. In the present study, focal cerebral ischemia was induced by middle cerebral artery occlusion for 90min followed by reperfusion. To observe the dose-dependent effect, pterostilbene (2.5-80mg/kg, ig) was administered for 3days before ischemia. To determine the time-dependent effect, pterostilbene (10mg/kg, ig) was administered as a single dose at 0, 1, or
3h after reperfusion. Twenty-four hours after I/R, pterostilbene dose-dependently improved neurological function, reduced brain infarct volume, and alleviated brain edema. The most effective dose was 10mg/kg; the therapeutic time window was within 1h after I/R and treatment immediately after reperfusion showed the best protective effect. The protective effect is further confirmed by the results that post-ischemic treatment with pterostilbene (10mg/kg) significantly improved motor function, alleviated blood brain barrier disruption, increased neurons survival and reduced cell apoptosis in cortical penumbral brain after cerebral I/R. We also found that pterostilbene (10mg/kg) significantly reversed the increased content of malondialdehyde and the decreased activity of superoxide dismutase in the ipsilateral hemisphere. Furthermore, pterostilbene decreased the oxidative stress markers 4-hydroxynonenal and 8-hydroxyguanosine positive cells in the cortical penumbra. All these findings indicate that pterostilbene dose- and time-dependently exerts a neuroprotective effect against acute cerebral I/R injury. This neuroprotective effect of pterostilbene may be associated with its inhibition of oxidative stress and subsequent neuronal apoptosis in the cortical penumbra.

KEYWORDS:
Apoptosis; Cerebral ischemia/reperfusion; Mice; Oxidative stress; Pterostilbene

PMID: 26086685 DOI: 10.1016/j.pbb.2015.06.009


Nanoemulsion for solubilization, stabilization, and in vitro release of pterostilbene for oral delivery.

Zhang Y1, Shang Z, Gao C, Du M, Xu S, Song H, Liu T.

Author information

Abstract

Pterostilbene, being extracted from many plants, has significant biological activities in preventing cancer, diabetes, and cardiovascular diseases so as to have great potential applications in pharmaceutical fields. But the poor solubility and stability of pterostilbene strictly restrained its applications. As a good protection and oral delivery system, an optimal nanoemulsion for pterostilbene was developed by using low-energy emulsification method. Systematic pseudoternary phase diagrams have been studied in optimization of nanoemulsion formulations. The prepared pterostilbene nanoemulsion was characterized by transmission electron microscope, Fourier transform Raman spectrum, and laser droplet size analyzer. Nanoemulsion droplets are circular with smooth margin, and the mean size is 55.8 ± 10.5 nm. The results illustrated that the nanoemulsion as oral delivery system dramatically improved the stability and solubility of pterostilbene, and in vitro release of pterostilbene was significantly improved (96.5% in pH 3.6 buffer; 13.2% in pH 7.4 buffer) in comparison to the pterostilbene suspension (lower than 21.4% in pH 3.6 buffer; 2.6% in pH 7.4 buffer).
Effects of pterostilbene and resveratrol on brain and behavior.

Poulose SM1, Thangthaeng N1, Miller MG1, Shukitt-Hale B2.

Author information

Abstract

Age is the greatest universal risk factor for neurodegenerative diseases. During aging, these conditions progress from minor loss of function to major disruptions in daily life, loss of independence and ultimately death. Because approximately 25% of the world population is expected to be older than age 65 by 2050, and no treatments exist to halt or reverse ongoing neurodegeneration, the need for effective prevention strategies is more pressing that ever before. A growing body of research supports the role of diet in healthy aging, particularly diets rich in bioactive phytochemical compounds. Recently, stilbenes such as resveratrol (3, 5, 4'-trans-trihydroxystilbene) and its analogue, pterostilbene, have gained a significant amount of attention for their potent antioxidant, anti-inflammatory, and anticarcinogenic properties. However, evidence for the beneficial effects of stilbenes on cerebral function is just beginning to emerge. In this review, we summarize the current knowledge on the role of resveratrol and pterostilbene in improving brain health during aging, with specific focus on antioxidant and anti-inflammatory signaling and behavioral outcomes.

KEYWORDS:
Aging; Brain-signaling; Inflammation; Polyphenols; Pterostilbene; Resveratrol

Pterostilbene, an Active Constituent of Blueberries, Stimulates Nitric Oxide Production via Activation of Endothelial Nitric Oxide Synthase in Human Umbilical Vein Endothelial Cells.

Park SH1, Jeong SO, Chung HT, Pae HO.
Endothelial dysfunction, a key process in development of cardiovascular diseases, is largely due to reduced nitric oxide (NO) derived from endothelial NO synthase (eNOS). Resveratrol has been reported to stimulate NO production via estrogen receptor α (ERα) activation in endothelial cells. Here, we investigated whether two natural methylated analogs of resveratrol, pterostilbene (Pts) and trans-3,5,4′-trimethoxystilbene (TMS), similarly to resveratrol, could influence endothelial NO release in human umbilical vein endothelial cells (HUVECs). In HUVECs exposed to Pts or TMS, NO production and phosphorylation of eNOS, protein kinase B (Akt), and ERα were measured by using a fluorimetric NO assay kit and Western blot analysis, respectively. Dimethylated Pts, but not trimethylated TMS, stimulated dose-dependent NO production via eNOS phosphorylation. Pts also stimulated dose-dependent phosphorylation of Akt, but not of ERα. NO production and eNOS phosphorylation in response to Pts were significantly abolished by the phosphoinositide 3-kinase (PI3K)/Akt inhibitor LY294002, but not by the ERα antagonist ICI182780. Our results suggest that Pts, but not TMS, is capable of inducing eNOS phosphorylation and the subsequent NO release, presumably, by activating PI3K/Akt pathway. The potential efficacy of Pts, an active constituent of blueberries, may aid in the prevention of cardiovascular diseases characterized by endothelial dysfunction.

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ERK5/HDAC5-mediated, resveratrol-, and pterostilbene-induced expression of MnSOD in human endothelial cells.

Gan W1, Dang Y1, Han X1, Ling S1, Duan J1, Liu J1, Xu JW1.

Author information

Abstract

SCOPE:
Mitochondrial oxidative stress is closely correlated with numerous cardiovascular diseases. Manganese superoxide dismutase (MnSOD) is an important antioxidant enzyme in mitochondria. Although polyphenols can induce the expression of MnSOD, their corresponding mechanisms remains unclear. In this study, we tested the hypothesis that resveratrol and pterostilbene can activate the expression of MnSOD through an AMPK-ERK5/HDAC5-KLF2 pathway.

METHODS AND RESULTS:
Our results revealed that two stilbenes reduced mitochondrial superoxide-free radicals, and endothelial cell senescence, and increased the mRNA expression of several genes related to mitochondrial function, including MnSOD. Moreover, two stilbenes upregulated the activation of human MnSOD promoter luciferase reporter gene and protein level in human umbilical vein endothelial cells. Similarly, two stilbenes also stimulated LKB1, AMPKα, extracellular-signal related kinase 5 (ERK5) phosphorylation, and histone acetylase 5 (HDAC5) and Kruppel-like factor 2 (KLF2) expression. The knockdown of AMP-activated protein kinase (AMPK), ERK5,
CONCLUSION:
Resveratrol and pterostilbene can activate MnSOD expression through ERK5/HDAC5 pathway, thus alleviating mitochondrial oxidative stress in endothelial cells that relates to cardiovascular disease.

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KEYWORDS:
ERK5; Gene expression; HDAC5; Mitochondrial superoxide dismutase; Stilbenes

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Pterostilbene, a natural dimethylated analog of resveratrol, inhibits rat aortic vascular smooth muscle cell proliferation by blocking Akt-dependent pathway.

Park ES1, Lim Y, Hong JT, Yoo HS, Lee CK, Pyo MY, Yun YP.

Author information

Abstract

Vascular smooth muscle cells (VSMCs) are the main cellular component in the arterial wall, and abnormal proliferation of VSMCs plays a central role in the pathogenesis of atherosclerosis and restenosis after angioplasty, and possibly in the development of hypertension. Pterostilbene, a natural dimethylated analog of resveratrol, is known to have diverse pharmacological activities including anti-cancer, anti-inflammation and anti-oxidant activities. The present study was designed to investigate the effects of pterostilbene on platelet-derived growth factor (PDGF)-BB-induced VSMCs proliferation as well as the molecular mechanisms of the antiproliferative effects. The cell growth of VSMCs was determined by cell counting and [(3)H]thymidine incorporation assays. Pterostilbene significantly inhibited the DNA synthesis and proliferation of PDGF-BB-stimulated VSMCs in a concentration-dependent manner. The inhibition percentages of pterostilbene at 1, 3 and 5microM to VSMCs proliferation were 68.5, 80.7 and 94.6%, respectively. The DNA synthesis of pterostilbene at 1, 3 and 5microM in VSMCs was inhibited by 47.4, 76.7 and 100%, respectively. Pterostilbene inhibited the PDGF-BB-stimulated phosphorylation of Akt kinase. However, pterostilbene did not change the expression of extracellular signal-related kinase (ERK) 1/2, PLCgamma1, phosphatidylinositol (PI)3 kinase
and PDGF-Rbeta phosphorylation. In addition, pterostilbene down-regulated the cell cycle-related proteins including the expression of cyclin-dependent kinase (CDK) 2, cyclin E, CDK4, cyclin D1, retinoblastoma (Rb) proteins and proliferative cell nuclear antigen (PCNA). These findings suggest that the inhibition of pterostilbene to the cell proliferation and DNA synthesis of PDGF-BB-stimulated VSMCs may be mediated by the suppression of Akt kinase. Furthermore, pterostilbene may be a potential anti-proliferative agent for the treatment of atherosclerosis and angioplasty restenosis.

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Effects of pterostilbene on treating hyperprolactinemia and related mechanisms.


Author information

Abstract

Hyperprolactinemia (HPRL) frequently causes primary menopause and reproductive disorders. Pterostilbene is known to have anti-inflammation and modulation on cell apoptosis. However, its role in treating HPRL and potential mechanisms remain unclear yet. Healthy female virgin SD rats were randomly assigned into control, HPRL model group, bromocriptine treatment group, and low (20 mg/kg) and high (40 mg/kg) pterostilbene treatment groups. All groups except control ones received metoclopramide hydrochloride injection for generating HPRL model. Uterus and ovarian index in all animals were monitored. Prolactin (PRL), estradiol (E2), follicle stimulating hormone (FSH) and luteinizing hormone (LH) were quantified by ELISA. Caspase 3 activity was assayed, with real time PCR measuring Bcl-2 and Bax mRNA levels. HPRL rats had lower uterus and ovarian index, accompanied with elevated PRL, caspase 3 activity, Bax expression, and decreased FSH, LH, E2 and Bcl-2 expression as compared to control group (p<0.05). Pterostilbene treatment significantly increased uterus and ovarian index, FSH, LH, E2 and Bcl-2 expression as compared to control group (p<0.05). 40 mg/kg pterostilbene had similar efficacy as those of bromocriptine. Pterostilbene exerts its function in the treatment of HPRL via modulating apoptosis-anti-apoptosis homeostasis, inhibiting serum PRL level, and regulating secretion of gonadotropin hormones.

KEYWORDS:
Hyperprolactinemia; cell apoptosis; prolactin; pterostilbene

PMID: 27508025 PMCID: PMC4969441

Pterostilbene attenuates the inflammatory reaction induced by ischemia/reperfusion in rat heart.

Lv M1, Liu K2, Fu S1, Li Z1, Yu X3.

Author information

Abstract

The role of pterostilbene (Pte) in inflammation induced by ischemia/reperfusion is not well understood. The aim of this study was to investigate whether Pte modulates neutrophil accumulation and the induction of tumor necrosis factor-α (TNF-α) in an ischemia/reperfusion (I/R)-injured rat heart model. Rats were randomly exposed to a sham operation, myocardial ischemia/reperfusion (MI/R) alone, MI/R+Pte, MI/R+Pte+L-NAME and MI/R+Pte+ (methylene blue) MB. The results demonstrated that compared with MI/R, Pte reduced the area of myocardial infarction, the levels of myocardial myeloperoxidase, serum creatinine kinase and lactate dehydrogenase, and the production of serum and myocardial TNF-α. These Pte-induced effects were eliminated by the administration of L-NAME, a nitric oxide (NO) synthase inhibitor, and MB, a cyclic guanosine monophosphate (cGMP) inhibitor. In conclusion, Pte produces cardioprotective and anti-inflammatory effects. These effects may be associated with an increase in NO production, the inhibition of neutrophil accumulation, and induction of TNF-α and cGMP signaling pathways in myocardium subjected to MI/R.

PMID: 25333895 DOI: 10.3892/mmr.2014.2719


Promising therapeutic potential of pterostilbene and its mechanistic insight based on preclinical evidence.

Kosuru R1, Rai U1, Prakash S1, Singh A2, Singh S3.

Author information

Abstract

Pterostilbene (PS) is a well-recognized antioxidant that primarily exists in blueberries, grapevines and heartwood of red sandalwood. Interest in this compound has been renewed in recent years, and studies have found that PS possesses an array of pharmacological properties, including chemopreventive, antiinflammatory, antidiabetic, antidyslipidemic, antiatherosclerotic and neuroprotective effects. However, the greater in vivo bioavailability of PS, as compared to resveratrol, is an added advantage for its efficacy. This review provides a summary regarding the sources, pharmacokinetic aspects and pharmacodynamics of PS, with a focus on the molecular mechanisms underlying its protective effects against cancer, brain injuries and heart disease.
Studies regarding the safety profile of PS have also been included. Based on the presently available evidence, we conclude that PS represents an active phytonutrient and a potential drug with pleiotropic health applications.

**KEYWORDS:**
AMPK; Cardiovascular disease; HO-1; NF-κB; Nrf2; Pterostilbene

PMID: 27475678 DOI: 10.1016/j.ejphar.2016.07.046


**Restoration of sirt1 function by pterostilbene attenuates hypoxia-reoxygenation injury in cardiomyocytes.**

Guo Y1, Zhang L2, Li F2, Hu CP3, Zhang Z4.

**Author information**

**Abstract**

Restoration of blood supply to ischemic myocardium causes cardiomyocyte damage, a process known as ischemia-reperfusion injury. Excess reactive oxygen species and intracellular calcium contribute to cell damage but the involvement of sirt1, a versatile protein deacetylase in reperfusion-induced cell damage remains unknown. Here, we found that hypoxia-reoxygenation, an in vitro model of ischemia-reperfusion injury, induced H9c2 cardiomyocyte apoptosis as revealed by caspase-3 assay, Hoechst 33258 staining, flow cytometric analysis and JC-1 staining. Molecular docking analysis showed that, pterostilbene, a natural dimethyl ether derivative of resveratrol, binds to the enzymatic active pocket of sirt1. Importantly, application of pterostilbene at low concentrations of 0.1-3.0 μM rescued H9c2 cells from apoptosis, an effect comparable with resveratrol at 20 μM. Mechanistically, pterostilbene exerted its cardioprotective effects via 1) stimulation of sirt1 activity, since pretreatment of H9c2 cells with splitomicin, an antagonist of sirt1, removed the effects of pterostilbene, and 2) enhancement of sirt1 expression. Therefore, the present study demonstrates that activation of sirt1 during ischemia-reperfusion is cardioprotective and that the natural compound-pterostilbene-could be used therapeutically to alleviate ischemia-reperfusion injury.

**KEYWORDS:**
Cardiomyocyte apoptosis; Ischemia-reperfusion injury; Pterostilbene; Sirt1

PMID: 26921129 DOI: 10.1016/j.ejphar.2016.02.052

Suppression of Nitric Oxide Production and Cardiovascular Risk Factors in Healthy Seniors and Hypercholesterolemic Subjects by a Combination of Polyphenols and Vitamins.

Qureshi AA, Khan DA, Mahjabeen W, Papasian CJ, Qureshi N.

Author information

Abstract

BACKGROUND:
Dysregulated immune function associated with ageing has been implicated in a variety of human diseases. We have demonstrated the anti-inflammatory properties of resveratrol, pterostilbene, morin hydrate, quercetin, δ-tocotrienol, riboflavin in a variety of experimental animal models, and determined that these compounds act by inhibiting proteasome activity.

AIMS:
To determine whether serum nitric oxide (NO) levels increase with age in humans, and whether the combined cholesterol-lowering and inflammation-reducing properties of resveratrol, pterostilbene, Morin hydrate, quercetin, δ-tocotrienol, riboflavin, and nicotinic acid would reduce cardiovascular risk factors in humans when used as nutritional supplements with, or without, other dietary changes.

METHODS:
Elderly human subjects were stratified into two groups based on total serum cholesterol levels. Initial total serum cholesterol levels were normal and elevated in Group 1 and 2 subjects, respectively. Baseline serum NO, C-reactive protein (CRP), γ-glutamyltransferase (γ-GT) activity, uric acid, total antioxidant status (TAS), total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglycerides levels were established over a four week period. Group 1 subjects subsequently received nutritional supplementation with one of two different combinations (NS-7 = 25 mg of each, resveratrol, pterostilbene, quercetin, δ-tocotrienol, nicotinic acid, morin hydrate or NS-6 = morin hydrate replaced with quercetin, 50 mg/capsule). Group 2 subjects also received these nutritional supplements (two capsules/d), but an AHA Step-1 diet was also implemented. After these interventions were administered for four weeks, the above parameters were re-measured and changes from baseline levels determined. Nitric acid (NO) levels in children, young adults, and seniors were also compared.

RESULTS:
The key results of the current study were: 1) that serum NO levels were significantly increased in seniors compared to both children (~80%) and young adults (~65%); 2) that the intake of two capsules/d of NS-7 or NS-6 for four weeks significantly (P < 0.05) decreased serum NO (39%, 24%), CRP (19%, 21%), uric acid (6%, 12%) levels, and γ-GT activity (8%, 6%), respectively in free-living healthy seniors; 3) that serum NO (36%, 29%), CRP (29%, 20%), uric acid (6%, 9%) γ-GT activity (9%, 18%), total cholesterol (8%, 11%), LDL-cholesterol (10%, 13%), and triglycerides (16%, 23%) levels were significantly (P < 0.02) decreased in hypercholesterolemic
subjects restricted to AHA Step-1 diet plus intake of SN-7 or SN-6 (two capsules/d), respectively; 4) that TAS was increased (3%, 9%; P < 0.05) in free-living healthy seniors receiving NS-7 or NS-6 alone, and in hypercholesterolemic subjects plus AHA Step-1 diet (20%, 12%; P < 0.02) with either of the combinations tested.

CONCLUSIONS:
Serum NO levels are elevated in elderly humans compared to children or young adults. Diet supplementation with combinations of resveratrol, pterostilbene, morin hydrate, quercetin, δ-tocotrienol, riboflavin, and nicotinic acid reduce cardiovascular risk factors in humans when used as nutritional supplements with, or without, other dietary changes.

PMID: 23125945 PMCID: PMC3486425 DOI: 10.4172/2155-9880.S5-008


Pterostilbene exerts antitumor activity via the Notch1 signaling pathway in human lung adenocarcinoma cells.


