

RESEARCH MONOGRAPH . COMPOUND PROFILE

Pterostilbene

A naturally occurring trans-3,5-dimethoxy-4'-hydroxystilbene isolated from Pterocarpus heartwood and Vaccinium berries, distinguished from resveratrol by two methoxy substitutions that confer approximately fourfold greater lipophilicity, superior oral bioavailability, longer plasma half-life, and enhanced blood-brain barrier penetration while preserving SIRT1, AMPK, Nrf2, and NF-kappaB modulatory pharmacology.

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ABSTRACT

Pterostilbene (trans-3,5-dimethoxy-4'-hydroxystilbene; CAS 537-42-8; molecular formula C₁₆H₁₆O₃; molecular weight 256.30 g/mol) is a dimethylated analog of resveratrol first isolated from *Pterocarpus marsupium* heartwood in 1940 and subsequently identified in *Vaccinium corymbosum* (blueberry), *Vaccinium ashei* (rabbiteye blueberry), *Vitis vinifera* (grape), and several other plant species. The two methoxy groups at the 3- and 5-positions of the A-ring replace two of the three free hydroxyl groups present in resveratrol, conferring approximately fourfold greater lipophilicity, substantially reduced first-pass glucuronidation and sulfation, oral bioavailability of approximately 60 to 80 percent (compared to approximately 20 percent for resveratrol), a plasma elimination half-life of approximately 105 minutes (compared to approximately 14 minutes for resveratrol), and enhanced penetration across the blood-brain barrier. These pharmacokinetic advantages have positioned pterostilbene as a bioavailability-optimized stilbenoid for research into the pleiotropic pharmacology shared with the broader stilbene class. The molecular pharmacology of pterostilbene centers on four principal signaling axes. First, pterostilbene activates sirtuin 1 (SIRT1) and downstream PGC-1 α deacetylation, promoting mitochondrial biogenesis, fatty acid oxidation, and cellular stress resistance. Second, it activates AMP-activated protein kinase (AMPK), suppressing hepatic gluconeogenesis, promoting glucose uptake, and enhancing lipid catabolism. Third, it activates the Nrf2/Keap1 antioxidant response element pathway by directly disrupting the Keap1-Nrf2 protein-protein interaction and by epigenetic derepression of the Nrf2 promoter, inducing

downstream expression of heme oxygenase-1 (HO-1), NAD(P)H quinone dehydrogenase 1 (NQO1), superoxide dismutase, and catalase. Fourth, it inhibits NF-kappaB and AP-1 transcriptional activity, attenuating pro-inflammatory mediator expression including inducible nitric oxide synthase, cyclooxygenase-2, tumor necrosis factor alpha, and interleukin-1 beta. Additional preclinical activity includes modulation of PI3K/Akt/mTOR signaling in oncology models, induction of apoptosis and autophagy in multiple cancer cell lines, and anti-angiogenic effects through suppression of vascular endothelial growth factor and matrix metalloproteinase-9. The clinical evidence base for pterostilbene in humans is modest but growing. The principal randomized controlled trial (Riche et al., 2014) evaluated pterostilbene at 50 mg and 125 mg twice daily for 6 to 8 weeks in 80 hypercholesterolemic adults and reported significant reductions in systolic blood pressure (7.8 mmHg, $p < 0.01$) and diastolic blood pressure (7.3 mmHg, $p < 0.001$) at 250 mg/day, with no adverse effects on hepatic, renal, or glucose markers. The same trial identified a significant increase in low-density lipoprotein cholesterol (17.1 mg/dL, $p = 0.001$) with pterostilbene monotherapy, an effect attenuated by concurrent grape extract administration. A second major clinical program evaluated the combination of nicotinamide riboside and pterostilbene (NRPT, marketed as Basis by Elysium Health) in a randomized, double-blind, placebo-controlled trial of 120 healthy adults aged 60 to 80, demonstrating dose-dependent increases in whole blood NAD⁺ of approximately 40 percent at the recommended dose and approximately 90 percent at double dose after four weeks (Dellinger et al., 2017). Subsequent NRPT trials have reported reduction of hepatic inflammation markers in nonalcoholic fatty liver disease and safety in acute kidney injury. Preclinical

