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

Eun-Seok Park\textsuperscript{a}, Yong Lim\textsuperscript{b}, Jin-Tae Hong\textsuperscript{a}, Hwan-Soo Yoo\textsuperscript{a}, Chong-Kil Lee\textsuperscript{a}, Myoung-Yun Pyo\textsuperscript{c}, Yeo-Pyo Yun\textsuperscript{a,\textast}

\textsuperscript{a} College of Pharmacy, Research Center for Bioresource and Health, CBITRC, Chungbuk National University, Cheongju 361-763, Republic of Korea
\textsuperscript{b} Research Institute of Veterinary Medicine, Chungbuk National University, Cheongju361-763, Republic of Korea
\textsuperscript{c} College of Pharmacy, Sookmyung Women’s University, Seoul 140-742, Republic of Korea

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 \([3H]\)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 5 \(\mu\)M to VSMCs proliferation were 68.5, 80.7 and 94.6%, respectively. The DNA synthesis of pterostilbene at 1, 3 and 5 \(\mu\)M in VSMCs was inhibited by 47.4, 76.7 and 100%, respectively. Pterostilbene inhibited the PDGF-BB-stimulated phosphorylation of Akt kinase. Furthermore, pterostilbene did not change the expression of extracellular signal-related kinase (ERK) 1/2, PLC\(\gamma\)1, phosphatidylinositol (PI)\(\gamma\)3 kinase and PDGF-RI\(\beta\) 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.

© 2010 Elsevier Inc. All rights reserved.

# 1. Introduction

Abnormal vascular smooth muscle cells (VSMCs) proliferation plays a fundamental role in the pathogenesis of vascular diseases, such as atherosclerosis, hypertension and restenosis (Ross, 1990; Schwartz, 1997). The release of growth factor is involved in the pathological processes of vascular lesions. Platelet-derived growth factor (PDGF)-BB secreted by injured endothelial cells and VSMCs as well as by platelets and macrophages, promotes the proliferation of fibroblast and VSMCs (Sachinidis et al., 1990). PDGF-BB initiated mitogenic signals through autophosphorylation of its respective PDGF beta-receptor on tyrosine residues, followed by downstream signal transduction and cell cycle progression (Ahn et al., 1999; Blenis, 1993). The binding of PDGF-BB to the PDGF receptor (PDGF-R) can activate three major signal transduction pathways, Akt, phospholipase C (PLC)\(\gamma\)1 and extracellular regulated kinase 1/2 (ERK1/2) (Claesson-Welsh, 1994; Heldin et al., 1998). Most of the growth factors such as insulin-like growth factor (IGF)-1 and PDGF bind to their respective receptors and then activate phosphatidylinositol (PI)\(\gamma\)3 kinase. Akt, a downstream target of PI3 kinase, is overexpressed in gastric adenocarcinomas, breast cancer, hepatocarcinoma and prostate carcinoma, and its activation correlates to cancer progression (Sekine et al., 2007). Thus, the screening of Akt inhibitors may be a potential strategy for the development of anti-cancer agents (Mullany et al., 2007).

It has been suggested since the 1980s that the enhanced activity of PDGF-R plays an important role in cancers and leukemias (Levitzki, 2004; Pietras et al., 2003) and has been identified as a prime player in the onset of the atherosclerotic plaque (Ross and Glomset, 1976; Rutherford and Ross, 1976). Furthermore, it is well established that...
PDGF-R plays a key role in the process of restenosis subsequent to balloon angioplasty and by-pass operation. Thus, the field of pharmacological intervention in PDGF-R signaling is moving in parallel in two directions: anti-cancer therapy and anti-restenosis therapy. In cancers, PDGF and its receptors are one of a number of players with very few exceptions, whereas in restenosis PDGF-R signaling seems to be the major player. It seems therefore that PDGF-R kinase inhibitors will move faster as anti-restenosis agents than as anti-cancer agents. (Levitzki, 2004).