Author information

Abstract

Although pterostilbene (PTE) has been shown to have potent antitumor activities against various cancer types, the molecular mechanisms of these activities remain unclear. In this study, we investigated the antitumor activity of PTE against human lung adenocarcinoma in vitro and in vivo and explored the role of the Notch1 signaling pathway in this process. PTE treatment resulted in a dose- and time-dependent decrease in the viability of A549 cells. Additionally, PTE exhibited strong antitumor activity, as evidenced not only by a reduced mitochondrial membrane potential (MMP) and a decreased intracellular glutathione content but also by increases in the apoptotic index and the level of reactive oxygen species (ROS). Furthermore, PTE treatment induced the activation of the Notch1 Intracellular Domain (NICD) protein and activated Hes1. DAPT (a gamma secretase inhibitor) and Notch1 siRNA prevented the induction of NICD and Hes1 activation by PTE treatment and sensitized the cells to PTE treatment. The down-regulation of Notch signaling also prevented the activation of pro-survival pathways (most notably the PI3K/Akt pathway) after PTE treatment. In summary, lung adenocarcinoma cells may enhance Notch1 activation as a protective mechanism in response to PTE treatment. Combining a gamma secretase inhibitor with PTE treatment may represent a novel approach for treating lung adenocarcinoma by inhibiting the survival pathways of cancer cells.

PMID: 23671619 PMCID: PMC3643961 DOI: 10.1371/journal.pone.0062652

Pterostilbene, a novel natural plant conduct, inhibits high fat-induced atherosclerosis inflammation via NF-κB signaling pathway in Toll-like receptor 5 (TLR5) deficient mice.

Zhang Y1, Zhang Y2.

Author information

Abstract

Atherosclerosis is a specific form of an artery wall thickens, a syndrome affecting arterial blood vessels due to a chronic inflammatory response in the walls of arteries, which is promoted by fat accumulation. Toll-like receptors (TLRs) play prominent roles in inflammatory responses. And TLR5 is overexpressed in several diseases. Here in our study, we investigated the effect of TLR5 in high fat-induced atherosclerosis via NF-κB signaling pathway modulating pro-inflammatory cytokines releasing. Our results found that high fat induced atherosclerosis in wild type mice with fat accumulation and inflammatory response through NF-κB activation. Contrastly, TLR5 knockout mice displayed lower fat accumulation and ameliorated inflammation after high fat feeding with NF-κB inactivation. In addition, pterostilbene, as a natural dimethyl ether derivative of resveratrol mainly from blueberries, has diverse pharmacological activities, especially anti-inflammation. Our study also found that pterostilbene displayed inhibited role in suppressing inflammatory response through inactivating NF-κB signaling pathway regulated by TLR5 down-regulation in high fat-induced mice. Moreover, in vitro experiments of vascular smooth muscle cells (VSMCs) challenged with LPS or TNF-α, further indicated that NF-κB was involved in atherosclerosis progression, leading to high secretion of pro-inflammatory cytokines. However, VSMCs from TLR5 deficient mice inhibited phosphorylated levels of NF-κB signaling pathway, finally resulting in down-regulation of inflammatory cytokines. Notably, pterostilbene also displayed suppressed role in inflammatory response via NF-κB inactivity in LPS or TNF-α-induced VSMCs by decreasing TLR5 expression. The results above indicated a novel therapeutic strategy of pterostilbene to protect against atherosclerosis via TLR5 regulation for clinic treatment in the future.

KEYWORDS:
Atherosclerosis; Inflammation; NF-κB; Pterostilbene; TLR5

PMID: 27261612 DOI: 10.1016/j.biopha.2016.04.031


Effect of substituted stilbenes on platelet function.

Messina F1, Guglielmini G2, Curini M1, Orsini S2, Gresele P3, Marcotullio MC1.
Stilbenes, including resveratrol, are polyphenols provided with protective actions on the cardiovascular system. Some natural derivatives of resveratrol, like pterostilbene, have a better bioavailability than the parent compound. The aim of the present study was to prepare different substituted stilbenes (dimethylallyloxy-stilbene, dimethylallyloxy-pterostilbene) and compare them with resveratrol, p-hydroxy-stilbene and pterostilbene for their biologic activities on platelet aggregation, platelet radical oxygen species (ROS) production, and platelet nitric oxide (NO) synthesis. The results show that the increase of stilbene derivative lipophilicity enhances their biologic activities.

KEYWORDS:
Dimethylallyloxy-stilbene; Platelet NOx production; Platelet ROS production; Platelet aggregation; Resveratrol

PMID: 26197385 DOI: 10.1016/j.fitote.2015.07.009


Pterostilbene exerts an anti-inflammatory effect via regulating endoplasmic reticulum stress in endothelial cells.


Author information

Abstract

Pterostilbene (PT), an analog of resveratrol, exerts a potent anti-inflammatory effect. However, the protective effects of PT against inflammation in endothelial cells have not been elucidated. Previous studies have confirmed that endoplasmic reticulum stress (ERS) plays an important role in regulating the pathological process of endothelial cell inflammation. In this study, we explored the effect of PT on the tumor necrosis factor-α (TNF-α)-induced inflammatory response in human umbilical vein endothelial cells (HUVECs) and elaborated the role of ERS in this process. TNF-α treatment significantly upregulated the levels of inflammation-related molecules in cell culture media, increased the adhesion of monocytes to HUVECs, and enhanced the expression of the MMP9 and ICAM proteins in HUVECs. Additionally, TNF-α potently increased ERS-related protein levels, such as GRP78 and p-eIF2α. However, PT treatment reversed the increased production of inflammatory cytokines and the adhesion of monocytes to HUVECs, as well as reduced the TNF-α-induced effects exerted by ERS-related molecules. Furthermore, thapsigargin (THA), an ERS inducer, attenuated the protective effect of PT against
TNF-α-induced inflammation and ERS in HUVECs. Additionally, the downregulation of ERS signaling using siRNA targeting eIF2α and IRE1 not only inhibited ERS-related molecules but also simulated the therapeutic effects of PT on TNF-α-induced inflammation. In summary, PT treatment potently attenuates inflammation in vascular endothelial cells, which at least partly depends on the reduction of ERS.

**KEYWORDS:**
Anti-inflammatory; Endoplasmic reticulum stress; Endothelial cells; Pterostilbene

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**Inhibition of nitric oxide and inflammatory cytokines in LPS-stimulated murine macrophages by resveratrol, a potent proteasome inhibitor.**

Qureshi AA1, Guan XQ, Reis JC, Papasian CJ, Jabre S, Morrison DC, Qureshi N.

**Author information**

**Abstract**

**BACKGROUND:**
Altered immune function during ageing results in increased production of nitric oxide (NO) and other inflammatory mediators. Recently, we have reported that NO production was inhibited by naturally-occurring proteasome inhibitors (quercetin, δ-tocotrienol, and riboflavin) in lipopolysaccharide (LPS)-stimulated RAW264.7 cells, and thioglycolate-elicited peritoneal macrophages from C57BL/6 mice. In a continuous effort to find more potent, non-toxic, commercially available, naturally-occurring proteasome inhibitors that suppress inflammation, the present study was carried out to describe the inhibition of NF-κB activation and NO, TNF-α, IL-6, IL-1β, and iNOS expression by trans-resveratrol, trans-pterostilbene, morin hydrate, and nicotinic acid in LPS-induced RAW 264.7 cells and thioglycolate-elicited peritoneal macrophages from C57BL/6 and BALB/c mice.

**RESULTS:**
The present results indicate that resveratrol, pterostilbene, and morin hydrate caused significant inhibition (>70% to 90%; P < 0.02) in the activities of chymotrypsin-like, trypsin-like, and post-acidic (post-glutamase) proteasome sites in RAW 264.7 cells at a dose of only 20 μM. These compounds also inhibited the production of NO by RAW-264.7 cells stimulated with LPS alone (>40%; P < 0.05), or LPS + interferon-γ (IFN-γ; >60%; P < 0.02). Furthermore, resveratrol, pterostilbene, morin hydrate, and quercetin suppressed secretion of TNF-α (>40%; P < 0.05) in LPS-stimulated RAW 264.7 cells, and suppressed NF-κB activation (22% to 45%; P < 0.05) in LPS-stimulated HEK293T cells. These compounds also significantly suppressed LPS-induced
expression of TNF-α, IL-1β, IL-6, and iNOS genes in RAW 264.7 cells, and also in thioglycolate-elicited peritoneal macrophages from C57BL/6 and BALB/c mice.

**CONCLUSIONS:**
The present results clearly demonstrate that resveratrol and pterostilbene are particularly potent proteasome inhibitors that suppress expression of genes, and production of inflammatory products in LPS-stimulated RAW 264.7 cells, and macrophages from C57BL/6 and BALB/c mice. Resveratrol and pterostilbene which are present in grapes, blueberries, and red wine, have been implicated as contributing factors to the lower incidence of cardiovascular disease in the French population, despite their relatively high dietary fat intake. Consequently, it appears likely that the beneficial nutritional effects of resveratrol and pterostilbene are due at least in part, to their ability to inhibit NF-κB activation by the proteasome, thereby suppressing activation of pro-inflammatory cytokines and iNOS genes, resulting in decreased secretion of TNF-α, IL-1β, IL-6, and NO levels, in response to inflammatory stimuli. This is the first report demonstrating that resveratrol and pterostilbene act as proteasome inhibitors, thus providing a mechanism for their anti-inflammatory effects.

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**Nutritional Supplement-5 with a Combination of Proteasome Inhibitors (Resveratrol, Quercetin, δ-Tocotrienol) Modulate Age-Associated Biomarkers and Cardiovascular Lipid Parameters in Human Subjects.**

Qureshi AA1, Khan DA, Mahjabeen W, Papasian CJ, Qureshi N.

**Author information**

**Abstract**

**BACKGROUND:**
Age-associated altered redox imbalances and dysregulated immune function, contribute to the development of a variety of age associated diseases. Inflammatory markers and lipid profiles are useful prognostic indicators of a variety of age-associated and cardiovascular diseases. We have previously studied the impact of several proteasome inhibitors on several markers of inflammation and lipid profiles in vitro, in vivo, in cell lines, animal models, and in human subjects. The current study represents an extension of this work. Our main hypothesis is that a combination of various naturally-occurring proteasome inhibitors, which inhibits nitric oxide (NO), and C-reactive protein (CRP) mediated inflammation, will have better efficacy in the prevention and treatment of age-associated disorders including cardiovascular disease.

**METHODS:**
Two double blind, randomized, placebo-controlled cross-over trials were conducted to determine the impact of a mixture of NS-5 (resveratrol, pterostilbene, quercetin, δ-tocotrienol, nicotinic acid) on serum NO, CRP, γ-glutamyl-transferase (γ-GT) activity, total antioxidant status (TAS), total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides levels. Healthy seniors (Group-1; n = 32) free-living (A, B; 16/group), and hypercholesterolemic (Group-2; n = 64) subjects on AHA-Step-1-diet were divided into two groups (C, D; 32/group). Baseline levels were established for parameters as mentioned above. Groups A, C were administered 4-capsules/d of NS-5 and groups B, D, placebo (starch) for 6-weeks. Groups were crossed-over, followed by a 2-week wash-out period. Groups A, C were given 4-capsules/d of placebo and groups B, D, 4-capsules/d of NS-5 for 6-weeks. Groups C, D were continued on AHA-Step-1-diet.

RESULTS:
All the subjects completed each phase in both studies without any complaints. There were significant (P < 0.01 - 0.05) decreases in the serum levels of NO (30%, 26%), CRP (29%, 21%), γ-GT activity (14%, 17%), and blood pressure (systolic/diastolic, 3/6%, 3/3%) of Groups A and B, respectively, of free-living healthy seniors without affecting the total, HDL-, LDL-cholesterol or triglycerides compared to their respective baseline values. However, serum levels of NO (36%, 43%), CRP (31%, 48%), γ-GT (17%, 20%), total cholesterol (19%, 15%), LDL-cholesterol (28%, 20%), triglycerides (11%, 18%) of Groups C and D were significantly (P < 0.01-0.05) decreased with NS-5 treatment of hypercholesterolemic subjects compared to baseline values, without affecting the serum HDL-cholesterol levels. The serum levels of total antioxidant status (TAS) were increased (10%, 14%; P < 0.05) in Groups A and B, increased (19%, 24%; P < 0.02), and blood pressure (systolic/diastolic, 5/6%, 3/5%) in Groups C and D with NS-5 treatment, compared to respective baseline values.

CONCLUSIONS:
The consumption of NS-5 mixture decreased significantly serum NO, CRP and γ-GT levels, improved TAS and lipid profiles at risk cardiovascular and hold promise for delaying onset of age-associated diseases.

KEYWORDS:
Anti-inflammatory and anti-ageing agents; C-reactive protein (CRP); Nitric oxide (NO); Quercetin; Resveratrol; Total antioxidant status (TAS); γ-glutamyl-transferase (γ-GT); δ-tocotrienol

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Association between pterostilbene and quercetin inhibits metastatic activity of B16 melanoma.

Ferrer P1, Asensi M, Segarra R, Ortega A, Benlloch M, Obrador E, Varea MT, Asensio G, Jordá L, Estrela JM.
Inhibition of cancer growth by resveratrol (trans-3,5,4′-trihydroxystilbene; RESV), a phytoalexin present in many plant species, is limited by its low bioavailability. Pterostilbene (3,5-dimethoxy-4′-hydroxystilbene; PTER) and quercetin (3,3′,4′,5,6-pentahydroxyflavone; QUER), two structurally related and naturally occurring small polyphenols, show longer half-life in vivo. In vitro growth of highly malignant B16 melanoma F10 cells (B16M-F10) is inhibited (56%) by short-time exposure (60 min/day) to PTER (40 microm) and QUER (20 microm) (approximate mean values of plasma concentrations measured within the first hour after intravenous administration of 20 mg/kg each polyphenol). Intravenous administration of PTER and QUER (20 mg/kg per day) to mice inhibits (73%) metastatic growth of B16M-F10 cell in the liver, a common site for metastasis development. The anti-metastatic mechanism involves: 1) a PTER-induced inhibition of vascular adhesion molecule 1 expression in the hepatic sinusoidal endothelium, which consequently decreases B16M-F10 cell adhesion to the endothelium through very late activation antigen 4; and 2) a QUER- and PTER-induced inhibition of Bcl-2 expression in metastatic cells, which sensitizes them to vascular endothelium-induced cytotoxicity. Our findings demonstrate that the association of PTER and QUER inhibits metastatic melanoma growth and extends host survival.

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[Chemical principles and bioactivities of blueberry].
[Article in Chinese]

Chen CF1, Li YD, Xu Z.

The bioactive principles contained in blueberries (Vaccinium) are various kind of anthocyanins (anthocyanidins, or phenolic aglycone, conjugated with sugar), chlorogenic acid, flavonoids, alpha-linolenic acid, pterostilbene, resveratrol, and vitamins. After oral administration, anthocyanins can pass through blood-brain barrier and thus appear in various organs and brain. Improve visual function by increasing rhodopsin regeneration and ocular health is the earliest reported bioactivities of anthocyanin. Recent studies demonstrated the benefit of blueberries to prevent the age-related chronic diseases such as cancer, diabetes, hyperlipidemia, hypertension, neurodegeneration, obesity, and osteoporosis through its apoptosis, antioxidant, antiinflammation, and antiangiogenesis effects. Blueberries can eradicate microorganisms for the prevention of symptomatic urinary tract infections in women. Thus, blueberries are recognized as one of the most nutritious foods and cultivated worldwide. However, how to prolong the
Epigenetic mechanisms are essential in regulating normal cellular functions and play an important role during the disease developmental stages. However, aberrant epigenetic mechanisms may lead to pathological consequences such as cancer, neurological disorders, bone and skeletal diseases, cardiovascular dysfunction, and metabolic syndrome. The molecular mechanisms of epigenetic modification include DNA methylation, histone modification (acetylation, methylation and phosphorylation), and microRNAs (miRNAs). Unlike genetic modifications, epigenetic states of genes are reversible and can be altered by certain intrinsic and extrinsic factors. In the past few decades, accumulated evidence shows that dietary phytochemicals with chemopreventive effects are also potent epigenetic regulators. Resveratrol and pterostilbene are stilbenoids, which have been reported to have anti-cancer, anti-inflammatory, anti-lipid, and anti-diabetic properties. Stilbenoids are also reported to improve cardiovascular disease. By altering DNA methylation and histone modification or by modulating miRNA expression, resveratrol, and pterostilbene become potent epigenetic modifiers. In this review, we summarize these studies and underlying mechanisms of resveratrol and pterostilbene and their influence on epigenetic mechanisms.
Multiple pathway assessment to predict anti-atherogenic efficacy of drugs targeting macrophages in atherosclerotic plaques.


Abstract

BACKGROUND:
Macrophages play a central role in atherosclerosis development and progression, hence, targeting macrophage activity is considered an attractive therapeutic. Recently, we documented nanomedicinal delivery of the anti-inflammatory compound prednisolone to atherosclerotic plaque macrophages in patients, which did however not translate into therapeutic efficacy. This unanticipated finding calls for in-depth screening of drugs intended for targeting plaque macrophages.

METHODS AND RESULTS:
We evaluated the effect of several candidate drugs on macrophage activity, rating overall performance with respect to changes in cytokine release, oxidative stress, lipid handling, endoplasmic reticulum (ER) stress, and proliferation of macrophages. Using this in vitro approach, we observed that the anti-inflammatory effect of prednisolone was counterbalanced by multiple adverse effects on other key pathways. Conversely, pterostilbene, T0901317 and simvastatin had an overall anti-atherogenic effect on multiple pathways, suggesting their potential for liposomal delivery.

CONCLUSION:
This dedicated assay setup provides a framework for high-throughput assessment. Further in vivo studies are warranted to determine the predictive value of this macrophage-based screening approach and its potential value in nanomedicinal drug development for cardiovascular patients.

Effect of resveratrol and pterostilbene on aging and longevity.

Li YR1,2, Li S3, Lin CC2,4,5.

Author information

Abstract

Over the past years, several studies have found that foods rich in polyphenols protect against age-related disease, such as atherosclerosis, cardiovascular disease, cancer, arthritis, cataracts, osteoporosis, type 2 diabetes (T2D), hypertension and Alzheimer's disease. Resveratrol and pterostilbene, the polyphenol found in grape and blueberries, have beneficial effects as anti-aging compounds through modulating the hallmarks of aging, including oxidative damage, inflammation, telomere attrition and cell senescence. In this review, we discuss the relationship between resveratrol and pterostilbene and possible aging biomarker, including oxidative stress, inflammation, and high-calorie diets. Moreover, we also discuss the positive effect of resveratrol and pterostilbene on lifespan, aged-related disease, and health maintenance. Furthermore, we summarize a variety of important mechanisms modulated by resveratrol and pterostilbene possibly involved in attenuating age-associated disorders. Overall, we describe resveratrol and pterostilbene potential for prevention or treatment of several age-related diseases by modulating age-related mechanisms.


KEYWORDS:
aging; healthspan; lifespan; pterostilbene; resveratrol


[Chemopreventive and chemotherapeutic effect of trans-resveratrol and its analogues in cancer].
[Article in Polish]

Mikstacka R1, Ignatowicz E.