pharmacology is extensive. In rodent models, pterostilbene at doses of 10 to 100 mg/kg has demonstrated neuroprotection in Alzheimer's disease models (aluminum chloride-induced, streptozotocin-induced, amyloid-beta 25-35-induced), improvement in spatial and working memory, antidiabetic activity through AMPK-mediated suppression of hepatic gluconeogenesis, anticancer activity across breast, colon, prostate, lung, gastric, pancreatic, and oral cancer cell lines and xenograft models, and anti-inflammatory activity in models of colitis, myocardial ischemia, and acute lung injury. The compound crosses the blood-brain barrier and has been characterized as a more potent neuromodulator than resveratrol at equivalent doses in aging and Alzheimer's disease models (Chang et al., 2012). Pterostilbene is commercially available as a dietary supplement and as a research-grade chemical from multiple suppliers. It is not approved as a pharmaceutical in any jurisdiction. The compound is generally recognized as safe at doses up to 250 mg/day based on the available human safety data, with the LDL cholesterol elevation representing the principal metabolic safety signal requiring monitoring. This monograph reviews the chemistry, natural sources, and synthesis of pterostilbene; the multi-target molecular pharmacology; pharmacokinetics and metabolism; the preclinical evidence base across neuroprotection, oncology, metabolic disease, and inflammation; the human clinical evidence; sourcing and quality verification; reconstitution and handling; stack-interaction considerations; adverse events and safety signals; and a comparative assessment of five stilbenoid and polyphenol alternatives against pterostilbene on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

Common name: Pterostilbene.

Chemical Abstracts Service registry number: 537-42-8.

International Union of Pure and Applied Chemistry name: 4-[(E)-2-(3,5-dimethoxyphenyl)ethenyl]phenol.

Alternative chemical names: trans-3,5-dimethoxy-4'-hydroxystilbene; 3,5-dimethoxy-4'-hydroxystilbene; 3',5'-dimethoxy-4-stilbenol.

PubChem CID: 5281727.

ChEBI ID: CHEBI:8633.

DrugBank ID: DB12517.

The compound is referenced in the phytochemistry literature under its botanical source names, principally as "the dimethylated stilbene from Pterocarpus" or "the blueberry stilbenoid." In the dietary supplement market, pterostilbene is sold under proprietary trade names including pTeroPure (ChromaDex, discontinued for new orders in 2019) and as a component of Basis (Elysium Health, in combination with nicotinamide riboside).

1.2 Structural class and chemistry

Pterostilbene is a stilbenoid, a member of the stilbene structural class defined by the 1,2-diphenylethylene (C6-C2-C6) carbon skeleton. Within this class, it belongs to the trans-stilbene subgroup bearing oxygenated substituents on both aromatic rings. The compound is the 3,5-di-O-methyl ether of resveratrol (trans-3,5,4'-trihydroxystilbene), with the two methoxy groups located on the A-ring (positions 3 and 5) and a single free hydroxyl group retained on the B-ring (position 4') [1].

Molecular formula: C₁₆H₁₆O₃.

Exact mass: 256.1099 g/mol (monoisotopic).

Molecular weight: 256.30 g/mol.

Physical properties: White to pale yellow crystalline powder. Melting point 89 to 92 degrees Celsius. Boiling point approximately 420 degrees Celsius. Density approximately 1.17 g/cm³. Practically insoluble in water; soluble in dimethyl sulfoxide, ethanol, methanol, and other polar organic solvents. The compound is sensitive to oxidation on prolonged air exposure and to photoisomerization under ultraviolet light, the latter producing the cis-isomer which has reduced biological activity.

Stereochemistry: The biologically active and commercially supplied form is the trans (E) geometric isomer, with the two aromatic rings in the trans configuration across the central ethylene bridge. The cis (Z) isomer is produced by ultraviolet irradiation and has substantially lower activity in most pharmacological assays. No chiral centers are present; the compound is achiral.

LogP: Approximately 3.4 (calculated), compared to approximately 1.6 for resveratrol. The approximately fourfold increase in lipophilicity relative to resveratrol is attributable to the replacement of two polar hydroxyl groups with nonpolar methoxy groups and is the principal structural basis for the enhanced oral bioavailability and membrane permeability of pterostilbene [2].