Pterostilbene (Fig. 1), a natural dimethylated analog of resveratrol from blueberries, is known to have diverse pharmacological activities such as anti-cancer, anti-inflammation and anti-oxidant activities (Remsberg et al., 2008). Pterostilbene has been suggested to possess anti-neoplastic activity as effective as resveratrol due to their close structural similarity (Rimando et al., 2004; Tolomeo et al., 2005). Resveratrol has been shown in numerous studies to exhibit beneficial effects in the control of atherosclerosis and heart disease (de la Lastra and Villegas, 2005; Fulda and Debatin, 2006). However, resveratrol has a low bioavailability to cells (Asensi et al., 2002). Thus, structural modifications of the resveratrol need to increase its bioavailability while preserving its beneficial activities (Ferrer et al., 2005). Structurally, pterostilbene has a better metabolic stability than resveratrol because it has only one hydroxyl group, while resveratrol has three. The dimethylether structure of pterostilbene was suggested to enhance its lipophilicity and increase membrane permeability, resulting in better pharmacokinetic profiles than resveratrol (Lin et al., 2009). However, a possible pharmacological mechanism of pterostilbene by which pterostilbene can cure the vascular diseases remains unknown.

In the present study, we sought to elucidate the anti-proliferative activity and the machinery target of pterostilbene in PDGF-BB-stimulated signaling pathway. Our findings provide evidence that pterostilbene can inhibit VSMCs proliferation and cell cycle progression via the cell cycle-related proteins by regulating Akt kinase in VSMCs.

2. Materials and methods

2.1. Materials

The cell culture materials and FBS were obtained from Gibco-BRL (Gaithersburg, MD, USA). [3H]Thymidine was purchased from Amersham Pharmacia Biotech (Buckinghamshire, UK). Pterostilbene was purchased from Sigma Chemical Co. (St. Louis, MO, USA), dissolved in dimethyl sulfoxide (DMSO) and added to Dulbecco’s modified Eagle’s medium (DMEM) with a maximum final concentration of 0.05%. Pre-exposure of VSMCs to DMSO 0.05% did not change their cell viability and cell proliferation, compared to control VSMCs. (data not shown) PDGF-BB was acquired from Upstate Biotechnology (Lake Placid, NY, USA), phospho-ERK1/2, phospho-Akt, phospho-PLCγ1, phospho-PDGF-Rβ, ERK1/2, Akt, PLCγ1, PDGF-Rβ and phospho-pRb antibodies were supplied by Cell Signaling Technology Inc. (Beverly, MA, USA), PCNA, cyclin D1, cyclin E, CDK2 and CDK4 antibodies were obtained from Santa Cruz Biotechnology Inc. (Santa Cruz, CA, USA). All other chemicals were of analytical grade.

Fig. 1. Inhibitory effects of pterostilbene on PDGF-BB-stimulated proliferation and DNA synthesis of rat aortic VSMCs. (A) Chemical structure of trans-3,5-dimethoxy-4′-hydroxystilbene (pterostilbene). (B) Effect of pterostilbene on the number of PDGF-BB-stimulated VSMCs. The VSMCs were pre-cultured in the serum-free medium in the presence or absence of pterostilbene (1–5 μM) for 24 h, and then stimulated by 25 ng/mL PDGF-BB for 24 h. The cells were trypsinized, and counted using a hemocytometer. The VSMCs were cultured in serum-starved medium in the presence or absence of pterostilbene (1–5 μM) for 24 h, and then stimulated with (C) 25 ng/mL PDGF-BB or (D) 5% FBS for 20 h before 1 μCi/mL [3H]Thymidine was added to the medium. The labeling reaction was quenched and quantified using a liquid scintillation counter, 4 h later. The data were reported as the mean ± S.E.M. from four different sets of experiments. *P<0.05 and **P<0.01 vs. only PDGF-BB-stimulated VSMCs.
2.2. Cell culture

Rat aortic vascular smooth muscle cells (VSMCs) were isolated by enzymatic dispersion using a slight modification of the method reported by Chamley et al. (1977). Briefly, the cells were cultured in DMEM supplement with 10% FBS, 100 U/mL penicillin, 100 mg/mL streptomycin, 8 mM HEPES and 2 mM L-glutamine at 37 °C in a humidified 5% CO2 incubator. The purity of the VSMCs cultures was >95%, as confirmed by immunocytochemical staining of α-smooth muscle actin. Passages 5–9 of the VSMCs were used in this study.

