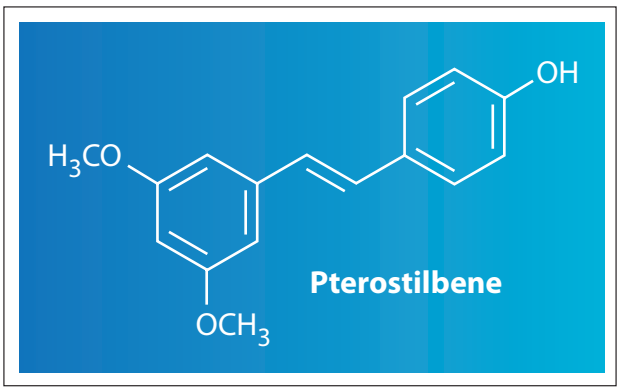
Pterostilbene Monograph



Introduction

Pterostilbene is a chemical classified as a benzylidene compound (more specifically a stilbene) and is biologically classified as a phytoalexin, which are antimicrobial substances that are part of the plant's defense system and are synthesized in response to pathogen infection. This monograph focuses on trans-pterostilbene.

Stilbenes are low molecular weight (approximately 200-300 g/mol), naturally occurring polyphenol compounds produced by a variety of plants that secrete them in response to environmental challenges such as viral, microbial, and fungal infection or excessive ultraviolet exposure.[1] Stilbenes are found in a wide range of plant families, including *Vitis* and *Vaccinium*.[2,3] These molecules are synthesized via the phenylpropanoid pathway and are structurally similar to estrogen.[4] Natural sources of pterostilbene include *Vitis vinifera*, *Vaccinium* spp., and *Pterocarpus* spp.

Ayurvedic medicine cites Darakchasava as a well-known Indian herbal preparation of *Vitis vinifera* that contains pterostilbene and is prescribed as a cardiotonic.[5] In addition, *Pterocarpus marsupium* has been used for many years in the treatment of diabetes mellitus. Pterostilbene was found to be one of the active constituents in the extracts (known as Vijyasar) of the *Pterocarpus marsupium* heartwood. It is suggested that pterostilbene might be one of the principal antidiabetic constituents in these extracts.[6-9]

Pterostilbene is known to have diverse pharmacological benefits for the prevention and treatment of a wide variety of diseases, including cancer,[10-15] dyslipidemia,[16] diabetes,[8,17,18] cardiovascular degeneration,[17] and pain.[19] As a potent chemopreventative, antioxidant, and anti-inflammatory agent, pterostilbene has the potential to ameliorate the effects of aging when used by healthy individuals.[7] Pterostilbene may be effective in correcting the dyslipidemia that leads to atherosclerosis and coronary heart disease, as it can increase the HDL/LDL cholesterol ratio.[20]

Colon cancer is one of the leading causes of cancer mortality in men and women in Western countries. Epidemiological studies have linked the consumption of fruits and vegetables to a reduced risk of colon cancer, in particular small fruits that are particularly rich sources of pterostilbene and other pharmacologically active stilbenes.[14] Recent advances in the study of colon cancer have stimulated an interest in diet and lifestyle as an effective means of prevention. As constituents of small fruits such as grapes and berries and their products, stilbenes are under intense investigation as cancer chemopreventive agents.[21] One of the best characterized stilbenes, resveratrol, is known to be an antioxidant and an anti-aging compound, as well as an anti-inflammatory agent.[22] Pterostilbene is closely related structurally to resveratrol and shows many of the same characteristics, as well as its own unique therapeutic potential.[21]