1.3 Natural sources

Pterostilbene was first isolated from the heartwood of *Pterocarpus marsupium* (Indian kino tree, Fabaceae) in 1940 and was subsequently identified in *Pterocarpus santalinus* (red sandalwood) heartwood [3]. The compound is a phytoalexin, synthesized by the plant in response to fungal infection, ultraviolet irradiation, or other biotic and abiotic stress. It has been identified in the following plant sources at varying concentrations:

- *Vaccinium corymbosum* (highbush blueberry): approximately 99 to 520 nanograms per gram of fresh fruit, the highest dietary concentration identified in commonly consumed foods [4].
- *Vaccinium ashei* (rabbiteye blueberry): similar concentrations to highbush blueberry.
- *Vitis vinifera* (grape): present in grape skins and in fungal-infected grape berries as a stress-induced phytoalexin.

- *Pterocarpus marsupium* heartwood: the richest natural source by concentration; heartwood extracts have been used in traditional Ayurvedic medicine for diabetes management.
- *Pterocarpus santalinus* (red sandalwood): present in heartwood.
- *Dracaena cochinchinensis* and *Dracaena cambodiana*: dragon's blood resin.
- Peanuts (*Arachis hypogaea*): trace amounts.

The dietary intake of pterostilbene from food sources is low (estimated at less than 1 mg/day from typical Western diets), substantially below the pharmacologically active concentrations studied in human trials. Supplemental sources are therefore required for achieving the 50 to 250 mg/day dose range evaluated in clinical research.

1.4 Synthesis

Pterostilbene can be obtained by extraction from natural plant sources (principally *Pterocarpus* heartwood), by chemical synthesis, or by biosynthetic production in engineered microorganisms.

Chemical synthesis: The most common synthetic route is a Horner-Wadsworth-Emmons reaction between 3,5-dimethoxybenzaldehyde and diethyl (4-methoxybenzyl)phosphonate, followed by demethylation of the 4'-methoxy group to yield the free 4'-hydroxyl. An alternative approach employs Wittig olefination or Heck cross-coupling reactions [5]. The Perkin condensation and Knoevenagel condensation have also been applied. Synthetic pterostilbene is typically purified by column chromatography and recrystallization from ethanol or hexane/ethyl acetate mixtures to greater than 97 percent purity. The trans-selectivity of the olefination reactions is high (typically greater than 95 percent E-isomer), and the product is characterized by nuclear magnetic resonance spectroscopy, mass spectrometry, and melting point determination.

Biosynthetic production: Pterostilbene can be produced in *Escherichia coli* and *Saccharomyces cerevisiae* strains engineered with the stilbene biosynthetic pathway. The pathway requires tyrosine ammonia lyase, p-coumarate:CoA ligase, stilbene synthase, and resveratrol O-methyltransferase; the last enzyme catalyzes the transfer of two methyl groups from S-adenosyl methionine to the 3- and 5-hydroxyl

positions of resveratrol [6]. Microbial production titers have improved substantially in recent years but remain below the cost-competitiveness threshold for commercial supply relative to chemical synthesis and plant extraction.

2. Abstract

Pterostilbene (trans-3,5-dimethoxy-4'-hydroxystilbene; CAS 537-42-8) is a naturally occurring dimethylated stilbenoid polyphenol that shares the core pharmacological profile of the broader stilbene class, principally resveratrol, while exhibiting substantially superior pharmacokinetic properties attributable to the two methoxy substitutions at the 3- and 5-positions of the A-ring. The compound was first isolated from *Pterocarpus marsupium* heartwood in 1940 and was identified in blueberries (*Vaccinium* spp.) in the early 2000s, an observation that catalyzed research interest in the compound as a dietary-source stilbenoid with translational potential [3, 4].

The pharmacokinetic advantages of pterostilbene over resveratrol are substantial. Oral bioavailability in rats is approximately 67 percent for pterostilbene compared to approximately 30 percent for resveratrol at equivalent doses, with peak plasma concentrations approximately 36-fold higher for pterostilbene [2]. The plasma elimination half-life in rodents is approximately 105 minutes for pterostilbene compared to approximately 14 minutes for resveratrol. The structural basis is the replacement of two free hydroxyl groups (which are rapidly conjugated by hepatic and intestinal UDP-glucuronosyltransferases and sulfotransferases) with methoxy groups that resist phase II conjugation [7]. The enhanced lipophilicity additionally promotes blood-brain barrier penetration, supporting central nervous system pharmacology that is difficult to achieve with resveratrol.