2.3. Cell proliferation assay

The level of VSMCs proliferation was measured by direct cell counting. Briefly, the cells were seeded at a concentration of 4 × 10^4 cells/well in a 12-well culture plate and grown in DMEM containing 10% FBS for 24 h. The cells were then cultured with serum-free (0.4% FBS) medium containing pterostilbene for 24 h. The cells were treated with 25 ng/mL PDGF-BB and counted 24 h later using a hemocytometer.

2.4. [3H]thymidine incorporation assay

DNA synthesis was assayed by measuring the level of [3H] thymidine incorporation into the cell DNA (Zhang et al., 2000). The VSMCs were seeded in 24-well culture plates at a concentration of 7000 cells/well and grown until they had reached 60% confluence. The medium was then replaced with serum-free (0.4% FBS), which consisted of DMEM containing various concentrations of pterostilbene. After 24 h, the cultures were exposed to 25 ng/mL PDGF-BB for 20 h before adding 1 μCi/mL [3H]thymidine to the medium. Four hours later, the labeling reactions were quenched by aspirating the medium and subjecting the cultures to sequential washes on ice with PBS containing 10% trichloroacetic acid and ethanol/ether (1:1, v/v). The acid-insoluble [3H]thymidine was extracted into 500 μL of 0.5 M NaOH/well. This solution was mixed with 3 mL of scintillation cocktail.

**Fig. 2.** Inhibitory effects of pterostilbene on PDGF-BB-stimulated CDK2, CDK4, cyclin D1, cyclin E, PCNA expression and pRb phosphorylation. Quiescent VSMCs were stimulated with 25 ng/mL PDGF-BB in the presence or in absence of pterostilbene at 1, 3 and 5 μM for 24 h. The cells were then lysed, and proteins were analyzed using 12% SDS-PAGE. Western blot analysis was performed with the antibodies specific for CDK2, CDK4, cyclin D1, cyclin E, PCNA and phospho-pRb. α-actin was used for normalization. (A) Representative data from three different experiments are presented. (B) After densitometric quantification, the data were expressed as the mean ± S.E.M. (n = 3). *P < 0.05 and **P < 0.01 vs. only PDGF-BB-stimulated.

2.5. Western blot analysis

The cell lysates were separated on SDS-PAGE containing 10–15% acrylamide gels according to the method described by Laemmli (1970). The proteins were transferred to PVDF membranes (Amer- sham Pharmacia Biotech, Buckinghamshire, UK), which were then blocked overnight at 4 °C in Tris-buffered saline containing 0.1% Tween 20 (TBS/T) and 5% bovine serum albumin (BSA). The membranes were then incubated with a 1:1000 dilution of phospho-ERK1/2, phospho-Akt, phospho-PLCγ1, Akt, PLCγ1, PCNA, CDK2, CDK4, cyclin D1, cyclin E and phospho-pRb antibodies. The blots were washed with TBS/T, and then incubated with a 1:5000 dilution of horseradish peroxidase-conjugated IgG secondary antibody (New England Biolabs, MA, USA). The proteins were detected using a chemiluminescent reaction (ECL plus kit, Amersham Pharma- cia Biotech, Buckinghamshire, UK) followed by exposure of the membranes to Hyperfilm ECL (Amerham Pharmacia Biotech, Buck- inghamshire, UK). The band intensities were quantified using Scion-Image® Software for Windows®.

2.6. Statistical analysis

The experimental results were expressed as means ± S.E.M. One-way analysis of variance (ANOVA) was used for multiple comparisons (GraphPad Prism version 4.00 for Windows, San Diego, CA, USA). If there was a significant variation between treated groups, the Dunnett test was applied. The data were considered significant when P<0.05.