Pharmacokinetics

Pterostilbene might show higher biological activity based on relatively higher bioavailability compared to resveratrol, since substitution of a hydroxy with a methoxy group increases the transport into cells and increases the metabolic stability of the molecule. Thus, pterostilbene is not as quickly glucuronidated and sulfated as resveratrol. In a recent study evaluating the pharmacokinetics and pharmacodynamics of trans-pterostilbene by intravenous administration of 20 mg/kg of pterostilbene into rats,[23] a glucuronidated pterostilbene metabolite was detected in serum and

urine. Another pharmacokinetic study carried out in rats showed the terminal elimination half-life and clearance of pterostilbene were 96.6 ± 23.7 minutes and 37.0 ± 2.5 mL/min/kg, respectively, while its absolute oral bioavailability was 12.5 ± 4.7 percent; in this study, pterostilbene demonstrated improved pharmacokinetic characteristics over its naturally occurring analog, resveratrol.[24]

Mechanisms of Action

Pterostilbene owes its potential to diverse pharmacological actions that may alleviate diseases associated with oxidative damage and aging and promotion of health and an extended lifespan when used by healthy individuals. In general terms, the pharmacological actions of trans-pterostilbene are anti-inflammatory, antineoplastic and antioxidant; these activities stem from biological interactions at a fundamental level for both control of gene expression and enzyme activity modulation.

Antimicrobial

Resveratrol and its derivatives, including pterostilbene, are thought to be the most important stilbenes in grapevines (*Vitis vinifera*). One of the mechanisms of these substances in the plant appears to be their activity as an antimicrobial. Pterostilbene exhibits potent antifungal properties that are 5-10 times stronger than resveratrol.[2,25] Pterostilbene also exhibits antiviral effects.[26] The protection of the plant from various pathogens appears to be an important mechanism of stilbenes such as pterostilbene, and these protections may extend to humans and animals as well.[1,20]

Antineoplastic

Pterostilbene exhibits anticancer effects via various molecular mechanisms.[10-15] Studies show the actions of pterostilbene include modulation of signal transduction pathways,[1] cell cycle regulatory genes,[15] cell differentiation genes,[27] oncogenes,[10-12] and tumor suppressor genes.[13-15]

Antioxidant Activities

Pterostilbene possesses potent, concentration-dependent, antioxidant effects.[9,21,28,29] It is becoming increasingly clear that the specific pharmacological activities attributable to individual natural stilbenes are governed by the unique structural differences that distinguish them. For example, resveratrol (with three hydroxyl groups) neutralizes reactive oxygen species (ROS) in whole blood and isolated lymphoblasts, whereas pinosylvin (with two hydroxyl groups) influences mainly intracellular ROS; pterostilbene (with two methoxy and one hydroxyl group) reduces extracellular ROS.[30] This localization of antioxidative effect allows the use of pterostilbene to target extracellular reactive oxygen species that are, among other things, responsible for tissue damage during chronic inflammation.

Pterostilbene's peroxyl radical scavenging activity appears to be similar to resveratrol. Pterostilbene exhibited moderate inhibition (IC_{50} = 19.8 μM) of cyclooxygenase (COX)-1 and was weakly active (IC_{50} = 83.9 μM) against COX-2; whereas, resveratrol strongly inhibited both isoforms of the enzyme with IC_{50} values of approximately 1 μM.[21]

Anti-inflammatory

In an *in vitro* colitis model, pterostilbene inhibited prostaglandin E2 production in human colon adenocarcinoma cells. An anti-inflammatory analysis was conducted in which interleukin-1β was introduced into canine chondrocytes followed by treatment with pterostilbene. Decreased levels of MMP-3 gene expression (a structural gene for Stromelysin-1 protein thought to be active in the development of atherosclerosis, tumor initiation, and metastasis) and tumor necrosis factor-alpha (TNF-α; a cytokine involved in systemic inflammation) were noted, compared with control levels. Increased TNF-α production has been implicated in a variety of human diseases, including cardiovascular disease and cancer.[28]