Author information
Abstract

Trans-resveratrol (3,5,4'-trihydroxy-trans-stilbene), a natural polyphenol, displays diversified bioactivities that are crucial in chemoprevention of cancer and cardiovascular diseases. Equally promising action is exerted by resveratrol analogues, mainly pterostilbene (3,5-dimethoxy-4'-hydroxy-trans-stilbene) and piceatannol (3,5,3', 4'-tetrahydroxy-trans-stilbene). Although fruits and their products are the main natural source of resveratrol and their analogues, recently these polyphenols have been commercially available in numerous pharmaceutical preparations and diet supplements. The aim of this review is to present the status of clinical studies on chemopreventive/chemotherapeutic effect of resveratrol and its analogues.

PMID: 20642113


Pterostilbene protects against myocardial ischemia/reperfusion injury via suppressing oxidative/nitrative stress and inflammatory response.

Yu Z1, Wang S2, Zhang X3, Li Y1, Zhao Q4, Liu T5.

Author information

Abstract

Recent studies have shown that pterostilbene (Pte) confers protection against myocardial ischemia/reperfusion injury. The oxidative/nitrative stress and inflammation induce injury after myocardial ischemia/reperfusion. The present study was designed to evaluate whether treatment with Pte attenuates oxidative/nitrative stress and inflammation in myocardial ischemia/reperfusion (MI/R). Rats were subjected to 30min of myocardial ischemia and 3h of reperfusion, and the rats were administered with vehicle or Pte. The results showed that Pte (10mg/kg) dramatically improved cardiac function and reduced myocardial infarction and myocardial apoptosis following MI/R. As an indicator of oxidative/nitrative stress, myocardial ONOO- content was markedly reduced after Pte treatment. And, Pte led to a dramatic decrease in superoxide generation and malondialdehyde (MDA) content and a dramatic increase in superoxide dismutase (SOD) activity. In addition, Pte treatment significantly reduced p38 MAPK activation and the expression of iNOS and gp91phox and increased phosphorylated eNOS expression. Pte treatment dramatically decreased myocardial TNF-α, and IL-1β levels and myeloperoxidase (MPO) activity. Furthermore, ONOO- suppression by either Pte or uric acid (UA), an ONOO- scavenger, reduced myocardial injury. In conclusion, Pte exerts a protective effect against MI/R injury by suppressing oxidative/nitrative stress. These results provide evidence that Pte might be a therapeutic approach for the treatment of MI/R injury.

KEYWORDS:
Inflammation; Myocardial ischemia/reperfusion injury; Oxidative/nitrative stress; Pterostilbene

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Nitric oxide mediates natural polyphenol-induced Bcl-2 down-regulation and activation of cell death in metastatic B16 melanoma.

Ferrer P1, Asensi M, Priego S, Benlloch M, Mena S, Ortega A, Obrador E, Esteve JM, Estrela JM.

Author information

Abstract

Intravenous administration to mice of trans-pterostilbene (t-PTER; 3,5-dimethoxy-4'-hydroxystilbene) and quercetin (QUER; 3,3',4',5,6-pentahydroxyflavone), two structurally related and naturally occurring small polyphenols, inhibits metastatic growth of highly malignant B16 melanoma F10 (B16M-F10) cells. t-PTER and QUER inhibit bcl-2 expression in metastatic cells, which sensitizes them to vascular endothelium-induced cytotoxicity. However, the molecular mechanism(s) linking polyphenol signaling and bcl-2 expression are unknown. NO is a potential bioregulator of apoptosis with controversial effects on Bcl-2 regulation. Polyphenols may affect NO generation. Short-term exposure (60 min/day) to t-PTER (40 microM) and QUER (20 microM) (approximate mean values of the plasma concentrations measured within the first hour after intravenous administration of 20 mg of each polyphenol/kg) down-regulated inducible NO synthetase in B16M-F10 cells and up-regulated endothelial NO synthetase in the vascular endothelium and thereby facilitated endothelium-induced tumor cytotoxicity. Very low and high NO levels down-regulated bcl-2 expression in B16M-F10 cells. t-PTER and QUER induced a NO shortage-dependent decrease in cAMP-response element-binding protein phosphorylation, a positive regulator of bcl-2 expression, in B16M-F10 cells. On the other hand, during cancer and endothelial cell interaction, t-PTER- and QUER-induced NO release from the vascular endothelium up-regulated neutral sphingomyelinase activity and ceramide generation in B16M-F10 cells. Direct NO-induced cytotoxicity and ceramide-induced mitochondrial permeability transition and apoptosis activation can explain the increased endothelium-induced death of Bcl-2-depleted B16M-F10 cells.

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Direct ingestion method for enhancing production and bioavailability of resveratrol and other phytoalexins in Vitis vinifera.

Leifer A, Barberio DM.

Author information

Abstract

Phytoalexins such as resveratrol and pterostilbene, produced de novo by many plant species, including grapevine (Vitis vinifera), play a role in plant defense against injury and pathogens. In human cell lines and in animal studies, phytoalexins have been shown to be highly beneficial, with protective effects against cancer, cardiovascular disease, neurodegenerative diseases, diabetes, hyperglycemia, as well as potential effects on longevity. However, in clinical studies, there are multiple factors that restrict this plethora of health benefits attributed to phytoalexins. One of these barriers is rapid metabolism in the intestines and liver. As a means to overcome this barrier, there is evidence that retaining resveratrol in the mouth for extended periods allows for higher plasma levels of resveratrol. Processing, transport or storage may cause degradation due to light and air exposure. When the berries have been picked, they may not be at their peak phytoalexin production due to lack of elicitor induction. To overcome these barriers inherent in phytoalexin production and uptake, it is proposed that berries and possibly the edible leaves be directly ingested off of a grapevine, without harvesting. In addition to the benefit of removing these barriers to potential health benefits, this method introduces a variety of known phytoalexin elicitors, in the form of plant wounding and human saliva, which may enhance the levels of phytoalexins dramatically. The combined effect of multiple phytoalexins may also play a role in enhanced health benefits. To test this hypothesis, experiments with direct ingestion would be performed, followed by testing the participants' plasma levels of resveratrol and potentially other phytoalexins. Proposed variables to be tested include: different subjects, elicitors, cultivars of grapevine, ripeness of fruit, and a range of time for the ingestion process. The potential implications include a direct means of obtaining, in clinically beneficial doses, the tremendous health benefits that have been documented for phytoalexins in vitro and in animal studies, but that have so far remained elusive in clinical studies. This study on direct ingestion may lead to alternative methods for obtaining these clinically beneficial doses.

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Pterostilbene protects against uraemia serum-induced endothelial cell damage via activation of Keap1/Nrf2/HO-1 signaling.

Chen ZW1, Miu HF1, Wang HP2, Wu ZN2, Wang WJ1, Ling YJ2, Xu XH2, Sun HJ2, Jiang X3.
Author information

Abstract

Chronic kidney disease causes uremia-related endothelial cell dysfunction associated with high risk for cardiovascular diseases. The vascular endothelium is permanently exposed to uraemic toxins including indoxyl sulfate, which provokes endothelial damage in subjects with end-stage renal disease. Pterostilbene (PT) is identified to be homologous derivative of resveratrol and exerts antioxidant and anti-inflammatory actions. However, the effects of PT on uraemic serum-induced endothelial cell damage have not been elucidated. In this study, we investigated the effects and mechanisms of PT on uraemic serum (US)-mediated injury in human umbilical vein endothelial cells (HUVECs). Treatment of US obviously reduced cell viability, inhibited superoxide dismutase activity and catalase activity, suppressed phosphorylated endothelial nitric oxide synthase (eNOS) protein level and eNOS activity, whereas promoted lactate dehydrogenase leakage, increased malondialdehyde, hydrogen peroxide, superoxide anions levels and NAD(P)H activity accompanied with increased nitrative stress and inflammatory response in HUVECs, and these changes were reversed after PT treatment. Under US environment, PT downregulated Kelch-like ECH-associated protein 1 (Keap1) and upregulated nuclear factor erythroid-2-related factor 2 (Nrf2) and its downstream target heme oxygenase-1 (HO-1) protein levels. Of note, the level of HO-1 was decreased after the transfection of cells with Nrf2-siRNA, and HO-1 inhibitor Snpp abolished the protective effects of PT on HUVECs in response to US. Collectively, our study demonstrated that PT is effective in reducing US-evoked endothelial cell dysfunction via suppression of oxidative/nitrative stress and inflammatory response, which at least partly depended on Keap1/Nrf2/HO-1 signaling pathway.

KEYWORDS:
Chronic kidney disease; Endothelial cell; Nrf2; Pterostilbene; Uremia

PMID: 29094331 DOI: 10.1007/s11255-017-1734-4


Protective Effects of Pterostilbene Against Myocardial Ischemia/Reperfusion Injury in Rats.

Wu M1,2, Lu S1, Zhong J1, Huang K1, Zhang S3.

Author information

Abstract

Pterostilbene (PTB) has been suggested to protect against myocardial ischemia/reperfusion (MI/R) injury. Gas6/Axl signaling has been suggested to play an important role in cell survival. However, the interaction between PTB and Gas6/Axl signaling in MI/R remains unclear. This study aims to evaluate the role of Gas6/Axl signaling in the protective effects of PTB against...
MI/R injury. In experiment 1, the rats were subjected to 30 min of ischemia, followed by 3, 6, and 12 h of reperfusion, respectively. In experiment 2, the rats were administered intraperitoneally with PTB or vehicle and subjected to MI/R injury. The results suggested that the expression of Gas6 and Axl decreased significantly after MI/R injury. PTB treatment conferred a cardioprotective effect with an improved post-ischemic cardiac function, a reduced myocardial infarct size, and decreased lactate dehydrogenase and creatine kinase-MB in the serum, a decreased oxidative stress and inflammation, and a reduced number of apoptotic cardiomyocytes. Moreover, PTB treatment up-regulated the expression of Gas6, Axl, and Bcl-2 and down-regulated Bax expression. Our findings suggest that PTB treatment exerts cardioprotection against MI/R injury via attenuating inflammatory response, oxidative stress, and apoptosis and up-regulating the expression of Gas6 and Axl. The application of PTB may be a new strategy for the treatment of MI/R injury.

KEYWORDS: Gas6/Axl signaling; inflammation; myocardial ischemia/reperfusion injury; oxidative stress; pterostilbene

PMID: 28054238 DOI: 10.1007/s10753-016-0504-2


Pterostilbene attenuates high glucose-induced oxidative injury in hippocampal neuronal cells by activating nuclear factor erythroid 2-related factor 2.


Author information

Abstract

In the present study, neuroblastoma (SH-SY5Y) cells were used to investigate the mechanisms mediating the potential protective effects of pterostilbene (PTE) against mitochondrial metabolic impairment and oxidative stress induced by hyperglycemia for mimicking the diabetic encephalopathy. High glucose medium (100mM) decreased cellular viability after 24h incubation which was evidenced by: (i) reduced mitochondrial complex I and III activities; (ii) reduced mitochondrial cytochrome C; (iii) increased reactive oxygen species (ROS) generation; (iv) decreased mitochondrial membrane potential (ΔΨm); and (v) increased lactate dehydrogenase (LDH) levels. PTE (2.5, 5, and 10μM for 24h) was nontoxic and induced the nuclear transition of Nrf2. Pretreatment of PTE (2.5, 5, and 10μM for 2h) displayed a dose-dependently neuroprotective effect, as indicated by significantly prevented high glucose-induced loss of cellular viability, generation of ROS, reduced mitochondrial complex I and III activities, reduced mitochondrial cytochrome C, decreased ΔΨm, and increased LDH levels. Moreover, the
levels of nuclear factor erythroid 2-related factor 2 (Nrf2), heme oxygenase-1 (HO-1) and glutathione S-transferase (GST) were elevated after PTE treatment. In addition, the elevation of nuclear Nrf2 by PTE treatment (10μM for 2h) was abolished by Nrf2 siRNA. Importantly, Nrf2 siRNA induced the opposite changes in mitochondrial complex I and III activities, mitochondrial cytochrome C, reactive species generation, ΔΨm, and LDH. Overall, the present findings were the first to show that pterostilbene attenuated high glucose-induced central nervous system injury in vitro through the activation of Nrf2 signaling, displaying protective effects against mitochondrial dysfunction-derived oxidative stress.

**KEYWORDS:**
High glucose; Neuroprotection; Nuclear factor erythroid 2-related factor 2 signaling; Oxidative stress; Pterostilbene

PMID: 28089584 DOI: 10.1016/j.bbadis.2017.01.005


**Pterostilbene exerts anticancer activity on non-small-cell lung cancer via activating endoplasmic reticulum stress.**

Ma Z1, Yang Y2,3,4, Di S1, Feng X5, Liu D6, Jiang S7, Hu W4, Qin Z5, Li Y4, Lv J4, Fan C8, Yan X9, Li X10.

**Author information**

**Abstract**

Pterostilbene (PT), the natural dimethylated analog of resveratrol (RSV), is a potent anticarcinogen for non-small-cell lung cancer (NSCLC), but its anti-NSCLC mechanisms remain unclear. In this study, we show that PT treatment time- and dose-dependently enhanced the endoplasmic reticulum stress (ERS) signaling (i.e., p-PERK, IRE1, ATF4, CHOP), thus decreasing the cell viability and inducing apoptosis in human PC9 and A549 NSCLC cell lines. Moreover, the decreased migratory and adhesive abilities, downregulation of intracellular glutathione (GSH) level, enhanced reactive oxygen species (ROS) generation, Caspase 3 activity and mitochondrial membrane depolarization were observed in NSCLC cells treated with PT. These effects were reversed by CHOP siRNA which inhibited the ERS signaling pathway, but were promoted by thapsigargin (a classical ERS inducer) in vitro. Besides, in vivo studies also verify that PT exerted anticancer activity by mobilizing ERS signaling and apoptosis-related proteins, and these effects were enhanced by thapsigargin. Therefore, ERS activation may represent a new mechanism of anti-NSCLC action by PT, and a novel therapeutic intervention for lung cancer.

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Anti-inflammatory activity of natural stilbenoids: A review.

Dvorakova M1, Landa P2.

Author information

Abstract

Resveratrol and other natural stilbenoids, including piceatannol, pterostilbene, and gnetol, are well-known anti-inflammatory compounds with indisputable activity in vitro as well as in vivo. Their molecular targets include inducible nitric oxide synthase, cyclooxygenases, leukotrienes, nuclear factor kappa B, tumor necrosis factor α, interleukins and many more. This anti-inflammatory activity together with their antioxidant activity is believed to stand behind their other positive health effects against cancer, cardiovascular and neurodegenerative diseases or diabetes. Thus, they are nowadays commercially marketed as nutraceuticals. Naturally, they are present in wine, grapes or berries. However, there is a rigorous debate about the real effect of these compounds on human health. It is argued that the concentration of stilbenoids in food and beverages is too low to have any therapeutic potential and this concentration is further reduced by their low bioavailability and extensive metabolism. Therefore, this review focuses on in vitro, in vivo, preclinical as well as clinical data available for various natural stilbenoids and summarizes the anti-inflammatory targets on molecular level, compares the relevance of the experimental studies, discusses the metabolism of stilbenoids and the potential activity of their metabolites and relates this knowledge to human health. Moreover, the ways to augment stilbenoids efficacy are suggested with special focus on multitargeted therapy and nanocarriers.

KEYWORDS:
Bioavailability; Encapsulation; Inflammation; Metabolites; Multi-targeted therapy; Natural stilbenes

PMID: 28803136 DOI: 10.1016/j.phrs.2017.08.002


Disparate Effects of Stilbenoid Polyphenols on Hypertrophic Cardiomyocytes In Vitro vs. in the Spontaneously Hypertensive Heart Failure Rat.

Akinwumi BC1,2, Raj P3,4,5, Lee DI6,7, Acosta C8,9, Yu L10,11, Thomas SM12, Nagabhushanam K13, Majeed M14,13, Davies NM15,16, Netticadan T17,18,19, Anderson HD20,21,22.

Author information

Abstract
Stilbenoids are bioactive polyphenols, and resveratrol (trans-3,5,4-trihydroxystilbene) is a representative stilbenoid that reportedly exerts cardioprotective actions. As resveratrol exhibits low oral bioavailability, we turned our attention to other stilbenoid compounds with a history of medicinal use and/or improved bioavailability. We determined the effects of gnetol (trans-3,5,20,60-tetrahydroxystilbene) and pterostilbene (trans-3,5-dimethoxy-40-hydroxystilbene) on cardiac hypertrophy. In vitro, gnetol and pterostilbene prevented endothelin-1-induced indicators of cardiomyocyte hypertrophy including cell enlargement and protein synthesis. Gnetol and pterostilbene stimulated AMP-activated protein kinase (AMPK), and inhibition of AMPK, using compound C or shRNA knockdown, abolished these anti-hypertrophic effects. In contrast, resveratrol, gnetol, nor pterostilbene reduced blood pressure or hypertrophy in the spontaneously hypertensive heart failure (SHHF) rat. In fact, AMPK levels were similar between Sprague-Dawley and SHHF rats whether treated by stilbenoids or not. These data suggest that the anti-hypertrophic actions of resveratrol (and other stilbenoids?) do not extend to the SHHF rat, which models heart failure superimposed on hypertension. Notably, SHHF rat hearts exhibited prolonged isovolumic relaxation time (an indicator of diastolic dysfunction), and this was improved by stilbenoid treatment. In conclusion, stilbenoid-based treatment as a viable strategy to prevent pathological cardiac hypertrophy, a major risk factor for heart failure, may be context-dependent and requires further study.

KEYWORDS: heart failure; hypertension; polyphenol; resveratrol; stilbenoid

PMID: 28157155 DOI: 10.3390/molecules22020204


Peripheral and Cerebral Resistance Arteries in the Spontaneously Hypertensive Heart Failure Rat: Effects of Stilbenoid Polyphenols.

Lee DI1,2, Acosta C3,4,5, Anderson CM6,7, Anderson HD8,9,10.

Author information

Abstract

Hypertension is associated with aberrant structure and mechanical properties of resistance arteries. We determined the effects of resveratrol, a non-flavonoid polyphenol found in foods such as red grapes, and structurally-similar analogues (pterostilbene and gnetol) on systolic blood pressure (SBP) and resistance arteries from the spontaneously hypertensive heart failure (SHHF) rat. SBP was elevated in 17-week-old SHHF vs. Sprague-Dawley rats (normotensive control; 194 ± 3 vs. 142 ± 6 mmHg, p < 0.01) and was unaffected by resveratrol, pterostilbene, or gnetol (2.5 mg/kg/d). Geometry and mechanical properties of pressurized mesenteric resistance arteries and middle cerebral arteries were calculated from media and lumen...
dimensions measured at incremental intraluminal pressures. SHHF arteries exhibited remodeling which consisted of augmented media-to-lumen ratios, and this was attenuated by stilbenoid treatment. Compliance was significantly reduced in SHHF middle cerebral arteries but not mesenteric arteries vis-à-vis increased wall component stiffness; stilbenoid treatment failed to normalize compliance and wall component stiffness. Our data suggest that neither AMPK nor ERK mediate stilbenoid effects. In conclusion, we observed arterial bed-specific abnormalities, where mesenteric resistance arteries exhibited remodeling and cerebral arteries exhibited remodeling and stiffening. Resveratrol, pterostilbene, and gnetol exhibited similar abilities to attenuate vascular alterations.

**KEYWORDS:**
compliance; polyphenol; remodeling; resistance arteries; resveratrol; stilbenoid

PMID: 28264510 DOI: 10.3390/molecules22030380
Cholesterol


Pterostilbene on metabolic parameters: a randomized, double-blind, and placebo-controlled trial.