3. Results

3.1. Inhibitory effects of pterostilbene on PDGF-BB-stimulated VSMCs proliferation and DNA synthesis

The effect of pterostilbene was assessed by direct cell counting to determine whether pterostilbene inhibited PDGF-BB-stimulated VSMCs proliferation. A treatment of VSMCs with pterostilbene and PDGF-BB for 24 h resulted in a significant decrease in cell numbers of cells in a concentration-dependent manner at doses of 1, 3 and 5 μM, by 68.5, 80.7 and 94.6%, respectively (Fig. 1B). The level of [³H] thymidine incorporation into the DNA was also measured as an index of cell proliferation. Stimulation of VSMCs with 25 ng/ml PDGF-BB caused a significant increase in the level of [³H]thymidine incorpora- tion, while pterostilbene inhibited the PDGF-BB-stimulated DNA synthesis in a concentration-dependent manner, with inhibitory percentages of 47.4, 76.7 and 100% at 1, 3 and 5 μM, respectively (Fig. 1C). However, pterostilbene did not inhibit the FBS-induced proliferation of VSMCs (Fig. 1D). Pterostilbene at 5 μM showed complete suppression of cell proliferation and DNA synthesis. Thus, pterostilbene inhibited both cell proliferation and DNA synthesis with IC₅₀ values of 1.53 ± 0.04 and 1.08 ± 0.02, respectively.

3.2. Inhibitory effects of pterostilbene on cell cycle regulatory protein expression

Rb protein is a key component of the molecular network controlling the restriction point of cell cycle. Hypophosphorylated pRb binds to the E2F family of transcription factors, and then transcription of E2F-responsive genes was preceded for cell cycle progression. Therefore, we investigated the impact of pterostilbene on pRb phosphorylation. Pretreatment with pterostilbene at concentra- tions of 1, 3 and 5 μM significantly inhibited PDGF-BB-stimulated Rb protein phosphorylation with inhibition percentages of 15.0, 60.5 and 98.2%, respectively. Furthermore, the expression of proliferative cell nuclear antigen (PCNA), a phospho-pRb-mediated gene product in the early G0/G1 and S phase of the cell cycle, was also inhibited by pterostilbene in the same pattern as the inhibition of Rb protein phosphorylation (Fig. 2). Cell cycle progression is tightly regulated through a complex network of positive and negative cell cycle regulatory molecules, such as CDKs and cyclins. To characterize the mechanism of pterostilbene-induced cell cycle arrest, the effects of pterostilbene on cell cycle events such as CDK2, cyclin E, CDK4 and cyclin D1 expressions were determined. There was an increase in the expression of CDK2 and cyclin E as well as CDK4 and cyclin D1 after the stimulation of VSMCs with PDGF-BB for 24 h, while the treatment with pterostilbene at 1, 3 and 5 μM resulted in the significant inhibition of the cell cycle-related proteins in a concentration- dependent pattern (Fig. 2).

3.3. Effect of pterostilbene on PDGF-BB-induced PDGF-Rβ phosphorylation

To further investigate the action mechanism of pterostilbene in the inhibition of PDGF-BB-induced cell growth, we determined the effect of pterostilbene on PDGF-Rβ activation. After pre-incubating the VSMCs with various concentrations of pterostilbene for 24 h, the VSMCs stimulated for 1 min with PDGF-BB, showed the marked phosphorylation of PDGF-Rβ. However, the treatment of VSMCs with pterostilbene at the range of 1, 3 and 5 μM had no effect on PDGF-Rβ phosphorylation (Fig. 3). Thus, this result suggests that pterostilbene is not acting as an antagonist for PDGF-R.