Miscellaneous Mechanisms

Studies show pterostilbene, like its cousin resveratrol, possesses hypolipidemic[16] and antidiabetic properties,[8,9,17,18,31] and may be efficacious in reversing the deleterious effects of aging such as cognitive function and working memory.[7] Pterostilbene has properties that make it a potential chemopreventive agent. For example, it inhibited the activity of CYP1A1, CYP1A2 and CYP1B1 *in vitro*. CYP1A1 and CYP1B1 are the inducible forms of cytochrome P450 enzymes in extrahepatic tissues responsible for the biochemical conversion of polycyclic aromatic hydrocarbons, heterocyclic amines, and estradiol to potentially carcinogenic intermediate metabolites. Pterostilbene inhibits human CYP1A1 catalytic activity with a Ki value of 0.57 μM, thus exhibiting a stronger inhibitory effect on CYP1A1 in comparison to resveratrol. Pterostilbene inhibits CYP1B1 with a Ki value of 0.91 μM, comparable to that of resveratrol.[32] Its effect on CYP1A2 is the most

potent, with a Ki value of 0.39 μM.[33] Pterostilbene exhibited an analgesic effect in Sprague-Dawley rats dosed intravenously with 20 mg/kg. The animals had an increased latency period to response in both tail-flick and hot-plate analgesic tests.[23]

Clinical Indications

Infection

Pterostilbene shows potent antiviral activity against hepatitis C virus (HCV) at 10 μM, with no associated toxicity.[26] Pterostilbene inhibited infectious particle assembly and secretion and caused a reduction of intracellular infectivity. Pterostilbene is also an agonist of the peroxisome proliferator-activated receptor α (PPAR-α) that is known to be required for HCV RNA replication.[16,34]

Cancer

Studies have demonstrated concentration-dependent anticancer activity of pterostilbene in many cancer cell lines in the range of 1-100 mcg/mL.[13] The induction of apoptosis by pterostilbene may be the key mechanism of its antitumor effects on human gastric cancer. Experimental evidence shows that pterostilbene has potential for the prevention or treatment of colon,[11,13,14,23,35] liver,[10] skin,[12,36,37] pancreatic,[38] lung,[39] and breast cancer.[40]

In a rat colon carcinogenesis model pterostilbene suppressed aberrant crypt foci formation, one of the earliest changes seen in the colon that may lead to cancer.[11] Additional animal data show oral pterostilbene dosing suppressed colon tumorigenesis and cell proliferation in rats injected with the colon cancer-causing substance azoxymethane.[35] An *in vitro* test using human colon adenoma cells showed pterostilbene reduced gene expression of Myc (a transcription factor persistently expressed in many cancers, causing unregulated cell proliferation), cyclin D (a protein that may contribute to tumorigenesis), and beta-catenin (a protein that helps regulate cell growth and adhesion), as well as decreased phosphorylation (and subsequent down-regulation) of nuclear factor-kappaB (NF-κB) p65 (which is associated with more advanced colon cancer and metastasis).[35]

Pterostilbene inhibited tumor invasion via suppression of multiple signal transduction pathways in human hepatocellular carcinoma cells,[10] including matrix metalloproteinase-9, and expression of vascular endothelial growth factor (VEGF), activator-protein-1 (AP-1), mitogen-activated protein kinase (MAPK), NF-κB, and others.

Gastric cancer is the second most prevalent cause of worldwide cancer-related deaths and is significantly correlated with dietary habits, including increased reliance on processed meats and decreased intake of polyphenol-containing fruits and vegetables. In an *in vitro* study of human gastric adenocarcinoma cells, pterostilbene inhibited cellular proliferation and induced apoptosis via a number of mechanisms, including activation of the caspase cascade, alteration of cell-cycle regulating proteins, and damage to mitochondrial membranes by ROS.[15]

Pterostilbene has significant potential for a therapeutic role in the treatment of melanoma. *In vitro* exposure of melanoma cells to pterostilbene showed a dose-dependent inhibition of cell growth in association with increased effector caspase activity.[37] *In vitro* growth of highly malignant mouse melanoma cells was inhibited by exposure to pterostilbene and quercetin at 40 μM and 20 μM, respectively.[12] Oral dosing failed to inhibit cell growth; however, intravenous co-administration of pterostilbene and quercetin to mice inhibited liver metastasis by 73 percent, most likely through an inhibition of vascular cellular adhesion molecule-1 (VCAM-1) expression.[12]