Riche DM1, Riche KD2, Blackshear CT3, McEwen CL4, Sherman JJ5, Wofford MR6, Griswold ME7.

Author information

Abstract

INTRODUCTION:
The purpose of this trial was to evaluate the effect of pterostilbene on metabolic parameters.

METHODS:
A prospective, randomized, double-blind, and placebo-controlled study that enrolled 80 patients with a total cholesterol ≥200 mg/dL and/or LDL ≥ 100 mg/dL. Subjects were divided into four groups: (1) pterostilbene 125 mg twice daily; (2) pterostilbene 50 mg twice daily; (3) pterostilbene 50 mg + grape extract (GE) 100 mg twice daily; (4) matching placebo twice daily for 6-8 weeks. Endpoints included lipids, blood pressure, and weight. Linear mixed models were used to examine and compare changes in parameters over time. Models were adjusted for age, gender, and race.

RESULTS:
LDL increased with pterostilbene monotherapy (17.1 mg/dL; P = 0.001) which was not seen with GE combination (P = 0.47). Presence of a baseline cholesterol medication appeared to attenuate LDL effects. Both systolic (-7.8 mmHg; P < 0.01) and diastolic blood pressure (-7.3 mmHg; P < 0.001) were reduced with high dose pterostilbene. Patients not on cholesterol medication (n = 51) exhibited minor weight loss with pterostilbene (-0.62 kg/m(2); P = 0.012).

CONCLUSION:
Pterostilbene increases LDL and reduces blood pressure in adults. This trial is registered with Clinicaltrials.gov NCT01267227.

PMID: 25057276 PMCID: PMC4099343 DOI: 10.1155/2014/459165

Protective effects of pterostilbene against acetaminophen-induced hepatotoxicity in rats.

El-Sayed el-SM1, Mansour AM, Nady ME.

Author information

Abstract

The present study was undertaken to evaluate the protective effect of pterostilbene against acetaminophen-induced hepatotoxicity. Silymarin was used as a standard hepatoprotective agent. A single dose of acetaminophen (800 mg/kg i.p.), injected to male rats, caused significant increases in serum levels of alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, bilirubin, total cholesterol, triglycerides, tumor necrosis factor alpha, and hepatic contents of malondialdehyde, nitric oxide, caspase-3, hydroxyproline, with significant decreases in serum HDL-cholesterol, total proteins, albumin, and hepatic activities of reduced glutathione, superoxide dismutase and catalase as compared with the control group. On the other hand, administration of each of pterostilbene (50 mg/kg, p.o.) and silymarin (100 mg/kg, p.o.) for 15 days before acetaminophen ameliorated liver function and oxidative stress parameters. Histopathological evidence confirmed the protection offered by pterostilbene from the tissue damage caused by acetaminophen. In conclusion, pterostilbene possesses multimechanistic hepatoprotective activity that can be attributed to its antioxidant, anti-inflammatory, and antiapoptotic actions.

KEYWORDS:
Acetaminophen; Antioxidant; Hepatotoxicity; Pterostilbene; Silymarin

PMID: 25201704 DOI: 10.1002/jbt.21604


Analysis of safety from a human clinical trial with pterostilbene.

Riche DM1, McEwen CL, Riche KD, Sherman JJ, Wofford MR, Deschamp D, Griswold M.

Author information

Abstract

OBJECTIVES:
The purpose of this trial was to evaluate the safety of long-term pterostilbene administration in humans.
METHODOLOGY:
The trial was a prospective, randomized, double-blind placebo-controlled intervention trial enrolling patients with hypercholesterolemia (defined as a baseline total cholesterol ≥200 mg/dL and/or baseline low-density lipoprotein cholesterol ≥100 mg/dL). Eighty subjects were divided equally into one of four groups: (1) pterostilbene 125 mg twice daily, (2) pterostilbene 50 mg twice daily, (3) pterostilbene 50 mg + grape extract (GE) 100 mg twice daily, and (4) matching placebo twice daily for 6-8 weeks. Safety markers included biochemical and subjective measures. Linear mixed models were used to estimate primary safety measure treatment effects.

RESULTS:
The majority of patients completed the trial (91.3%). The average age was 54 years. The majority of patients were females (71%) and Caucasians (70%). There were no adverse drug reactions (ADRs) on hepatic, renal, or glucose markers based on biochemical analysis. There were no statistically significant self-reported or major ADRs.

CONCLUSION:
Pterostilbene is generally safe for use in humans up to 250 mg/day.

PMID: 23431291 PMCID: PMC3575612 DOI: 10.1155/2013/463595


Long term induction by pterostilbene results in autophagy and cellular differentiation in MCF-7 cells via ROS dependent pathway.

Chakraborty A1, Bodipati N, Demonacos MK, Peddinti R, Ghosh K, Roy P.

Author information

Abstract

This study shows the effect of pterostilbene on intracellular neutral lipid accumulation in MCF-7 breast cancer cells leading to growth arrest and autophagy. On exposing the breast cancer cells with 30 μM pterostilbene for 72 h there was almost 2-folds increase in neutral lipids and triglycerides. Also the phytochemical caused a 4-folds increase in the expression of adipogenic differentiation marker c/EBPα. Further, pterostilbene inhibited 3β-hydroxysterol-Δ(7)-reductase, the enzyme which catalyzes the last step conversion of 7-dehydrocholesterol to cholesterol, and thereby causes the intracellular accumulation of the former sterol. These results were associated with over-expression of oxysterol binding protein homologue and liver X receptor (LXR) by ~7-folds. Pterostilbene also caused a simultaneous increase in the expression autophagic marker proteins Beclin 1 and LC3 II (microtubule-associated protein 1 light chain 3) by approximately 6-folds, which leads to an alternative pathway of autophagy. These effects were observed in association with the loss of mitotic and metastatic potential of MCF-7 cells which was abolished
in the presence of catalase (ROS scavenger) or 3MA (autophagic inhibitor). Thus the present data shows that the long term exposure to pterostilbene causes growth arrest in MCF-7 cells which may be due to differentiation of the mammary carcinoma cells into normal epithelial cell like morphology and activation of autophagy.

PMID: 22273805 DOI: 10.1016/j.mce.2012.01.009


Pterostilbene, a new agonist for the peroxisome proliferator-activated receptor alpha-isoform, lowers plasma lipoproteins and cholesterol in hypercholesterolemic hamsters.

Rimando AM1, Nagmani R, Feller DR, Yokoyama W.

Author information

Abstract

Resveratrol, a stilbenoid antioxidant found in grapes, wine, peanuts and other berries, has been reported to have hypolipidemic properties. We investigated whether resveratrol and its three analogues (pterostilbene, piceatannol, and resveratrol trimethyl ether) would activate the peroxisome proliferator-activated receptor alpha (PPARalpha) isoform. This nuclear receptor is proposed to mediate the activity of lipid-lowering drugs such as the fibrates. The four stilbenes were evaluated at 1, 10, 100, and 300 microM along with ciprofibrate (positive control), for the activation of endogenous PPARalpha in H4IIEC3 cells. Cells were transfected with a peroxisome proliferator response element-AB (rat fatty acyl CoA beta-oxidase response element)-luciferase gene reporter construct. Pterostilbene demonstrated the highest induction of PPARalpha showing 8- and 14-fold increases in luciferase activity at 100 and 300 microM, respectively, relative to the control. The maximal luciferase activity responses to pterostilbene were higher than those obtained with the hypolipidemic drug, ciprofibrate (33910 and 19460 relative luciferase units, respectively), at 100 microM. Hypercholesterolemic hamsters fed with pterostilbene at 25 ppm of the diet showed 29% lower plasma low density lipoprotein (LDL) cholesterol, 7% higher plasma high density lipoprotein (HDL) cholesterol, and 14% lower plasma glucose as compared to the control group. The LDL/HDL ratio was also statistically significantly lower for pterostilbene, as compared to results for the control animals, at this diet concentration. Results from in vitro studies showed that pterostilbene acts as a PPARalpha agonist and may be a more effective PPARalpha agonist and hypolipidemic agent than resveratrol. In vivo studies demonstrate that pterostilbene possesses lipid and glucose lowering effects.

PMID: 15853379 DOI: 10.1021/jf0580364

Anti-inflammatory action of pterostilbene is mediated through the p38 mitogen-activated protein kinase pathway in colon cancer cells.

Paul S1, Rimando AM, Lee HJ, Ji Y, Reddy BS, Suh N.

Author information

Abstract

Oxidative/nitrosative stress and generation of proinflammatory cytokines are hallmarks of inflammation. Because chronic inflammation is implicated in several pathologic conditions in humans, including cancers of the colon, anti-inflammatory compounds may be useful chemopreventive agents against colon cancer. Stilbenes, such as resveratrol, have diverse pharmacologic activities, which include anti-inflammation, cancer prevention, a cholesterol-lowering effect, enhanced insulin sensitivity, and increased life span. We previously showed that pterostilbene (trans-3,5-dimethoxy-4'-hydroxystilbene), a structural analogue of resveratrol, is present in blueberries and that pterostilbene inhibited expression of certain inflammation-related genes in the colon and suppressed aberrant crypt foci formation in rats. Here, we examined molecular mechanisms of the action of pterostilbene in colon cancer. Pterostilbene reduced cell proliferation, down-regulated the expression of c-Myc and cyclin D1, and increased the level of cleaved poly(ADP-ribose) polymerase. A combination of cytokines (tumor necrosis factor-alpha, IFN-gamma, and bacterial endotoxin lipopolysaccharide) induced inflammation-related genes such as inducible nitric oxide synthase and cyclooxygenase-2, which was significantly suppressed by treatment with pterostilbene. We further identified upstream signaling pathways contributing to the anti-inflammatory activity of pterostilbene by investigating multiple signaling pathways, including nuclear factor-kappaB, Janus-activated kinase-signal transducer and activator of transcription, extracellular signal-regulated kinase, p38, c-Jun NH(2)-terminal kinase, and phosphatidylinositol 3-kinase. Cytokine induction of the p38-activating transcription factor 2 pathway was markedly inhibited by pterostilbene among the different mediators of signaling evaluated. By silencing the expression of the p38 alpha isoform, there was significant reduction in cytokine induction of inducible nitric oxide synthase and cyclooxygenase-2. Our data suggest that the p38 mitogen-activated protein kinase cascade is a key signal transduction pathway for eliciting the anti-inflammatory action of pterostilbene in cultured HT-29 colon cancer cells.

PMID: 19549798 PMCID: PMC2753521 DOI: 10.1158/1940-6207.CAPR-08-0224


Anti-hyperlipidememic and anti-peroxidative role of pterostilbene via Nrf2 signaling in experimental diabetes.
Nuclear factor erythroid 2-related factor (Nrf2), a key transcription factor triggers the expression of antioxidant and detoxification genes thereby providing cellular protective functions against oxidative stress-mediated disorders. Recent research has identified that pharmacological activation of Nrf2 also regulates the largest cluster of genes associated with lipid metabolism. With this background, this paper highlights the anti-hyperlipidemic and anti-peroxidative role of pterostilbene (PTS), an Nrf2 activator, in streptozotocin (STZ)-induced diabetic model. PTS administration to diabetic mice for 5 weeks significantly regulated blood glucose levels through the elevation of insulin secretion. The circulatory and liver lipid profiles of total cholesterol (TC), triglycerides (TG) and non-esterified fatty acids (NEFA) were maintained to normal levels upon PTS treatment. Moreover, PTS administration also normalized the circulatory levels of very low-, low- and high density lipoprotein cholesterol (VLDL-, LDL-, HDL-) and also reduced lipid peroxidation in STZ-induced diabetic mice. In addition, Nrf2 and its downstream targets, superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx) enzyme activities and glutathione (GSH) levels were significantly elevated in liver tissues of diabetic mice upon PTS administration. Further, H&E staining of diabetic mouse liver showed collapse in hepatic microvesicles due to altered lipid metabolism. Both structural and functional alterations were attenuated by PTS indicating its role in diabetic dyslipidemia through Nrf2-mediated mechanism that could be considered as a promising therapeutic agent.

**KEYWORDS:**
Diabetes; Dyslipidemia; Lipids; Nrf2; Pterostilbene; Streptozotocin

PMID: 26921755 DOI: 10.1016/j.ejphar.2016.02.054


**Suppression of Nitric Oxide Production and Cardiovascular Risk Factors in Healthy Seniors and Hypercholesterolemic Subjects by a Combination of Polyphenols and Vitamins.**

Qureshi AA1, Khan DA, Mahjabeen W, Papasian CJ, Qureshi N.

**Author information**

**Abstract**

**BACKGROUND:**
Dysregulated immune function associated with ageing has been implicated in a variety of human diseases. We have demonstrated the anti-inflammatory properties of resveratrol, pterostilbene, morin hydrate, quercetin, δ-tocotrienol, riboflavin in a variety of experimental animal models, and determined that these compounds act by inhibiting proteasome activity.

AIMS:
To determine whether serum nitric oxide (NO) levels increase with age in humans, and whether the combined cholesterol-lowering and inflammation-reducing properties of resveratrol, pterostilbene, Morin hydrate, quercetin, δ-tocotrienol, riboflavin, and nicotinic acid would reduce cardiovascular risk factors in humans when used as nutritional supplements with, or without, other dietary changes.

METHODS:
Elderly human subjects were stratified into two groups based on total serum cholesterol levels. Initial total serum cholesterol levels were normal and elevated in Group 1 and 2 subjects, respectively. Baseline serum NO, C-reactive protein (CRP), γ-glutamyltransferase (γ-GT) activity, uric acid, total antioxidant status (TAS), total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglycerides levels were established over a four week period. Group 1 subjects subsequently received nutritional supplementation with one of two different combinations (NS-7 = 25 mg of each, resveratrol, pterostilbene, quercetin, δ-tocotrienol, nicotinic acid, morin hydrate or NS-6 = morin hydrate replaced with quercetin, 50 mg/capsule). Group 2 subjects also received these nutritional supplements (two capsules/d), but an AHA Step-1 diet was also implemented. After these interventions were administered for four weeks, the above parameters were re-measured and changes from baseline levels determined. Nitric acid (NO) levels in children, young adults, and seniors were also compared.

RESULTS:
The key results of the current study were: 1) that serum NO levels were significantly increased in seniors compared to both children (~80%) and young adults (~65%); 2) that the intake of two capsules/d of NS-7 or NS-6 for four weeks significantly (P < 0.05) decreased serum NO (39%, 24%), CRP (19%, 21%), uric acid (6%, 12%) levels, and γ-GT activity (8%, 6%), respectively in free-living healthy seniors; 3) that serum NO (36%, 29%), CRP (29%, 20%), uric acid (6%, 9%) γ-GT activity (9%, 18%), total cholesterol (8%, 11%), LDL-cholesterol (10%, 13%), and triglycerides (16%, 23%) levels were significantly (P < 0.02) decreased in hypercholesterolemic subjects restricted to AHA Step-1 diet plus intake of SN-7 or SN-6 (two capsules/d), respectively; 4) that TAS was increased (3%, 9%; P < 0.05) in free-living healthy seniors receiving NS-7 or NS-6 alone, and in hypercholesterolemic subjects plus AHA Step-1 diet (20%, 12%; P < 0.02) with either of the combinations tested.

CONCLUSIONS:
Serum NO levels are elevated in elderly humans compared to children or young adults. Diet supplementation with combinations of resveratrol, pterostilbene, morin hydrate, quercetin, δ-tocotrienol, riboflavin, and nicotinic acid reduce cardiovascular risk factors in humans when used as nutritional supplements with, or without, other dietary changes.

PMID: 23125945 PMCID: PMC3486425 DOI: 10.4172/2155-9880.S5-008
**Design, synthesis, biological evaluation and docking studies of pterostilbene analogs inside PPARalpha.**

Mizuno CS1, Ma G, Khan S, Patny A, Avery MA, Rimando AM.

**Author information**

**Abstract**

Pterostilbene, a naturally occurring analog of resveratrol, has previously shown PPARalpha activation in H4IIEC3 cells and was found to decrease cholesterol levels in animals. In this study, analogs of pterostilbene were synthesized and their ability to activate PPARalpha was investigated. Among analogs that was synthesized (E)-4-[(3,5-dimethoxystyryl)phenyl dihydrogen phosphate showed activity higher than pterostilbene and control drug ciprofibrate. Docking of the stilbenes inside PPARalpha showed the presence of important hydrogen bond interactions for PPARalpha activation.

PMID: 18272370 DOI: 10.1016/j.bmc.2008.01.051

**Nutritional Supplement-5 with a Combination of Proteasome Inhibitors (Resveratrol, Quercetin, δ-Tocotrienol) Modulate Age-Associated Biomarkers and Cardiovascular Lipid Parameters in Human Subjects.**

Qureshi AA1, Khan DA, Mahjabeen W, Papasian CJ, Qureshi N.

**Author information**

**Abstract**

**BACKGROUND:**
Age-associated altered redox imbalances and dysregulated immune function, contribute to the development of a variety of age associated diseases. Inflammatory markers and lipid profiles are useful prognostic indicators of a variety of age-associated and cardiovascular diseases. We have previously studied the impact of several proteasome inhibitors on several markers of inflammation and lipid profiles in vitro, in vivo, in cell lines, animal models, and in human subjects. The current study represents an extension of this work. Our main hypothesis is that a
combination of various naturally-occurring proteasome inhibitors, which inhibits nitric oxide (NO), and C-reactive protein (CRP) mediated inflammation, will have better efficacy in the prevention and treatment of age-associated disorders including cardiovascular disease.

METHODS:
Two double blind, randomized, placebo-controlled cross-over trials were conducted to determine the impact of a mixture of NS-5 (resveratrol, pterostilbene, quercetin, δ-tocotrienol, nicotinic acid) on serum NO, CRP, γ-glutamyl-transferase (γ-GT) activity, total antioxidant status (TAS), total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides levels. Healthy seniors (Group-1; n = 32) free-living (A, B; 16/group), and hypercholesterolemic (Group-2; n = 64) subjects on AHA-Step-1-diet were divided into two groups (C, D; 32/group). Baseline levels were established for parameters as mentioned above. Groups A, C were administered 4-capsules/d of NS-5 and groups B, D, placebo (starch) for 6-weeks. Groups were crossed-over, followed by a 2-week wash-out period. Groups A, C were given 4-capsules/d of placebo and groups B, D, 4-capsules/d of NS-5 for 6-weeks. Groups C, D were continued on AHA-Step-1-diet.

RESULTS:
All the subjects completed each phase in both studies without any complaints. There were significant (P < 0.01 - 0.05) decreases in the serum levels of NO (30%, 26%), CRP (29%, 21%), γ-GT activity (14%, 17%), and blood pressure (systolic/diastolic, 3/6%, 3/3%) of Groups A and B, respectively, of free-living healthy seniors without affecting the total, HDL-, LDL-cholesterol or triglycerides compared to their respective baseline values. However, serum levels of NO (36%, 43%), CRP (31%, 48%), γ-GT (17%, 20%), total cholesterol (19%, 15%), LDL-cholesterol (28%, 20%), triglycerides (11%, 18%) of Groups C and D were significantly (P < 0.01-0.05) decreased with NS-5 treatment of hypercholesterolemic subjects compared to baseline values, without affecting the serum HDL-cholesterol levels. The serum levels of total antioxidant status (TAS) were increased (10%, 14%; P < 0.05) in Groups A and B, increased (19%, 24%; P < 0.02), and blood pressure (systolic/diastolic, 5/6%, 3/5%) in Groups C and D with NS-5 treatment, compared to respective baseline values.