3.4. Effects of pterostilbene on Akt, ERK1/2 and PLCγ1 phosphorylation

PDGF-BB binding to PDGF-Rβ is associated with dimerization, autophosphorylation, clustering and activation of PDGF-R tyrosine kinase (Hughes et al., 1996), leading to VSMCs proliferation through activation of PI3K/Akt, mitogen-activated protein (MAP) and PLCγ1 (Matsumoto et al., 2005). Therefore, it was hypothe- sized that ERK1/2, Akt and PLCγ1 pathways may be involved in the inhibition of pterostilbene to PDGF signaling pathway. The effects of pterostilbene on phosphorylation of ERK1/2, Akt and PLCγ1, were examined. Pterostilbene had no effects on the phosphorylation of PDGF-BB-induced ERK1/2 and PLCγ1 (Fig. 4A and B).
However, pretreatment with pterostilbene significantly inhibited PDGF-BB-induced Akt phosphorylation in a concentration-dependent manner by 44.7, 68.7 and 98.1% at doses of 1, 3 and 5 μM (Fig. 4C). The effect of pterostilbene on the expression of PI3K, upstream component of Akt, was determined. To determine whether Akt inhibitor may suppress the cell proliferation in VSMCs, LY294002, an Akt inhibitor, was treated to the smooth muscle cells. LY294002 at the concentration of 2 μM inhibited the DNA synthesis of VSMCs by 51.6% compared with the control. The combined treatment of LY294002 with pterostilbene in VSMCs inhibited DNA synthesis by approximately 99.6% compared with control (Fig. 4D), indicated that these may be either synergic or additive effect of cell proliferation. These results indicate that the inhibition of Akt activation may be involved in the pterostilbene-induced inhibition of cell cycle progression and VSMCs proliferation.

4. Discussion

VSMCs proliferation in response to vessel injury is associated with several pathophysiological conditions such as inflammation, pulmonary hypertension, and coronary artery restenosis following balloon angioplasty, eventually leading to cardiovascular diseases (Ross, 1993). Inhibition of VSMCs proliferation is important in the treatment of cardiovascular disease. In the present study, we investigated the anti-proliferative activity of pterostilbene on VSMCs and the related signal transduction in cultured VSMCs.

It was found that pterostilbene inhibited the proliferation and DNA synthesis of VSMCs stimulated with PDGF-BB (Fig. 1B and C). Moreover, the anti-proliferative effect of pterostilbene was not due to cellular cytoxicity, as demonstrated by MTT assays (data not shown). These results indicate that pterostilbene has a potent...
inhibitory effect on PDGF-BB-stimulated VSMCs proliferation and may be useful for the treatment of vascular diseases and restenosis after angioplasty. It was reported that the cell division of VSMCs occurred following their exit from the G1 phase and entry into the S phase in response to the release mitogens upon a vascular injury (Ross, 1995). G1 phase is reported to be a major point of control for cell proliferation in mammalian cells (Fang and Newport, 1991). Beyond this point, the cells are committed to DNA replication, and further cell cycle progression proceeds independently of growth factor stimulation. The Rb protein is a key component of the molecular network controlling the restriction point, which maintains the hypophosphorylated state to bind the E2F family of transcription factors and inhibits the transcription of E2F-responsive genes essential for cell cycle progression and DNA synthesis. A treatment of VSMCs with pterostilbene resulted in the inhibition of pRb phosphorylation, which was correlated well with the inhibition of PDGF-BB-stimulated cell proliferation and DNA synthesis in a concentration-dependent manner. Considering that pRb can be phosphorylated by a number of cell cycle regulatory molecules, such as CDKs and cyclins (Braun-Dullaeus et al., 2004; Sherr, 1996; Sherr and Roberts, 1999), the effects of pterostilbene on expressions of CDK2, cyclin E, CDK4, and cyclin D1 were tested. Accordingly, pterostilbene inhibited CDK2, cyclin E, CDK4 and cyclin D1 expressions (Fig. 2), indicating that cell cycle arrest in the G1-phase might be due to the downregulation of CDKs/cyclins complex expression and pRb phosphorylation (Dzau et al., 2002). Therefore, the inhibition of CDK2, cyclin E, CDK4 and cyclin D1 expressions as well as Rb protein phosphorylation may be sufficient to achieve cell cycle arrest. The expression of PCNA, a phospho-pRb-mediated gene product in the early G0/G1 and S phases of the cell cycle (Tomita et al., 2005), was also inhibited by pterostilbene in Fig. 2.