Pterostilbene and resveratrol are both effective in inhibiting carcinogenesis in mouse epidermis. In a mouse model, resveratrol and pterostilbene inhibited 12-O-tetradecanoylphorbol-13-acetate (TPA)-activated NF-κB and AP-1 activation, in addition to reduced COX-2 and inducible nitric oxide synthase (iNOS) activity.[41]

A rat liver epithelial cell model showed that pretreatment with pterostilbene was effective in preventing gap junction damage by hydrogen peroxide and the loss of intercellular communication that leads to unregulated cell proliferation.[42]

Aging

The ability of pterostilbene to reduce the deleterious effects of aging was demonstrated in a study of resveratrol and six resveratrol analogues. Aged rats fed a diet containing pterostilbene showed a reversal of age-related cognitive behavioral deficits.[7]

Inflammation

Stilbenes have been shown to inhibit the activity of ROS. *In vitro* studies comparing pterostilbene, resveratrol, and pinosylvin showed that pterostilbene added to whole blood and the culture medium of activated polymorphonuclear leukocytes targets mainly extracellular reactive oxygen species, the

site of tissue damage during chronic inflammation.[30] Pterostilbene suppressed lipopolysaccharide-induced expression of iNOS and COX-2.[27] Researchers found that pterostilbene also inhibited lipopolysaccharide-induced activation of phosphoinositide 3-kinase/serine-threonine kinase Akt, extracellular signal-regulated kinase 1/2, and p38 MAPK. This showed that pterostilbene downregulates inflammatory iNOS and COX-2 gene expression in macrophages by inhibiting the activation of NF-κB and by interfering with the activation of PI3K/Akt/IKK and MAPK pathways.[27]

Diabetes/Dyslipidemia

Investigations conducted to evaluate the hypolipidemic activity of pterostilbene against streptozotocin-nicotinamide-induced diabetic rats showed it to be effective in ameliorating dyslipidemia, which is thought to play a significant role in the increased cardiovascular mortality seen in diabetics.[17] Oral administration of high-dose pterostilbene (40 mg/kg body weight) for six weeks significantly reduced serum VLDL and LDL cholesterol and increased serum HDL cholesterol. Triglycerides, phospholipids, free fatty acids, and total cholesterol were reduced.[17] Pterostilbene also increased antioxidant activity in diabetic rats, who demonstrated normalization of lipid peroxidation with pterostilbene treatment.[18]

Administration of pterostilbene significantly reduced pathological changes seen in liver and kidney of diabetic rats. Pterostilbene given at 40 mg/kg significantly decreased plasma glucose and increased insulin levels in normal and diabetic rats. Pterostilbene administration also resulted in a significant reduction of glycosylated hemoglobin.[31]

Pterostilbene was found *in vitro* to be a PPAR-α agonist, which can lower both plasma cholesterol and glucose. Feeding hypercholesterolemic hamsters a diet containing 25 ppm pterostilbene resulted in a 29-percent lower plasma LDL cholesterol, seven-percent higher HDL cholesterol, 14-percent lower glucose, and a lower LDL/HDL ratio, compared to controls.[16] Intraperitoneal administration of pterostilbene in rats significantly lowered blood glucose, an effect comparable to that of metformin.[9]

Side Effects and Toxicity

Pterostilbene is not known to be toxic or cause adverse effects in humans. In mice fed trans-pterostilbene for 28 days at doses up to 3000 mg/kg body weight/day, equivalent to 500 times the estimated mean human intake (25 mg/day), no significant toxic effects or adverse biochemical parameters were noted, compared to controls.[43]

Dosage

Data extrapolation from animal studies suggest a dose of 50-100 mg twice daily.

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