CONCLUSIONS:
The consumption of NS-5 mixture decreased significantly serum NO, CRP and γ-GT levels, improved TAS and lipid profiles at risk cardiovascular and hold promise for delaying onset of age-associated diseases.

KEYWORDS:
Anti-inflammatory and anti-ageing agents; C-reactive protein (CRP); Nitric oxide (NO); Quercetin; Resveratrol; Total antioxidant status (TAS); γ-glutamyl-transferase (γ-GT); δ-tocotrienol

PMID: 24319627 PMCID: PMC3851026 DOI: 10.4172/2155-9880.1000238

Occurrence of resveratrol and pterostilbene in age-old darakchasava, an ayurvedic medicine from India.

Paul B1, Masih I, Deopujari J, Charpentier C.

Author information

Abstract

'Darakchasava' is a well known Indian herbal preparation of which the main ingredient is Vitis vinifera L. This 'ayurvedic' medicine is prescribed as a cardiotonic and also given for other disorders. HPLC analysis of this age old formulation revealed the presence of polyphenols like resveratrol and pterostilbene. These phenolic compounds are now known as antioxidants, cancer chemopreventive agents, and also known to reduce mortality from coronary heart disease by increasing high density lipoproteins like cholesterol and inhibiting platelet aggregation (Soleas, J.S., Diamandis, E.P., Goldberg, D.M., 1997. Resveratrol: a molecule whose time has come? and gone? Clin. Biochem. 30 (2), 91-113). The study of darakchasava becomes interesting in the light of these findings. A brief introduction of this medicinal preparation, its formulation, its analysis by HPLC, and some of its properties are discussed in this article.

PMID: 10624864


Chemical characterisation of bioactive compounds in Medicago sativa growing in the desert of Oman.

Hanif MA1,2, Al-Maskari AY2, Al-Sabahi JN3, Al-Hdhrami I2, Khan MM2, Al-Azkawi A4, Hussain AI5.

Author information

Abstract

Medicago sativa Linn growing in Omani desert were chemically characterised using flame photometry, inductively coupled plasma, gas chromatography-mass spectrometry and high performance liquid chromatographic (HPLC) analysis. HPLC analyses were performed to determine the phenolics and flavonoids present in M. sativa. The major compounds detected in M. sativa leaves were protchaechenic acid (3.22%), hydroxyl benzoic acid (1.05%), β-Phenyl caffeate (0.97%) and kaempherol (0.89%). Pterostilbene, a cholesterol-lowering compound, was detected in M. sativa.

KEYWORDS:
GC; HPLC; ICP analysis; Medicago sativa; medical plant
Synergistic combinatorial antihyperlipidemic study of selected natural antioxidants; modulatory effects on lipid profile and endogenous antioxidants.

Hannan PA1, Khan JA2, Ullah I1, Ullah S1.

Author information

Abstract

BACKGROUND:
Hyperlipidemia, a major pathological condition associated with disrupted lipid levels and physiological redox homeostasis. The excessive release of reactive oxygen species (ROS) leads to enhanced lipid peroxidation, aggravated atherosclerosis and oxidative stress. Integration of natural antioxidant blends in alone or with conventional treatments can alleviate these issues synergistically contributing least side effects. Published literature reported the efficacy of natural antioxidants as individual and in combinations in various conditions but less data is available on their evaluation in low dose ratio blends particularly in hypercholesterolemic diet.

METHODS:
Antihyperlipidemic effects of selected natural antioxidants; the phenolic oligomeric proanthocyanidins (OPC) and pterostilbene (PT) with niacin (NA) were investigated in current study. Their effects on lipid profile, lipid peroxidation and their aptitude to establish redox state between oxidants and antioxidants in body were evaluated in high cholesterol diet fed animal model. Male albino rabbits (n = 6) weighing 1.2-1.6 kg, supplemented with high cholesterol diet (400 mg/kg) for 12 weeks were used in the experiment. Antioxidants were administered individual high (100 mg/kg) and in low dose combinations (total dose = 100 mg/kg). Student's t test and one way analysis of variance (ANOVA) followed by Dunnet's test were used as statistical tools for evaluation.

RESULTS:
The results showed synergistic effects of low dose antioxidant blends. Therapies retarded elevation in blood lipid levels, lipid peroxidation and blood antioxidant depletion and consequently contributed in reestablishing redox homeostasis. The LDL/HDL ratio and atherogenic index were suppressed significantly in blend therapies with maximum effects of 59.3 and 25 % (p >0.001) observed in 50:30:20 ratios of OPC, NA and PT, compared to individual therapies 37 and 18 % max respectively. Moreover the results were also in close proximity with the statin therapy (52.66, 26.28 %).

CONCLUSION:
This study provides an evidence for natural antioxidants blends superiority over individual therapy in chronic diseases like hyperlipidemia. Such therapies in human equivalent doses can help in mitigating chronic illnesses in general populations.

**KEYWORDS:**
Atherosclerosis; Hyperlipidemia; Lipid peroxidation; Redox homeostasis; Synergism

PMID: 27613388 PMCID: PMC5016891 DOI: 10.1186/s12944-016-0323-3


**Biological/chemopreventive activity of stilbenes and their effect on colon cancer.**

Rimando AM1, Suh N.

**Author information**

**Abstract**

Colon cancer is one of the leading causes of cancer death in men and women in Western countries. Epidemiological studies have linked the consumption of fruits and vegetables to a reduced risk of colon cancer, and small fruits are particularly rich sources of many active phytochemical stilbenes, such as resveratrol and pterostilbene. Recent advances in the prevention of colon cancer have stimulated an interest in diet and lifestyle as an effective means of intervention. As constituents of small fruits such as grapes, berries and their products, stilbenes are under intense investigation as cancer chemopreventive agents. One of the best-characterized stilbenes, resveratrol, has been known as an antioxidant and an anti-aging compound as well as an anti-inflammatory agent. Stilbenes have diverse pharmacological activities, which include cancer prevention, a cholesterol-lowering effect, enhanced insulin sensitivity, and increased lifespan. This review summarizes results related to the potential use of various stilbenes as cancer chemopreventive agents, their mechanisms of action, as well as their pharmacokinetics and efficacy for the prevention of colon cancer in animals and humans.

PMID: 18843589 DOI: 10.1055/s-0028-1088301
Glucose


Pterostilbene impact on retinal endothelial cells under high glucose environment.

Shen H1, Rong H2.

Author information

Abstract

Diabetic retinopathy (DR) has complicated pathogenic factors. Studies showed that DR belongs to chronic inflammatory disease, and retinal endothelial cells oxidation by free radicals is one of its mechanisms. Pterostilbene, as the homologous derivative of resveratrol, has obvious antioxidant effect. Its influence on the DR has not been studied. This study intended to investigate the effect and mechanism of pterostilbene on human retinal endothelial cells (hRECs) under high glucose environment to illustrate pterostilbene impact on DR and provide basis for DR clinical treatment. hRECs cultured in high glucose environment were treated by 1.0 mmol/L pterostilbene. MTT assay was applied to test cell proliferation. ELISA was used to detect inflammatory factor TNF-α and IL-1β content. Real time PCR and Western blot were performed to examine NF-κB mRNA and protein expression. ROS and SOD activities were analyzed. Under high glucose environment, hRECs proliferation increased, TNF-α and IL-1β expression elevated, and NF-κB protein level upregulated significantly. On the other side, ROS production increased and SOD activity decreased obviously (P < 0.05). Pterostilbene can suppress hRECs over proliferation, decrease TNF-α and IL-1β, inhibit NF-κB protein expression, reduce ROS production, and increase SOD activity markedly compared with high glucose group (P < 0.05). Pterostilbene may delay DR progress through alleviating inflammation and antioxidation to suppress hRECs over proliferation.

KEYWORDS: Diabetic retinopathy; inflammatory factor; pterostilbene; retinal endothelial cell

PMID: 26722449 PMCID: PMC4680394


Pterostilbene improves glycaemic control in rats fed an obesogenic diet: involvement of skeletal muscle and liver.

Gómez-Zorita S1, Fernández-Quintela A, Aguirre L, Macarulla MT, Rimando AM, Portillo MP.
Author information

Abstract

This study aims to determine whether pterostilbene improves glycaemic control in rats showing insulin resistance induced by an obesogenic diet. Rats were divided into 3 groups: the control group and two groups treated with either 15 mg kg(-1) d(-1) (PT15) or 30 mg kg(-1) d(-1) of pterostilbene (PT30). HOMA-IR was decreased in both pterostilbene-treated groups, but this reduction was greater in the PT15 group (-45% and -22% respectively vs. the control group). The improvement of glycaemic control was not due to a delipidating effect of pterostilbene on skeletal muscle. In contrast, GLUT4 protein expression was increased (+58% and +52% vs. the control group), suggesting an improved glucose uptake. The phosphorylated-Akt/total Akt ratio was significantly enhanced in the PT30 group (+25%), and therefore a more efficient translocation of GLUT4 is likely. Additionally, in this group the amount of cardiotrophin-1 was significantly increased (+65%). These data suggest that the effect of pterostilbene on Akt is mediated by this cytokine. In the liver, glucokinase activity was significantly increased only in the PT15 group (+34%), and no changes were observed in glucose-6-phosphatase activity. The beneficial effect of pterostilbene on glycaemic control was more evident with the lower dose, probably because in the PT15 group both the muscle and the liver were contributing to this effect, but in the PT30 group only the skeletal muscle was responsible. In conclusion, pterostilbene improves glycaemic control in rats showing insulin resistance induced by an obesogenic diet. An increase in hepatic glucokinase activity, as well as in skeletal muscle glucose uptake, seems to be involved in the anti-diabetic effect of this phenolic compound.

PMID: 25998070 DOI: 10.1039/c5fo00151j


Pterostilbene, a dimethyl ether derivative of resveratrol, reduces fat accumulation in rats fed an obesogenic diet.

Gómez-Zorita S1, Fernández-Quintela A, Lasa A, Aguirre L, Rimando AM, Portillo MP.

Author information

Abstract

The current study aimed to demonstrate the effects of pterostilbene in rats fed an obesogenic diet. For this purpose, pterostilbene was administered at doses of 15 mg/kg body weight/day (PT15 group) or 30 mg/kg body weight/day (PT30 group) for 6 weeks. Pterostilbene reduced adipose tissue mass -15.1% (PT15) and -22.9% (PT30). In this tissue, it decreased malic enzyme (-39.4 and -49.5% for PT15 and PT30 groups, respectively) and fatty acid synthase (-45 and -53.4% for PT15 and PT30) activities. Acetyl-CoA carboxylase activity was reduced and AMPK activity was increased only in the PT30 group. In the liver, pterostilbene (PT30) reduced malic enzyme (-
and glucose-6-P dehydrogenase (-43.2%) activities and increased carnitine palmitoyltransferase-1a (37.5%) and acyl-coenzyme A oxidase (42.5%) activities. This increased oxidative capacity was not associated with increased mitochondriogenesis. Among biochemical serum parameters, only insulin was modified by pterostilbene (-31.6%) in the PT15 group. The amounts of pterostilbene in serum and tissues from rats in the PT30 group were in not all cases 2-fold greater than those found in the PT15 group. In conclusion, pterostilbene shows antiobesity properties due, at least in part, to reduced lipogenesis in adipose tissue and increased fatty acid oxidation in liver.

KEYWORDS:
adipose tissue; bioavailability; fatty acid oxidation; lipogenesis; pterostilbene

PMID: 25083823 DOI: 10.1021/jf501318b


Analysis of safety from a human clinical trial with pterostilbene.

Riche DM1, McEwen CL, Riche KD, Sherman JJ, Wofford MR, Deschamp D, Griswold M.

Author information

Abstract

OBJECTIVES:
The purpose of this trial was to evaluate the safety of long-term pterostilbene administration in humans.

METHODOLOGY:
The trial was a prospective, randomized, double-blind placebo-controlled intervention trial enrolling patients with hypercholesterolemia (defined as a baseline total cholesterol ≥200 mg/dL and/or baseline low-density lipoprotein cholesterol ≥100 mg/dL). Eighty subjects were divided equally into one of four groups: (1) pterostilbene 125 mg twice daily, (2) pterostilbene 50 mg twice daily, (3) pterostilbene 50 mg + grape extract (GE) 100 mg twice daily, and (4) matching placebo twice daily for 6-8 weeks. Safety markers included biochemical and subjective measures. Linear mixed models were used to estimate primary safety measure treatment effects.

RESULTS:
The majority of patients completed the trial (91.3%). The average age was 54 years. The majority of patients were females (71%) and Caucasians (70%). There were no adverse drug reactions (ADRs) on hepatic, renal, or glucose markers based on biochemical analysis. There were no statistically significant self-reported or major ADRs.

CONCLUSION:
Pterostilbene is generally safe for use in humans up to 250 mg/day.

PMID: 23431291 PMCID: PMC3575612 DOI: 10.1155/2013/463595


**Effect of pterostilbene on hepatic key enzymes of glucose metabolism in streptozotocin- and nicotinamide-induced diabetic rats.**

Pari L1, Satheesh MA.

**Author information**

**Abstract**

The purpose of this study was to investigate the effect of pterostilbene and its effect on key enzymes of glucose metabolism. Diabetic rats were orally administered with pterostilbene (10, 20, 40 mg/kg) for 2, 4 and 6 weeks on glucose was determined. Administration of pterostilbene at 40 mg/kg significantly decreases plasma glucose. Based on these data, the higher dose, 40 mg/kg pterostilbene, was selected for further evaluation. Oral administration of pterostilbene for 6 weeks on glucose, insulin levels and hepatic enzymes in normal and streptozotocin (STZ)-nicotinamide-induced diabetic rats. A significant decrease in glucose and significant increase in plasma insulin levels were observed in normal and diabetic rats treated with pterostilbene. Treatment with pterostilbene resulted in a significant reduction of glycosylated hemoglobin and an increase in total hemoglobin level. The activities of the hepatic enzymes such as hexokinase was significantly increased whereas glucose-6-phosphatase, fructose-1,6-bisphosphatase were significantly decreased by the administration of pterostilbene in diabetic rats. A comparison was made between the action of pterostilbene and the antidiabetic drug--metformin.

PMID: 16616938 DOI: 10.1016/j.lfs.2006.02.036


**Pterostilbene Ameliorates Streptozotocin-Induced Diabetes through Enhancing Antioxidant Signaling Pathways Mediated by Nrf2.**

Elango B, Dornadula S, Paulmurugan R1, Ramkumar KM.

**Author information**
Abstract

Nuclear factor erythroid 2-related factor 2 (Nrf2) remains a master regulator of cytoprotective and antioxidant genes. In this study, we investigated the antidiabetic role of pterostilbene (PTS) in streptozotocin (STZ)-induced diabetic model through Nrf2-mediated antioxidant mechanisms. The ability of PTS to activate Nrf2 in MIN6 cells was assessed by dissociation of the Nrf2-Keap1 complex at different time points and by expression of ARE-driven downstream target genes of Nrf2. Immunoblot experiments examining Nrf2 activation and phosphorylation indicated that it conferred cytoprotection against STZ-induced cellular damage. In STZ-induced diabetic mice, PTS administration significantly decreased blood glucose levels through the improvement of insulin secretion. In addition, we also observed insulin-positive cells with recovered islet architecture in the pancreas of STZ-induced diabetic mice after treatment with PTS. The activation of Nrf2 and expression of its downstream target genes were observed upon PTS treatment, thereby reducing oxidative damage to pancreas. Furthermore, PTS treatment significantly reverted the abundance of key glucose metabolism enzymes, such as hexokinase, glucose-6-phosphatase, glucose-6-phosphate dehydrogenase, and fructose-1,6-bisphosphatase, to near-normal levels in liver tissue of STZ-induced diabetic mice. These results clearly indicate that PTS maintains glucose homeostasis, suggesting the possibility that it is a future candidate for use in diabetes management.

PMID: 26700463 DOI: 10.1021/acs.chemrestox.5b00378


Effects of pterostilbene in brown adipose tissue from obese rats.

Aguirre L1,2, Milton-Laskibar I1, Hijona E3,4, Bujanda L3,4, Rimando AM5, Portillo MP6,7.

Erratum in
Erratum to: volume 73, issue 3 of Journal of Physiology and Biochemistry. [J Physiol Biochem. 2017]

Author information

Abstract

In recent years, much attention has been paid by the scientific community to phenolic compounds as active biomolecules naturally present in foods. Pterostilbene is a resveratrol dimethylether derivative which shows higher bioavailability. The aim of the present study was to analyze the effect of pterostilbene on brown adipose tissue thermogenic markers in a model of genetic obesity, which shows reduced thermogenesis. The experiment was conducted with 30 Zucker (fa/fa) rats that were distributed in three experimental groups: control and two groups orally administered with pterostilbene at 15 and 30 mg/kg body weight/day for 6 weeks. Gene
expression of uncoupling protein 1 (Ucp1), peroxisome proliferator-activated receptor γ co-activator 1 α (Pgc-1α), carnitine palmitoyl transferase 1b (Cpt1b), peroxisome proliferator-activated receptor α (Ppara), nuclear respiratory factor 1 (Nfr1), and cyclooxygenase-2 (Cox-2); protein expression of PPARα, PGC-1α, p38 mitogen-activated protein kinase (p38 MAPK), UCP1 and glucose transporter (GLUT4); and enzyme activity of CPT 1b and citrate synthase (CS) were assessed in interscapular brown adipose tissue. With the exception of Pgc-1α expression, all these parameters were significantly increased by pterostilbene administration. These results show for the first time that pterostilbene increases thermogenic and oxidative capacity of brown adipose tissue in obese rats. Whether these effects effectively contribute to the antiobesity properties of these compound needs further research.

KEYWORDS:
Brown adipose tissue; Fatty acid oxidation; GLUT4; Obese rats; Pterostilbene

PMID: 28243863 DOI: 10.1007/s13105-017-0556-2


Pterostilbene suppressed irradiation-resistant glioma stem cells by modulating GRP78/miR-205 axis.

Huynh TT1, Lin CM2, Lee WH3, Wu AT4, Lin YK5, Lin YF6, Yeh CT7, Wang LS8.

Author information

Abstract

Glioblastoma multiforme (GBM) is the most aggressive type characterized by relapse and resistance even with the combination of radio- and chemotherapy. The presence of glioma stem cells (GSCs) has been shown to contribute to tumorigenesis, recurrence and treatment resistance. Particularly, CD133-positive glioma cells have been shown to represent the subpopulation that confers glioma radioresistance and suggested to be the source of tumor recurrence after radiation. Thus, a better understanding and the development of agents which target GSCs could potentially lead to a significant improvement in treating GBM patients. Here, we demonstrated that GRP78 (an antistress protein) was highly expressed in GBM cells along with β-catenin and Notch and correlated to the development of GSCs. CD133+ GSCs exhibited enhanced migration/invasion and self-renewal abilities. When GRP78 was silenced, GSC properties were suppressed and the sensitivity towards irradiation increased. In addition, the level of microRNA 205 appeared to be negatively associated with GRP78 expression. Our previous study indicated that pterostilbene (PT) possessed anticancer stem cell properties in hepatocellular carcinoma. Thus, we examined whether PT is also effective against GSCs. We found that PT-treated GSCs exhibited suppressed self-renewal and irradiation-resistant abilities. PT-mediated effects were associated with an increase of miR-205. Finally, we showed that PT treatment suppressed tumorigenesis in GSC xenograft mice. In conclusion, we provided evidence that GRP78/miR-205 axis played an important role in GSC maintenance and irradiation resistance. PT treatment suppressed GSC
development via negatively modulating GRP78 signaling. PT may be considered for combined therapeutic agent to enhance irradiation efficacy in GBM patients.