The up-regulation of PDGF-R expression is associated with the development and progression of cardiovascular diseases such as hypertension (Mulvany, 1990) and atherosclerosis (Ross, 1993). PDGF acts as a potent mitogen for VSMCs proliferation through the phosphorylation of the PDGF-R (Majesky et al., 1990). In this study, PDGF-BB-induced PDGF-Rβ tyrosine phosphorylation in VSMCs is not altered by pterostilbene (Fig. 3), suggesting that PDGF-BB may not be the direct target of pterostilbene for the inhibition of VSMCs proliferation. Pterostilbene did not inhibit the FBS-induced proliferation of VSMCs (Fig. 1D), indicating that the inhibitory effect of pterostilbene on VSMC proliferation may be specific for PDGF-mediated events, although other growth factors are not tested. Akt, ERK1/2 and PLCγ1 are the downstream components of PDGF signaling pathway. A number of receptor tyrosine kinases, including the receptors for PDGF-BB, activate PI3K/Akt, ERK1/2 kinase and PLCγ1, and their signaling pathways are important in early intracellular mitogenic signal transduction for cell growth and survival (Muller, 1997). Among the MAP kinase family, ERK1/2 has been implicated in the growth of various cell types including MCF7, CHO, Jurkat-T and VSMCs (Hommes et al., 2003; Robinson and Cobb, 1997). PLCγ1 mediates a central downstream signal transduction route for various growth factors, including PDGF-BB (Heldin et al., 1998). PI3K positively regulates cell survival. Akt, a serine/threonine protein kinase, is activated through the PI3K pathway (Higaki and Shimokado, 1999). This kinase has been implicated in VSMCs proliferation, cell cycle progression and cell survival (Higaki and Shimokado, 1999; Waltenberger, 1997). The expressions of PLCγ1, ERK1/2, and Akt kinase phosphorylation are increased by PDGF-BB, and pterostilbene inhibited PDGF-BB-induced phosphorylation of Akt (Fig. 4C), but neither ERK1/2 (Fig. 4A) nor PLCγ1 (Fig. 4B), indicating that Akt protein is a potential target for pterostilbene. Akt, referred to as PKB or Rac, plays a critical role in controlling cell survival and apoptosis. This protein kinase is activated by insulin and various growth and survival factors in a wortmannin-sensitive pathway involving PI-3 kinase (Burgering and Cofer, 1995; Franke et al., 1995). An inhibition of DNA synthesis can be observed when VSMCs were treated with LY294002, an Akt inhibitor. The combined treatment of LY294002 with pterostilbene in VSMCs showed the completely suppression of DNA synthesis, indicating that these may be either a synergic or additive effect of cell proliferation. These results supported the hypothesis that the inhibitory effects of pterostilbene on Akt activation can be effective to block PDGF-BB-stimulated VSMCs proliferation. Our results indicate that the inhibition of Akt expression stimulated by PDGF-BB may be involved in the inhibition of VSMCs proliferation by pterostilbene although the molecular mechanism of pterostilbene for the inhibition effect of VSMCs proliferation was not still fully clarified. Akt inhibitors have been widely used in treatment of hypertension and angina by exhibiting an array of beneficial effects in the cardiovascular system (Myllarniemi et al., 1999).

Polyphenols contribute to the vasoprotective, antiangiogenic, antithrombotic, vasorelaxant and anti-inflammatory effects of acute or chronic administration of plant polyphenols found in patients (Stoclet et al., 2004). Resveratrol, one of polyphenol compounds, inhibited the growth of human VSMCs (Minoyan and Fujise, 2003). Pterostilbene with a structure similar to resveratrol may have an inhibitory effect on the growth of human vascular smooth muscle cell. Thus, pterostilbene may have beneficial effects on the VSMCs proliferation-related diseases such as atherosclerosis, restenosis after angioplasty and development of hypertension.

In summary, our study demonstrated that pterostilbene inhibits PDGF-BB-induced rat aortic VSMCs growth and cell cycle through inhibition of Akt-dependent pathway. Therefore, pterostilbene may be a potential candidate for preventing or treating vascular diseases and restenosis after angioplasty.

Acknowledgment

This work was supported by Priorite Research Centers Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (2009-0094035).

References