**KEYWORDS:**
CD133+ glioma stem cells; Glucose-regulated protein, 78 kDa (GRP78); Irradiation resistance; Pterostilbene; miR-205

PMID: 25736407 DOI: 10.1016/j.jnutbio.2014.11.015

**The antioxidant role of pterostilbene in streptozotocin-nicotinamide-induced type 2 diabetes mellitus in Wistar rats.**

Amarnath Satheesh M1, Pari L.

**Author information**

**Abstract**

The antioxidant effect of pterostilbene on streptozotocin-nicotinamide-induced diabetic rats has been assessed. The activity of superoxide dismutase, catalase, glutathione peroxidase, glutathione-S-transferase and reduced glutathione was significantly decreased in liver and kidney of diabetic animals when compared with normal control. There were significant improvements in these activities after treatment with pterostilbene at a dose of 40 mg kg\(^{-1}\) for six weeks. The increased levels of lipid peroxidation measured as thiobarbituric acid reactive substances (TBARS) in liver and kidney of diabetic rats were also normalized by treatment with pterostilbene. Chronic treatment of pterostilbene remarkably reduced the pathological changes observed in liver and kidney of diabetic rats. These results indicated the antioxidant property of pterostilbene.

PMID: 17132211 DOI: 10.1211/jpp.58.11.0009


**Pterostilbene, a new agonist for the peroxisome proliferator-activated receptor alpha-isoform, lowers plasma lipoproteins and cholesterol in hypercholesterolemic hamsters.**

Rimando AM1, Nagmani R, Feller DR, Yokoyama W.

**Author information**
Abstract

Resveratrol, a stilbenoid antioxidant found in grapes, wine, peanuts and other berries, has been reported to have hypolipidemic properties. We investigated whether resveratrol and its three analogues (pterostilbene, piceatannol, and resveratrol trimethyl ether) would activate the peroxisome proliferator-activated receptor alpha (PPARalpha) isoform. This nuclear receptor is proposed to mediate the activity of lipid-lowering drugs such as the fibrates. The four stilbenes were evaluated at 1, 10, 100, and 300 microM along with ciprofibrate (positive control), for the activation of endogenous PPARalpha in H4IIEC3 cells. Cells were transfected with a peroxisome proliferator response element-AB (rat fatty acyl CoA beta-oxidase response element)-luciferase gene reporter construct. Pterostilbene demonstrated the highest induction of PPARalpha showing 8- and 14-fold increases in luciferase activity at 100 and 300 microM, respectively, relative to the control. The maximal luciferase activity responses to pterostilbene were higher than those obtained with the hypolipidemic drug, ciprofibrate (33910 and 19460 relative luciferase units, respectively), at 100 microM. Hypercholesterolemic hamsters fed with pterostilbene at 25 ppm of the diet showed 29% lower plasma low density lipoprotein (LDL) cholesterol, 7% higher plasma high density lipoprotein (HDL) cholesterol, and 14% lower plasma glucose as compared to the control group. The LDL/HDL ratio was also statistically significantly lower for pterostilbene, as compared to results for the control animals, at this diet concentration. Results from in vitro studies showed that pterostilbene acts as a PPARalpha agonist and may be a more effective PPARalpha agonist and hypolipidemic agent than resveratrol. In vivo studies demonstrate that pterostilbene possesses lipid and glucose lowering effects.

PMID: 15853379 DOI: 10.1021/jf0580364


Anti-hyperlipidemic and anti-peroxidative role of pterostilbene via Nrf2 signaling in experimental diabetes.

Bhakkivalakshmi E1, Sireesh D1, Sakthivadivel M2, Sivasubramanian S2, Gunasekaran P2, Ramkumar KM3.

Author information

Abstract

Nuclear factor erythroid 2-related factor (Nrf2), a key transcription factor triggers the expression of antioxidant and detoxification genes thereby providing cellular protective functions against oxidative stress-mediated disorders. Recent research has identified that pharmacological activation of Nrf2 also regulates the largest cluster of genes associated with lipid metabolism. With this background, this paper highlights the anti-hyperlipidemic and anti-peroxidative role of pterostilbene (PTS), an Nrf2 activator, in streptozotocin (STZ)-induced diabetic model. PTS administration to diabetic mice for 5 weeks significantly regulated blood glucose levels through
the elevation of insulin secretion. The circulatory and liver lipid profiles of total cholesterol (TC), triglycerides (TG) and non-esterified fatty acids (NEFA) were maintained to normal levels upon PTS treatment. Moreover, PTS administration also normalized the circulatory levels of very low-, low- and high density lipoprotein cholesterol (VLDL-, LDL-, HDL-C) and also reduced lipid peroxidation in STZ-induced diabetic mice. In addition, Nrf2 and its downstream targets, superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx) enzyme activities and glutathione (GSH) levels were significantly elevated in liver tissues of diabetic mice upon PTS administration. Further, H&E staining of diabetic mouse liver showed collapse in hepatic microvesicles due to altered lipid metabolism. Both structural and functional alterations were attenuated by PTS indicating its role in diabetic dyslipidemia through Nrf2-mediated mechanism that could be considered as a promising therapeutic agent.

**KEYWORDS:**
Diabetes; Dyslipidemia; Lipids; Nrf2; Pterostilbene; Streptozotocin

PMID: 26921755 DOI: 10.1016/j.ejphar.2016.02.054


**Pterostilbene attenuates high glucose-induced oxidative injury in hippocampal neuronal cells by activating nuclear factor erythroid 2-related factor 2.**


**Author information**

**Abstract**

In the present study, neuroblastoma (SH-SY5Y) cells were used to investigate the mechanisms mediating the potential protective effects of pterostilbene (PTE) against mitochondrial metabolic impairment and oxidative stress induced by hyperglycemia for mimicking the diabetic encephalopathy. High glucose medium (100mM) decreased cellular viability after 24h incubation which was evidenced by: (i) reduced mitochondrial complex I and III activities; (ii) reduced mitochondrial cytochrome C; (iii) increased reactive oxygen species (ROS) generation; (iv) decreased mitochondrial membrane potential ($\Delta\Psi_m$); and (v) increased lactate dehydrogenase (LDH) levels. PTE (2.5, 5, and 10μM for 24h) was nontoxic and induced the nuclear transition of Nrf2. Pretreatment of PTE (2.5, 5, and 10μM for 2h) displayed a dose-dependently neuroprotective effect, as indicated by significantly prevented high glucose-induced loss of cellular viability, generation of ROS, reduced mitochondrial complex I and III activities, reduced mitochondrial cytochrome C, decreased $\Delta\Psi_m$, and increased LDH levels. Moreover, the levels of nuclear factor erythroid 2-related factor 2 (Nrf2), heme oxygenase-1 (HO-1) and glutathione S-transferase (GST) were elevated after PTE treatment. In addition, the elevation of
nuclear Nrf2 by PTE treatment (10μM for 2h) was abolished by Nrf2 siRNA. Importantly, Nrf2 siRNA induced the opposite changes in mitochondrial complex I and III activities, mitochondrial cytochrome C, reactive species generation, ΔΨm, and LDH. Overall, the present findings were the first to show that pterostilbene attenuated high glucose-induced central nervous system injury in vitro through the activation of Nrf2 signaling, displaying protective effects against mitochondrial dysfunction-derived oxidative stress.

KEYWORDS:
High glucose; Neuroprotection; Nuclear factor erythroid 2-related factor 2 signaling; Oxidative stress; Pterostilbene

PMID: 28089584 DOI: 10.1016/j.bbadis.2017.01.005


De novo biosynthesis of pterostilbene in an Escherichia coli strain using a new resveratrol O-methyltransferase from Arabidopsis.

Heo KT1,2, Kang SY1, Hong YS3,4.

Author information

Abstract

BACKGROUND:
Pterostilbene, a structural analog of resveratrol, has higher oral bioavailability and bioactivity than that of the parent compound; but is far less abundant in natural sources. Thus, to efficiently obtain this bioactive resveratrol analog, it is necessary to develop new bioproduction systems.

RESULTS:
We identified a resveratrol O-methyltransferase (ROMT) function from a multifunctional caffeic acid O-methyltransferase (COMT) originating from Arabidopsis, which catalyzes the transfer of a methyl group to resveratrol resulting in pterostilbene production. In addition, we constructed a biological platform to produce pterostilbene with this ROMT gene. Pterostilbene can be synthesized from intracellular L-tyrosine, which requires the activities of four enzymes: tyrosine ammonia lyase (TAL), p-coumarate:CoA ligase (CCL), stilbene synthase (STS) and resveratrol O-methyltransferase (ROMT). For the efficient production of pterostilbene in E. coli, we used an engineered E. coli strain to increase the intracellular pool of L-tyrosine, which is the initial precursor of pterostilbene. Next, we tried to produce pterostilbene in the engineered E. coli strain using L-methionine containing media, which is used to increase the intracellular pool of S-adenosyl-L-methionine (SAM). According to this result, pterostilbene production as high as 33.6 ± 4.1 mg/L was achieved, which was about 3.6-fold higher compared with that in the parental E. coli strain harboring a plasmid for pterostilbene biosynthesis.
CONCLUSION:
As a potential phytonutrient, pterostilbene was successfully produced in E. coli from a glucose medium using a single vector system, and its production titer was also significantly increased using a L-methionine containing medium in combination with a strain that had an engineered metabolic pathway for L-tyrosine. Additionally, we provide insights into the dual functions of COMT from A. thaliana which was characterized as a ROMT enzyme.

KEYWORDS:
De novo biosynthesis; Pterostilbene; Resveratrol O-methyltransferase

PMID: 28202018 PMCID: PMC5312575 DOI: 10.1186/s12934-017-0644-6


Antihyperglycemic activity of phenolics from Pterocarpus marsupium.

Manickam M1, Ramanathan M, Jahromi MA, Chansouria JP, Ray AB.

Author information

Abstract

Glucose levels in rats with hyperglycemia induced by streptozotocin were determined after i.p. administration of marsupsin (1), pterosupin (2), and pterostilbene (3), three important phenolic constituents of the heartwood of Pterocarpus marsupium. Marsupsin and pterostilbene significantly lowered the blood glucose level of hyperglycemic rats, and the effect was comparable to that of 1,1-dimethylbiguanide (metformin).

PMID: 9214733 DOI: 10.1021/np9607013


Engineering yeast for high-level production of stilbenoid antioxidants.

Li M1, Schneider K1, Kristensen M1, Borodina I1, Nielsen J1,2,3.

Author information

Abstract
Stilbenoids, including resveratrol and its methylated derivatives, are natural potent antioxidants, produced by some plants in trace amounts as defense compounds. Extraction of stilbenoids from natural sources is costly due to their low abundance and often limited availability of the plant. Here we engineered the yeast Saccharomyces cerevisiae for production of stilbenoids on a simple mineral medium typically used for industrial production. We applied a pull-push-block strain engineering strategy that included overexpression of the resveratrol biosynthesis pathway, optimization of the electron transfer to the cytochrome P450 monooxygenase, increase of the precursors supply, and decrease of the pathway intermediates degradation. Fed-batch fermentation of the final strain resulted in a final titer of 800 mg l-1 resveratrol, which is by far the highest titer reported to date for production of resveratrol from glucose. We further integrated heterologous methyltransferases into the resveratrol platform strain and hereby demonstrated for the first time de novo biosynthesis of pinostilbene and pterostilbene, which have better stability and uptake in the human body, from glucose.

PMID: 27833117 PMCID: PMC5105057 DOI: 10.1038/srep36827


**Pterostilbene Inhibits Lipogenic Activity similar to Resveratrol or Caffeine but Differently Modulates Lipolysis in Adipocytes.**

Gomez-Zorita S1,2,3, Belles C1,4, Briot A1, Fernández-Quintela A2,3, Portillo MP2,3, Carpéné C1.

**Author information**

**Abstract**

The anti-obesity effects of resveratrol shown in rodents are not transposed into an efficient therapy of human obesity. Consequently, the search for molecules mimicking or surpassing resveratrol actions is ongoing. The natural phenolic compound pterostilbene exhibits beneficial health effects and has the capacity to limit fat mass in animal models. In this study, we tested whether pterostilbene modulates triacylglycerol accumulation/breakdown. Prolonged exposure to pterostilbene or resveratrol inhibited adipocyte differentiation in 3T3-F442A preadipocytes. Acute effects on lipolysis, antilipolysis and lipogenesis were determined for pterostilbene in mouse adipocytes, and compared with resveratrol. Pterostilbene was also tested on glycerol release and glucose uptake in subcutaneous human adipocytes. Dose-response analyses did not reveal a clear lipolytic effect in both species. The antilipolytic effect of insulin was improved by pterostilbene at 1-10 μM in mouse fat cells only, while at 1 mM, the phenolic compound was antilipolytic in human fat cells in a manner not additive to insulin. Pterostilbene dose-dependently inhibited glucose incorporation into lipids similarly to resveratrol and caffeine. However, only the former did not inhibit insulin-stimulated glucose uptake. Indeed, pterostilbene abolished the insulin lipogenic effect without inhibiting its antilipolytic action and rapid
activation of glucose uptake. Pterostilbene therefore exhibits a unique panel of direct interactions with adipocytes that relies on its reported anti-obesity and antidiabetic properties.

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KEYWORDS:
adipogenesis; adipose tissue; glucose transport; human; insulin; polyphenols

PMID: 28627722 DOI: 10.1002/ptr.5852


Dietary Phenolic Compounds Interfere with the Fate of Hydrogen Peroxide in Human Adipose Tissue but Do Not Directly Inhibit Primary Amine Oxidase Activity.

Carpéné C1, Hasnaoui M1, Balogh B2, Matyus P2, Fernández-Quintela A3, Rodríguez V3, Mercader J4, Portillo MP3.

Author information

Abstract

Resveratrol has been reported to inhibit monoamine oxidases (MAO). Many substrates or inhibitors of neuronal MAO interact also with other amine oxidases (AO) in peripheral organs, such as semicarbazide-sensitive AO (SSAO), known as primary amine oxidase, absent in neurones, but abundant in adipocytes. We asked whether phenolic compounds (resveratrol, pterostilbene, quercetin, and caffeic acid) behave as MAO and SSAO inhibitors. AO activity was determined in human adipose tissue. Computational docking and glucose uptake assays were performed in 3D models of human AO proteins and in adipocytes, respectively. Phenolic compounds fully inhibited the fluorescent detection of H2O2 generated during MAO and SSAO activation by tyramine and benzylamine. They also quenched H2O2-induced fluorescence in absence of biological material and were unable to abolish the oxidation of radiolabelled tyramine and benzylamine. Thus, phenolic compounds hampered H2O2 detection but did not block AO activity. Only resveratrol and quercetin partially impaired MAO-dependent [(14)C]-tyramine oxidation and behaved as MAO inhibitors. Phenolic compounds counteracted the H2O2-dependent benzylamine-stimulated glucose transport. This indicates that various phenolic compounds block downstream effects of H2O2 produced by biogenic or exogenous amine oxidation without directly inhibiting AO. Phenolic compounds remain of interest regarding their capacity to limit oxidative stress rather than inhibiting AO.

PMID: 26881018 PMCID: PMC4736399 DOI: 10.1155/2016/2427618

Pterocarpus marsupium extract (Vijayasar) prevented the alteration in metabolic patterns induced in the normal rat by feeding an adequate diet containing fructose as sole carbohydrate.

Grover JK, Vats V, Yadav SS.

Author information

Abstract

Insulin resistance (hyperinsulinaemia) is now recognized as a major contributor to the development of glucose intolerance, dyslipidaemia and hypertension in non-insulin-dependent diabetes mellitus (NIDDM) patients. Sedentary lifestyle, consumption of energy-rich diet, obesity, longer lifespan, etc., are important reasons for this rise (J. R. Turtle, Int J Clin Prac 2000; 113: 23). Aqueous extracts of Pterocarpus marsupium Linn bark (PM), Ocimum sanctum Linn leaves (OS) and Trigonella foenumgraecum Linn seeds (FG) have been shown to exert hypoglycaemic/antihyperglycaemic effect in experimental as well as clinical setting. As no work has been carried out so far to assess the effect of PM, OS and FG on fructose-induced hyperglycaemia, hyperinsulinaemia and hypertriglyceridaemia, we undertook this study to assess whether these extracts attenuate the metabolic alteration induced by fructose-rich diet in rats. Five groups of rats (eight each) were fed chow diet, 66% fructose diet, 66% fructose diet + PM leaves extract (1 g/kg/day), 66% fructose diet + OS leaves extract (200 mg/kg/day) and 66% fructose diet + FG seeds extract (2 g/kg/day) for 30 days. Fructose feeding to normal rats for 30 days significantly increased serum glucose, insulin and triglyceride levels in comparison with control. Treatment with all the three plants extract for 30 days significantly lowered the serum glucose levels in comparison with control group. However, only PM extract substantially prevented hypertriglyceridaemia and hyperinsulinaemia, while OS and FG had no significant effect on these parameters. Results of this study, in addition to previous clinical benefits of PM seen in NIDDM subjects, are suggestive of usefulness of PM bark (Vijayasar) in insulin resistance, the associated disorder of type 2 diabetes; however, OS and FG may not be useful. Though several antidiabetic principles (-epicatechin, pterosupin, marsupin and pterostilbene) have been identified in the PM, yet future studies are required to certify their efficacy and safety before clinical scenario.

PMID: 15955128 DOI: 10.1111/j.1463-1326.2005.00414.x


Pterostilbene ameliorates insulin sensitivity, glycemic control and oxidative stress in fructose-fed diabetic rats.

Kosuru R1, Singh S2.
AIMS: The present investigation was designed to explore the effectiveness of pterostilbene (PT) on insulin resistance, metabolic syndrome and oxidative stress in fructose-fed insulin resistant rats.

MAIN METHODS: Age-matched, male Sprague-Dawley rats (330±30g body weight) were allocated into five groups (n=10). Control (C) group received 65% cornstarch, and the diabetic (D) group received 65% fructose for eight weeks. The third group (D+PT20) received 65% fructose and PT 20mg/kg/day for eight weeks. The fourth group (D+PT40) received 65% fructose and PT 40mg/kg/day for eight weeks. The fifth group (D+M) received 65% fructose and metformin (M) 100mg/kg/day for eight weeks. PT was dissolved in 10% β-cyclodextrin and given orally to rats. Several biochemical parameters were determined to assess the PT efficacy against insulin resistance, metabolic complications, and hepatic oxidative stress.

KEY FINDINGS: Significantly high HOMA-IR (p<0.001) values in D group compared to C group indicate the presence of insulin resistance. Significantly high levels of TBARS (p<0.001) and decreased levels of SOD (p<0.001) and GSH (p<0.001) in hepatic tissues of D group indicate oxidative stress associated with insulin resistance. Pterostilbene treatment to fructose-fed diabetic rats significantly decreased HOMA-IR (p<0.001) values. Furthermore, PT treatment significantly decreased hepatic TBARS (p<0.001) and increased SOD (p<0.001) and GSH (p<0.001) levels in fructose-fed diabetic rats.

SIGNIFICANCE: Current study reveals that PT is successful in ameliorating glycemic control, insulin sensitivity while diminishing metabolic disturbances and hepatic oxidative stress in a fructose-induced T2DM rat model.

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KEYWORDS: HbA1c; Hepatic oxidative stress; Insulin resistance; Pterostilbene; Type 2 diabetes

PMID: 28629731 DOI: 10.1016/j.jfs.2017.06.015


Role of pterostilbene in attenuating immune mediated devastation of pancreatic beta cells via Nrf2 signaling cascade.
Sireesh D1, Ganesh MR2, Dhamodharan U1, Sakthivadivel M3, Sivasubramanian S3, Gunasekaran P3, Ramkumar KM4.

Author information

Abstract

Nrf2 (nuclear factor erythroid 2-related factor-2) is a transcription factor that regulates oxidative/xenobiotic stress response and also suppress inflammation. Nrf2 signaling is associated with an increased susceptibility to various kinds of stress. Nrf2 has been shown as a promising therapeutic target in various human diseases including diabetes. Our earlier studies showed Pterostilbene (PTS) as a potent Nrf2 activator, and it protects the pancreatic β-cells against oxidative stress. In this study, we investigated PTS confer protection against cytokine-induced β-cell apoptosis and its role on insulin secretion in streptozotocin (STZ)-induced diabetic mice. The Nrf2 activation potential of PTS was assessed by dissociation of the Nrf2-Keap1 complex and by expression of ARE-driven downstream target genes in MIN6 cells. Further, the nuclear Nrf2 translocation and blockage of apoptotic signaling as demonstrated by the reduction of BAX/Bcl-2 ratio, Annexin-V positive cells and caspase-3 activity conferred the cytoprotection of PTS against cytokine-induced cellular damage. In addition, PTS treatment markedly improved glucose homeostasis and abated inflammatory response evidenced by the reduction of proinflammatory cytokines in diabetic mice. The inhibition of β-cell apoptosis by PTS as assessed by BAX/Bcl-2 ratio and caspase-3 activity in the pancreas was associated with the activation of Nrf2 and the expression of its downstream target genes. PTS also inhibited the activation of iNOS and decreased nitric oxide (NO) formation in the pancreas of diabetic animals. The results obtained from both in vitro and in vivo experiments showed that PTS improves β-cell function and survival against cytokine stress and also prevents STZ-induced diabetes.

KEYWORDS:
Cytokine cocktail; Diabetes; MIN6; Nrf2; Streptozotocin

PMID: 28343084 DOI: 10.1016/j.jnutbio.2017.02.015

Exploiting the aglycon promiscuity of glycosyltransferase Bs-YjiC from Bacillus subtilis and its application in synthesis of glycosides.

Dai L1, Li J1, Yao P1, Zhu Y1, Men Y1, Zeng Y1, Yang J1, Sun Y2.

Author information

Abstract
Glycosylation is a prominent biological mechanism for structural and functional diversity of natural products. Uridine diphosphate-dependent glycosyltransferases with aglycon promiscuity are generally recognised as effective biocatalysts for glycodiversification of natural products for practical applications. In this study, the aglycon promiscuity of glycosyltransferase Bs-YjiC from Bacillus subtilis 168 was explored. Bs-YjiC, with uridine diphosphate glucose (UDPG) as sugar donor, exhibited robust capabilities to glycosylate 19 structurally diverse types of drug-like scaffolds with regio- and stereospecificities and form O-, N- and S-linkage glycosides. Twenty-four glycosides of 17 aglycons were purified from scale-up reactions using Bs-YjiC as a biocatalyst, and their structures were confirmed by nuclear magnetic resonance spectra. Furthermore, a one-pot reaction by coupling Bs-YjiC to sucrose synthase from Arabidopsis thaliana was applied to glycosylate pterostilbene. Without adding the costly UDPG as sugar donor, 9mM (3.8g/L) pterostilbene 4’-O-β-glucoside was obtained by periodic feeding of pterostilbene. These results suggest the aglycon promiscuity of Bs-YjiC and demonstrate its significant application prospect in biosynthesis of valuable natural products.

**KEYWORDS:**
Aglycon promiscuity; Bacillus subtilis 168; Glycosylation; Glycosyltransferase sucrose synthase; Natural products

PMID: 28315700 DOI: 10.1016/j.jbiotec.2017.03.009
Pterostilbene-induced changes in gut microbiota composition in relation to obesity.

Etxeberria U1, Hijona E2,3, Aguirre L4,5, Milagro F1,4, Bujanda L2,3, Rimando AM6, Martínez JA1,4, Portillo MP4,5.

Abstract

SCOPE:
Nutritional interventions based on the use of natural bioactive compounds might offer new possibilities for reshaping obesity-associated bacterial dysregulation or dysbiosis and improving health. We evaluated whether pterostilbene supplementation could induce changes in gut microbiota composition and whether these modifications were associated with improvements in metabolic variables.

METHODS AND RESULTS:
Zucker (fa/fa) rats were given a standard diet supplemented (n = 10) or not (n = 9) with pterostilbene (15 mg/kg body weight/day) by oral gavage for 6 weeks. Faecal samples at the beginning and at the end of the intervention period were analyzed by Illumina Mi-Seq sequencing approach. Pterostilbene exerted protective antiobesity effects, improved metabolic function (insulin sensitivity), and induced structural changes in gut microbiota composition. A decrease in the levels of Firmicutes and an increase in Verrucomicrobia phyla were detected in the pterostilbene-treated group. Bacterial species belonging to genera Akkermansia and Odoribacter were also increased. A strong inverse correlation between Akkermansia muciniphila and body weight was evidenced. Odoribacter splanchnicus showed a negative correlation with adiposity.

CONCLUSION:
Pterostilbene modifies intestinal bacteria composition toward a healthier microbial profile and suggests that the antiobesity effects induced in Zucker rats could be associated with an enrichment of the mucin-degrading bacterial members, namely Akkermansia and Odoribacter genus.

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KEYWORDS:
Akkermansia; Insulin sensitivity; Odoribacter; Polyphenols; Verrucomicrobia

PMID: 27377854 DOI: 10.1002/mnfr.201500906
Stilbene derivatives promote Ago2-dependent tumour-suppressive microRNA activity.

Hagiwara K, Kosaka N, Yoshioka Y, Takahashi RU, Takeshita F, Ochiya T.

Author information

Abstract

It is well known that natural products are a rich source of compounds for applications in medicine, pharmacy, and biology. However, the exact molecular mechanisms of natural agents in human health have not been clearly defined. Here, we demonstrate for the first time that the polyphenolic phytoalexin resveratrol promotes expression and activity of Argonaute2 (Ago2), a central RNA interference (RNAi) component, which thereby inhibits breast cancer stem-like cell characteristics by increasing the expression of a number of tumour-suppressive miRNAs, including miR-16, -141, -143, and -200c. Most importantly, resveratrol-induced Ago2 resulted in a long-term gene silencing response. We also found that pterostilbene, which is a natural dimethylated resveratrol analogue, is capable of mediating Ago2-dependent anti-cancer activity in a manner mechanistically similar to that of resveratrol. These findings suggest that the dietary intake of natural products contributes to the prevention and treatment of diseases by regulating the RNAi pathway.

PMID: 22423322

Identification of molecular pathways affected by pterostilbene, a natural dimethylether analog of resveratrol.

Pan Z, Agarwal AK, Xu T, Feng Q, Baerson SR, Duke SO, Rimando AM.

Author information

Abstract
BACKGROUND:
Pterostilbene, a naturally occurring phenolic compound produced by agronomically important plant genera such as Vitis and Vaccinium, is a phytoalexin exhibiting potent antifungal activity. Additionally, recent studies have demonstrated several important pharmacological properties associated with pterostilbene. Despite this, a systematic study of the effects of pterostilbene on eukaryotic cells at the molecular level has not been previously reported. Thus, the aim of the present study was to identify the cellular pathways affected by pterostilbene by performing transcript profiling studies, employing the model yeast Saccharomyces cerevisiae.

METHODS:
S. cerevisiae strain S288C was exposed to pterostilbene at the IC50 concentration (70 μM) for one generation (3 h). Transcript profiling experiments were performed on three biological replicate samples using the Affymetrix GeneChip Yeast Genome S98 Array. The data were analyzed using the statistical methods available in the GeneSifter microarray data analysis system. To validate the results, eleven differentially expressed genes were further examined by quantitative real-time RT-PCR, and S. cerevisiae mutant strains with deletions in these genes were analyzed for altered sensitivity to pterostilbene.

RESULTS:
Transcript profiling studies revealed that pterostilbene exposure significantly down-regulated the expression of genes involved in methionine metabolism, while the expression of genes involved in mitochondrial functions, drug detoxification, and transcription factor activity were significantly up-regulated. Additional analyses revealed that a large number of genes involved in lipid metabolism were also affected by pterostilbene treatment.

CONCLUSION:
Using transcript profiling, we have identified the cellular pathways targeted by pterostilbene, an analog of resveratrol. The observed response in lipid metabolism genes is consistent with its known hypolipidemic properties, and the induction of mitochondrial genes is consistent with its demonstrated role in apoptosis in human cancer cell lines. Furthermore, our data show that pterostilbene has a significant effect on methionine metabolism, a previously unreported effect for this compound.

PMID: 18366703
Genomic analysis of pterostilbene predicts its antiproliferative effects against pancreatic cancer in vitro and in vivo.

McCormack DE, Mannal P, McDonald D, Tighe S, Hanson J, McFadden D.

Author information

Abstract

BACKGROUND:
To investigate the inhibitory role of pterostilbene in pancreatic cancer, we conducted a genomic analysis of pterostilbene-treated pancreatic cancer cells. We also investigated the effect of pterostilbene upon the carcinogenic markers, manganese superoxide dismutase, cytochrome C, Smac/DIABLO, and STAT3 phosphorylation in vitro. The antiproliferative effects of pterostilbene were further evaluated in an in vivo model.

METHODS:
Pancreatic cancer cells were treated with pterostilbene and evaluated with DNA microarray analysis. Pterostilbene-treated cells were analyzed for cytochrome C, Smac/DIABLO, manganese superoxide dismutase (MnSOD)/antioxidant activity, and STAT3 phosphorylation using ELISA. Data were statistically analyzed using ANOVA. Pterostilbene was then administered to nude mice for 8 weeks, and tumor growth rates were recorded and statistically analyzed.

RESULTS:
Microarray analysis of pterostilbene-treated cells revealed upregulation of pro-apoptosis genes. In vitro, pterostilbene treatment altered levels of phosphorylated STAT3, MnSOD/antioxidant activity, cytochrome C, and Smac/DIABLO. In nude mice, oral pterostilbene inhibited tumor growth rates.

CONCLUSION:
Pterostilbene alters gene expression in pancreatic cancer and increases the antiproliferative markers cytochrome C, Smac/DIABLO, and MnSOD/antioxidant activity. It was also shown to inhibit phosphorylated STAT3, a marker of accelerated tumorigenesis, and decrease pancreatic tumor growth in vivo. Further studies are warranted to elucidate the effects of pterostilbene in humans.

PMID: 22450950
Invadopodia-associated proteins blockade as a novel mechanism for 6-shogaol and pterostilbene to reduce breast cancer cell motility and invasion.

Hong BH\(^1\), Wu CH, Yeh CT, Yen GC.

Author information

Abstract

SCOPE:
Invadopodia are actin-rich membrane protrusions of tumor cells that are thought to initiate the local migration and invasion during cancer metastasis. The blockade of invadopodia-associated proteins has been reported as a promising approach for prevention of tumor metastasis. The aim of this study was to investigate the modulatory effects of 6-shogaol and pterostilbene on invadopodia in aggressive breast cancer cells.

METHODS AND RESULTS:
By wound-healing, transwell, and gelatin zymography assays, we found that 6-shogaol and pterostilbene effectively attenuated the motility and invasion of MDA-MB-231 cells, and suppressed the activities of matrix metalloproteinase-2 (MMP-2) and matrix metalloproteinase-9 (MMP-9). Further investigation into the underlying molecular mechanisms revealed that the levels of key modulators of invadopodium maturation, including c-Src kinase, cortactin, and membrane type 1-matrix metalloproteinase (MT1-MMP) decreased when cells were treated with 6-shogaol or pterostilbene.

CONCLUSION:
These data suggest that the repression of these factors might affect the maturation of invadopodia, inhibiting the metastasis of MDA-MB-231 cells. In conclusion, the present study demonstrates for the first time that 6-shogaol and pterostilbene can inhibit invadopodium formation and MMP activity in highly invasive breast cancer cells. We suggest that these compounds may be clinically useful in chemopreventive treatments for metastatic breast cancer.

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PMID: 23417847

Scavenging of hydroxyl radical by resveratrol and related natural stilbenes after hydrogen peroxide attack on DNA.


Author information

Abstract

Resveratrol (3,5,4′-trihydroxystilbene) is of interest due to its role in prevention and therapy of degenerative diseases as cancer and aging. However, depending on its concentration and cell type studied, resveratrol activity appears conflicting. It exerts antioxidant action, as a scavenger of free radicals and as promoter of antioxidant enzyme activity, but resveratrol acts also as a pro-oxidant. Here we present experimental and theoretical studies for resveratrol and two methoxy-derivatives found in plants, pterostilbene and 3,5,4′-trimethoxystilbene. We show that both methoxy-derivatives induce less DNA damage than resveratrol. The protective effects of the three molecules against oxidative DNA damage induced by hydrogen peroxide treatment were analyzed on mammalian cells in vitro. Our data show for the first time that methoxylated derivatives of resveratrol are very efficient in reducing DNA damage: using the same concentration of the three molecules we obtain a relative reduction of 85.5% (pterostilbene), 43.7% (trimethoxystilbene) and 21.1% (resveratrol). Analysis of the crystal structures of pterostilbene and 3,5,4′-trimethoxystilbene, compared to resveratrol, show fewer intermolecular interactions and a lack of planarity, due to packing forces, which is confirmed by density functional theory (DFT) calculations. We also describe the results of DFT calculations (including water solvent effects) in which the three stilbene species scavenge the hydroxyl radical (associated with the H2O2 insult).

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KEYWORDS:
DNA protection; Hydrogen peroxide; Hydroxyl radical; Pterostilbene; Resveratrol

PMID: 24075811


Pterostilbene as a potential novel telomerase inhibitor: molecular docking studies and its in vitro evaluation.

Tippani R, Prakhya LJ, Porika M, Sirisha K, Abbagani S, Thammidala C.

Author information

Abstract
Pterostilbene is a naturally occurring dimethyl ether analog of resveratrol identified in several plant species. Telomerase is important in tumor initiation and cellular immortalization. Given the striking correlations between telomerase activity and proliferation capacity in tumor cells, telomerase had been considered as a potentially important molecular target in cancer therapeutics. Molecular docking studies were performed on pterostilbene with the crystal structure of telomerase (3DU6). Pterostilbene was evaluated for its in vitro cytotoxicity in breast (MCF7) and lung cancer (NCI H-460) cell lines, antimitotic activity in green grams and telomerase activity. Curcumin was used as a standard. Docking results indicated good interaction between pterostilbene and the active site of telomerase and the docked energy of pterostilbene was -7.10 kcal/mol. Pterostilbene showed strong inhibitory effect on in vitro telomerase activity and cell growth in both the cell lines tested in a dose dependent manner. Cancer cells treated with 80 µM pterostilbene exhibited significant telomerase inhibition, after 72 hours (MCF-7 and NCI H-460; 81.52% and 74.69% reduction, respectively, compared to control). The IC50 of pterostilbene for anti-proliferative activity in MCF7 and NCI H-460 cell lines were found to be 30.0 and 47.2 µM, respectively. The best antimitotic activity was obtained with 80 µM of pterostilbene (100% reduction in water imbibition). All the above results were comparable to that of curcumin. The drug-related properties of pterostilbene were calculated using Molinspiration, Osiris Property Explorer and ACD/Chemsketch softwares. Pterostilbene obeyed Lipinski's Rule of Five indicating its therapeutic potential in humans. It was found that the telomerase inhibitory activity exhibited by pterostilbene was dependent of the cell viability and has the potential to be a new drug candidate against breast and lung cancers.

PMID: 24433502


Urokinase-type plasminogen activator expression and Rac1/WAVE-2/Arp2/3 pathway are blocked by pterostilbene to suppress cell migration and invasion in MDA-MB-231 cells.

Ko HS1, Kim JS1, Cho SM1, Lee HJ1, Ahn KS1, Kim SH1, Lee EO2.

Author information

Abstract

Breast cancer is the most common malignancy among females, and cancer invasion and metastasis are the leading causes of cancer death in breast cancer patients. Pterostilbene, a naturally occurring dimethyl ether analogue of resveratrol, has been demonstrated to possess anti-cancer effects. However, inhibitory effects of pterostilbene on cell migration and invasion and its underlying mechanisms are not fully understood. In this study, we investigated the anti-invasive mechanisms of pterostilbene in human breast cancer cell line MDA-MB-231 cells. Pterostilbene
effectively inhibited serum-induced migration and invasion without affecting the viability of breast cancer cells. The mRNA expression and activity of urokinase-type plasminogen activator (uPA) were markedly reduced by pterostilbene treatment. Moreover, pterostilbene attenuated nuclear factor κB (NF-κB) transcriptional activity and DNA binding of NF-κB on uPA promoter. In addition, pterostilbene significantly impaired the activity of Rac1 and the expression of WASP-family verprolin-homologous protein-2 (WAVE-2) and actin-related protein 2/3 (Arp2/3). Overall, these results suggest that pterostilbene caused considerable suppression of cell migration and invasion through blocking NF-κB-mediated uPA expression and Rac1/WAVE/Arp2/3 pathway.

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KEYWORDS:
Arp2/3; Invasion; MDA-MB-231 cells; Migration; NF-κB; Pterostilbene; Rac1; WAVE; uPA

PMID: 24440300


Involvement of the Nrf2 pathway in the regulation of pterostilbene-induced apoptosis in HeLa cells via ER stress.

Zhang B¹, Wang XQ, Chen HY, Liu BH.

Author information

Abstract

Among the various cancer cell lines, HeLa cells were found to be sensitive to pterostilbene (Pte), a compound that is enriched in small fruits such as grapes and berries. However, the mechanism involved in the cytotoxicity of Pte has not been fully characterized. Using biochemical and free radical biological experiments in vitro, we identified the pro-apoptotic profiles of Pte and evaluated the level of redox stress-triggered ER stress during HeLa cell apoptosis. The data showed a strong dose-response relationship between Pte exposure and the characteristics of HeLa apoptosis in terms of changes in apoptotic morphology, DNA fragmentation, and activated caspases in the intrinsic apoptotic pathway. During drug exposure, alterations in the intracellular redox homeostasis that favor oxidation were necessary to cause ER stress-related apoptosis, as demonstrated by enzymatic and non-enzymatic redox modulators. A statistically significant and dose-dependent increase (P < 0.05) was found with regard to the unique expression levels of Nrf2/ARE downstream target genes in HeLa cells undergoing late apoptosis, levels that were restored with anti-oxidant application with the Pte treatment. Our research demonstrated that Pte trigged ER stress by redox homeostasis imbalance, which was negatively regulated by a following activation of Nrf2.
Understanding the mode of action of a pterostilbene derivative as anti-inflammatory agent.

Nikhil K¹, Sharan S¹, Palla SR², Sondhi SM², Peddinti RK², Roy P³.

Abstract

Inflammatory response plays an important role not only in the normal physiology, but also in the pathology of certain diseases such as cancers. In our previous study, we found a novel derivative of pterostilbene (PTER), to be an effective inducer of apoptosis in human breast and prostate cancer cells affecting various cellular targets. Herein, we further attempted to investigate its anti-inflammatory potential followed by its probable mode of action. The newly developed compound was tested for its anti-inflammatory actions in lipopolysaccharide (LPS) stimulated RAW264.7 macrophages and carrageenan induced rat paw edema models. Our data showed that the derivative inhibited the expression of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) as well as the downstream products like nitric oxide (NO) and PGE2, at much lower doses as compared to PTER. This effect was found to be associated with the inhibition of phosphorylation/degradation of IκB-α and nuclear translocation of the p-NFκB p65. Moreover, inhibition of mitogen-activated protein kinases (MAPKs) and activator protein-1 (AP-1) was also observed. In addition, the newly developed compound also reduced the paw edema, the tissue content of NO, PGE2 and expression of iNOS and COX-2 proteins within the tissues after λ-carrageenan stimulation. Taken together, our findings provide the possibility that the PTER derivative might have enhanced cancer chemopreventive potential based on its stronger anti-NFκB and anti-inflammatory activities as compared to its natural counterpart, i.e., PTER. Thus, this compound can be used towards the development of an effective anti-inflammatory agent.

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KEYWORDS:
Anti-inflammatory; Carrageenan; Lipopolysaccharide; NFκB; Pterostilbene derivative; RAW 264.7 macrophage

PMID: 25981112

The resveratrol analogue trimethoxystilbene inhibits cancer cell growth by inducing multipolar cell mitosis.

Traversi G¹, Fiore M², Percario Z¹, Degrassi F², Cozzi R¹.

Author information

Abstract

Natural compounds are extensively studied for their potential use in traditional and non-traditional medicine. Several natural and synthetic Resveratrol analogues have shown interesting biological activities in the field of cancer chemoprevention. In the present study, we have focused on the ability of Resveratrol and two methoxylated derivatives (Trimethoxystilbene and Pterostilbene) to inhibit human cancer cell growth particularly analyzing their ability to interfere with tubulin dynamics at mitosis. We show that Trimethoxystilbene, differently from Resveratrol and Pterostilbene, alters microtubule polymerization dynamics in HeLa cells specifically inducing multipolar spindles and mitotic arrest coupled to a reduction of cell growth and an increase in apoptotic death by mitotic catastrophe. This work demonstrates that the structural modification of Rsv causes substantial changes in the mechanism of action of the derivatives. The presence of three extra methyl groups renders Trimethoxy very efficient in impairing cell proliferation by inducing mitotic catastrophe in cancer cells. © 2016 Wiley Periodicals, Inc.

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KEYWORDS:
apoptosis; cancer cell growth; mitotic catastrophe; resveratrol analogues; tubulin polymerization

PMID: 27739192
**Reviews**


**Pterostilbene: Biomedical applications.**

Estrela JM, Ortega A, Mena S, Rodriguez ML, Asensi M.

**Author information**

**Abstract**

Resveratrol and its naturally dimethylated analog, pterostilbene, show similar biological activities. However, the higher in vivo bioavailability of pterostilbene represents a fundamental advantage. The main focus of this review is on biomedical applications of pterostilbene. The metabolism and pharmacokinetics of this stilbene in inflammatory dermatoses and photoprotection, cancer prevention and therapy, insulin sensitivity, blood glycemia and lipid levels, cardiovascular diseases, aging, and memory and cognition are addressed. Safety and toxicity, as well as recommendations for future research and biomedical uses, are discussed. This review includes comparisons between pterostilbene and other polyphenols, with particular emphasis on resveratrol. Potential benefits of using combinations of different polyphenols are considered. Based on present evidences we conclude that pterostilbene is an active phytonutrient and also a potential drug with multiple biomedical applications.

PMID: 23808710


**Promising therapeutic potential of pterostilbene and its mechanistic insight based on preclinical evidence.**

Kosuru R, Rai U, Prakash S, Singh A, Singh S.

**Author information**

**Abstract**

Pterostilbene (PS) is a well-recognized antioxidant that primarily exists in blueberries, grapevines and heartwood of red sandalwood. Interest in this compound has been renewed in recent years, and studies have found that PS possesses an array of pharmacological properties, including chemopreventive, antiinflammatory, antidiabetic, antidyslipidemic, antiatherosclerotic...
and neuroprotective effects. However, the greater in vivo bioavailability of PS, as compared to resveratrol, is an added advantage for its efficacy. This review provides a summary regarding the sources, pharmacokinetic aspects and pharmacodynamics of PS, with a focus on the molecular mechanisms underlying its protective effects against cancer, brain injuries and heart disease. Studies regarding the safety profile of PS have also been included. Based on the presently available evidence, we conclude that PS represents an active phytonutrient and a potential drug with pleiotropic health applications.

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KEYWORDS: AMPK; Cardiovascular disease; HO-1; NF-κB; Nrf2; Pterostilbene

PMID: 27475678


Targeting cancer stem cells and signaling pathways by phytochemicals: Novel approach for breast cancer therapy.

Dandawate PR, Subramaniam D, Jensen RA, Anant S

Abstract

Breast cancer is the most common form of cancer diagnosed in women worldwide and the second leading cause of cancer-related deaths in the USA. Despite the development of newer diagnostic methods, selective as well as targeted chemotherapies and their combinations, surgery, hormonal therapy, radiotherapy, breast cancer recurrence, metastasis and drug resistance are still the major problems for breast cancer. Emerging evidence suggest the existence of cancer stem cells (CSCs), a population of cells with the capacity to self-renew, differentiate and be capable of initiating and sustaining tumor growth. In addition, CSCs are believed to be responsible for cancer recurrence, anticancer drug resistance, and metastasis. Hence, compounds targeting breast CSCs may be better therapeutic agents for treating breast cancer and control recurrence and metastasis. Naturally occurring compounds, mainly phytochemicals have gained immense attention in recent times because of their wide safety profile, ability to target heterogeneous populations of cancer cells as well as CSCs, and their key signaling pathways. Therefore, in the present review article, we summarize our current understanding of breast CSCs and their signaling pathways, and the phytochemicals that affect these cells including curcumin, resveratrol, tea polyphenols (epigallocatechin-3-gallate, epigallocatechin), sulforaphane, genistein, indole-3-carbinol, 3, 3'-di-indolylmethane, vitamin E, retinoic acid, quercetin,
parthenolide, triptolide, 6-shogaol, pterostilbene, isoliquiritigenin, celastrol, and koenimb. These phytochemicals may serve as novel therapeutic agents for breast cancer treatment and future leads for drug development.

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**KEYWORDS:**
Breast cancer; Cancer stem cells; Curcumin; Phytochemicals; Signaling pathways

PMID: 27609747
Occurrence of resveratrol and pterostilbene in age-old darakchasava, an ayurvedic medicine from India.

Paul B¹, Masih I, Deopujari J, Charpentier C.

Abstract

'Darakchasava' is a well known Indian herbal preparation of which the main ingredient is Vitis vinifera L. This 'ayurvedic' medicine is prescribed as a cardiotonic and also given for other disorders. HPLC analysis of this age old formulation revealed the presence of polyphenols like resveratrol and pterostilbene. These phenolic compounds are now known as antioxidants, cancer chemopreventive agents, and also known to reduce mortality from coronary heart disease by increasing high density lipoproteins like cholesterol and inhibiting platelet aggregation (Soleas, J.S., Diamandis, E.P., Goldberg, D.M., 1997. Resveratrol: a molecule whose time has come? and gone? Clin. Biochem. 30 (2), 91-113). The study of darakchasava becomes interesting in the light of these findings. A brief introduction of this medicinal preparation, its formulation, its analysis by HPLC, and some of its properties are discussed in this article.

PMID: 10624864

Nanoemulsion for solubilization, stabilization, and in vitro release of pterostilbene for oral delivery.

Zhang Y¹, Shang Z, Gao C, Du M, Xu S, Song H, Liu T.

Abstract

Pterostilbene, being extracted from many plants, has significant biological activities in preventing cancer, diabetes, and cardiovascular diseases so as to have great potential applications in pharmaceutical fields. But the poor solubility and stability of pterostilbene strictly restrained
its applications. As a good protection and oral delivery system, an optimal nanoemulsion for pterostilbene was developed by using low-energy emulsification method. Systematic pseudo-ternary phase diagrams have been studied in optimization of nanoemulsion formulations. The prepared pterostilbene nanoemulsion was characterized by transmission electron microscope, Fourier transform Raman spectrum, and laser droplet size analyzer. Nanoemulsion droplets are circular with smooth margin, and the mean size is $55.8 \pm 10.5$ nm. The results illustrated that the nanoemulsion as oral delivery system dramatically improved the stability and solubility of pterostilbene, and in vitro release of pterostilbene was significantly improved (96.5% in pH 3.6 buffer; 13.2% in pH 7.4 buffer) in comparison to the pterostilbene suspension (lower than 21.4% in pH 3.6 buffer; 2.6% in pH 7.4 buffer).

PMID: 24831090


Pharmacometrics of pterostilbene: preclinical pharmacokinetics and metabolism, anticancer, antiinflammatory, antioxidant and analgesic activity.

Remsberg CM$^1$, Yáñez JA, Ohgami Y, Vega-Villa KR, Rimando AM, Davies NM.

Author information

Abstract

The present study evaluated the preclinical pharmacokinetics and pharmacodynamics of trans-pterostilbene, a constituent of some plants. Right jugular vein cannulated male Sprague-Dawley rats were dosed i.v. with 20 mg/kg of pterostilbene and samples were analysed by the reverse phase HPLC method. Serum AUC, serum t(1/2), urine t(1/2), Cl(total) and Vd(beta) were 17.5 +/- 6.6 microg/h/mL, 1.73 +/- 0.78 h, 17.3 +/- 5.6 h, 0.960 +/- 0.025 L/h/kg and 2.41 +/- 1.13 L/kg (mean +/- SEM), respectively. A pterostilbene glucuronidated metabolite was detected in both serum and urine. The in vitro metabolism in rat liver microsomes furthermore suggests phase II metabolism of pterostilbene. Pterostilbene demonstrated concentration-dependent anticancer activity in five cancer cell lines (1-100 microg/mL). An in vitro colitis model showed concentration-dependent suppression of PGE(2) production in the media of HT-29 cells. Antiinflammatory activity was examined by inducing inflammation in canine chondrocytes followed by treatment with pterostilbene (1-100 microg/mL). The results showed decreased levels of MMP-3, sGAG and TNF-alpha compared with control levels. Pterostilbene exhibited concentration-dependent antioxidant capacity measured by the ABTS method. Pterostilbene increased the latency period to response in both tail-flick and hot-plate analgesic tests.

PMID: 17726731

The berry constituents quercetin, kaempferol, and pterostilbene synergistically attenuate reactive oxygen species: involvement of the Nrf2-ARE signaling pathway.

Saw CL¹, Guo Y², Yang AY², Paredes-Gonzalez X², Ramirez C³, Pung D⁴, Kong AN⁵.

Author information

Abstract

Quercetin, kaempferol, and pterostilbene are abundant in berries. The anti-oxidative properties of these constituents may contribute to cancer chemoprevention. However, their precise mechanisms of action and their combinatorial effects are not completely understood. Nuclear factor (erythroid-derived 2)-like 2 (Nrf2) regulates anti-oxidative stress enzymes and Phase II drug metabolizing/detoxifying enzymes by binding to antioxidant response element (ARE). This study aimed to investigate the anti-oxidative stress activities of quercetin, kaempferol, and pterostilbene individually and in combination, as well as the involvement of the Nrf2-ARE signaling pathway. Quercetin, kaempferol, and pterostilbene all exhibited strong free-radical scavenging activity in the DPPH assay. The MTS assay revealed that low concentration combinations we tested were relatively non-toxic to HepG2-C8 cells. The results of the DCFH-DA assay and combination index (CI) indicated that quercetin, kaempferol, and pterostilbene attenuated intracellular reactive oxygen species (ROS) levels when pretreated individually and had synergistic effects when used in combination. In addition, the combination treatment significantly induced ARE and increased the mRNA and protein expression of Nrf2-regulated genes. Collectively, our study demonstrated that the berry constituents quercetin, kaempferol, and pterostilbene activated the Nrf2-ARE signaling pathway and exhibited synergistic anti-oxidative stress activity at appropriate concentrations.

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KEYWORDS:
Antioxidant response element (ARE); Kaempferol; Nuclear factor (erythroid-derived 2)-like 2 (Nrf2); Pterostilbene; Quercetin; Reactive oxygen species

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Plant stilbenes induce endoplasmic reticulum stress and their anti-cancer activity can be enhanced by inhibitors of autophagy.

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**BACKGROUND:**
Environmental conditions or chemical agents can interfere with the function of the endoplasmic reticulum, and the resulting endoplasmic reticulum (ER) stress can be toxic to the cell if it is not relieved. The classical compensatory response to ER stress is the unfolded protein response (UPR) that reduces protein load in the ER. However, autophagy may also compensate by removing large insoluble protein aggregates. Agents that stress the ER can have anti-cancer activity, and novel applications of ER stress inducing agents are being investigated. Plant stilbenes are a class of stress responsive molecules that includes resveratrol, which are being investigated as potential therapeutics in humans for conditions such as aging or cancer.

**RESULTS:**
We performed a screen of 1726 small, drug like molecules to identify those that could activate an ER-stress responsive luciferase gene. After secondary screening, we determined that the plant stilbenes pterostilbene and piceatannol were the most potent inducers of ER stress from this group. ER stress can be particularly toxic to cells with high ER load, so we examined their effect on cells expressing the Wnt family of secreted glycoprotein growth factors. Molecular analysis determined that these ER stress-inducing stilbenes could block Wnt processing and also induce autophagy in acute lymphoblastic leukemia cells expressing Wnt16. Combining pterostilbene (to induce ER stress) with chloroquine (to inhibit autophagy) lead to significant cellular toxicity in cells from aggressive acute lymphoblastic leukemia.

**CONCLUSIONS:**
Plant stilbenes are potent inducers of ER stress. However, their toxicity is more pronounced in cancer cells expressing Wnt growth factors. The toxicity of stilbenes in these ALL cells can be potentiated by the addition of autophagy inhibitors, suggesting a possible therapeutic application.
A pterostilbene derivative suppresses osteoclastogenesis by regulating RANKL-mediated NFκB and MAPK signaling in RAW264.7 cells.

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Abstract

BACKGROUND:
A dysfunctional osteoclast activity is often the cause of bone destructive diseases, such as osteoporosis, periodontitis, erosive arthritis, and cancer. The NFκB ligand (RANKL) has been identified as a major mediator of bone resorption. Agents that suppress RANKL signaling have the potential to inhibit bone resorption or osteoclastogenesis. The present study aimed to determine the effect of a pterostilbene derivative (PTERC-T) for suppressing RANKL or tumor cells-induced osteoclastogenesis in RAW264.7 murine macrophages.

METHODS:
Cytotoxicity was measured by MTT assay and inhibitory effect on osteoclastogenesis was analyzed by counting the number of tartrate-resistant acid phosphatase (TRAP)-positive multinucleated cells and measuring the expression levels of the osteoclast-specific genes. The reactive oxygen species (ROS) generation was detected by FACS. Further, signaling pathways were analyzed by immunofluorescence and immunoblot analyses.

RESULTS:
PTERC-T suppressed the differentiation of monocytes to osteoclasts in a dose and time-dependent manner. The expression of osteoclast marker genes like TRAP, cathepsin K (CTSK), matrix metalloproteinase 9 (MMP9) and transcription factors c-Fos, and nuclear factor of activated T cells cytoplasmic 1 (NFATc1) were also diminished by PTERC-T. PTERC-T scavenged intracellular ROS generation within osteoclast precursors during RANKL-stimulated osteoclastogenesis. Mechanistically, PTERC-T abrogated the phosphorylation of MAPKs (ERK and JNK) and inhibited RANKL-induced activation of NFκB by suppressing IκBα phosphorylation and preventing NFκB/p65 nuclear translocation.
CONCLUSIONS:
This study thus identifies PTERC-T as an inhibitor of osteoclast formation and provides evidence for its role in preventing osteoporosis and other bone related disorders. However, further studies are needed to establish its efficacy in vivo.

KEYWORDS:
MAPK; NFκB; Osteoclastogenesis; PTERC-T; RANKL

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Pterostilbene is a naturally-occurring phytoalexin identified in several plant species. It belongs to a group of phenolic compounds known as stilbenes, and is found in the heartwood of sandalwood (Pterocarpus santalinus) [1] and P. marsupium [2]. It was also identified in the leaves of Vitis vinifera [3], in infected grape berries of var. Chardonnay and Gamay [4], and in healthy and immature berries of var. Pinot Noir and Gamay [5]. Pterostilbene has also been found in berries of some Vaccinium species [5]. Pterostilbene, one of the most extensively studied secondary metabolites found in grapes and wine, is a dimethylether analog of resveratrol that is well known for its hypolipidemic activity. A considerable amount of research effort has been expended to address the biochemical and physiological effects of pterostilbene in animal and microbial systems. For example, the antioxidative activity of pterostilbene was first demonstrated in vitro by its inhibition of methyl linoleate oxidation [6]. Pterostilbene was reported to scavenge 1,1-diphenyl-2-picryl-hydrazyl (DPPH) free radicals and to inhibit the oxidation of citronellal, and lipid peroxidation in rat liver microsomes and in cultured human fibroblasts [7]. Pterostilbene isolated from Anogeissus acuminata (Family Combretaceae) is cytotoxic against a number of cancer cell lines, including human breast cancer and murine lymphoid neoplasma cells [8,9]. More recently, it has been demonstrated that pterostilbene can reduce cholesterol levels in vivo in hamsters through the activation of the peroxisome proliferator-activated receptor α (PPARα) [10]. Pterostilbene has been reported to reduce glucose and increase plasma insulin levels significantly in normal and diabetic rats [11]. Furthermore, pterostilbene has been shown to be cancer-chemopreventive [8,12] and anti-inflammatory [13].

Investigation of the pathogen-host interactions of Vitis vinifera has led to the hypothesis that resistance is not due to preformed physical or chemical factors, but rather to an active defense mechanism that is triggered by the pathogen, of which stress metabolites including resveratrol, α-viniferin and ε-viniferin are an important component [14]. Pterostilbene, produced in leaf tissues by various species of the Vitaceae family following fungal infection, proved to have more potent antifungal activity than resveratrol (reviewed in [3,15,16]). However, the mechanism by which pterostilbene inhibits fungi is not well understood. Results from early studies suggested that the biological activities of the compound mainly involved effects on the plasma membrane [5,17], and destruction of ribosomes, endoplasmic reticulum, and mitochondrial membranes [17].
Further information on its precise mechanism of action would be useful not only for its potential development as a drug, but also in understanding its ecological significance to producing plant species. In the present study, using transcript profiling analysis, we monitored the gene expression profile of yeast cells treated with pterostilbene in an effort to identify the molecular pathways affected by this compound.