The molecular pharmacology centers on activation of SIRT1, AMPK, and Nrf2 signaling, and inhibition of NF-kappaB-driven inflammation. These pathways converge on mitochondrial biogenesis, oxidative stress defense, metabolic regulation, and suppression of pro-inflammatory gene expression. Additional preclinical targets include PI3K/Akt/mTOR pathway modulation in oncology, PPAR-alpha activation in neuroprotection and lipid metabolism, and epigenetic modulation through effects on histone acetylation and DNA methylation [8, 9].

The preclinical evidence base is extensive across neuroprotection (Alzheimer's disease models, cerebral ischemia, aging-related cognitive decline), oncology (breast, colon, prostate, lung, gastric, pancreatic, and oral cancer models), metabolic disease (diabetes, obesity, nonalcoholic fatty liver disease), cardiovascular

protection, and anti-inflammatory applications. Chang et al. (2012) demonstrated that low-dose pterostilbene, but not resveratrol at equivalent doses, produced significant neuromodulatory effects in aging SAMP8 mice through upregulation of PPAR-alpha and modulation of cellular stress markers, establishing pterostilbene as the more pharmacologically active stilbenoid in central nervous system applications [8].

The human clinical evidence base consists of a small number of randomized controlled trials. The Riche et al. (2014) trial in 80 hypercholesterolemic adults demonstrated blood pressure reduction at 250 mg/day with a concurrent LDL cholesterol increase that represents the principal metabolic safety signal [10, 11]. The Dellinger et al. (2017) NRPT trial demonstrated safe and sustained NAD⁺ elevation in healthy elderly adults using the combination of nicotinamide riboside and pterostilbene [12]. Subsequent NRPT trials have extended safety and efficacy observations to nonalcoholic fatty liver disease and acute kidney injury populations [13, 14].

Pterostilbene is sold as a dietary supplement and research chemical. It is not approved as a pharmaceutical in any jurisdiction. Investigators should treat the compound as a research tool with promising but incompletely validated clinical pharmacology, manage the LDL cholesterol signal as a monitoring consideration, and apply analytical verification to all research-grade material.

3. Discovery and Development History

3.1 Isolation and early characterization

Pterostilbene was first isolated and identified in 1940 from the heartwood of *Pterocarpus marsupium*, a tree native to the Indian subcontinent long used in Ayurvedic medicine for the management of diabetes and related metabolic conditions [3]. The compound was characterized as a stilbenoid phytoalexin and was noted for its structural relationship to resveratrol, itself first isolated from white hellebore (*Veratrum grandiflorum*) roots in 1940 by Takaoka. The two compounds share the trans-stilbene core but differ in the substitution pattern on the A-ring: resveratrol bears three free hydroxyl groups (3, 5, and 4'), while pterostilbene bears two methoxy groups (3 and 5) and one free hydroxyl (4').

3.2 Identification in dietary sources

The identification of pterostilbene in *Vaccinium* berries (blueberries) in the early 2000s by Rimando et al. (2004) at the United States Department of Agriculture Agricultural Research Service marked a transition in the research trajectory of the compound [4]. The USDA group quantified pterostilbene in blueberry fruit at approximately 99 to 520 ng/g fresh weight and noted the structural and pharmacological similarities to resveratrol. The dietary source identification catalyzed research interest from both the natural products pharmacology community and the dietary supplement industry.

3.3 Bioavailability characterization

The landmark pharmacokinetic comparison between pterostilbene and resveratrol was published by Kapetanovic et al. (2011) at the National Cancer Institute [2]. This study administered equimolar oral doses of both compounds to Sprague-Dawley rats and demonstrated that pterostilbene achieved approximately 36-fold higher peak plasma concentrations, approximately 67 percent oral bioavailability (compared to approximately 30 percent for resveratrol), and substantially longer plasma persistence. The reduced susceptibility to hepatic and intestinal glucuronidation

was identified as the principal mechanistic basis. This study established the pharmacokinetic rationale for pterostilbene as a superior research tool for stilbenoid pharmacology.

3.4 Commercial development

ChromaDex Corporation developed a branded pterostilbene ingredient (pTeroPure) for the dietary supplement market and supplied material for the Riche et al. (2014) clinical trial. In 2019, ChromaDex ceased new pterostilbene orders following the publication of data demonstrating the LDL cholesterol increase in human subjects, a commercial decision that reduced but did not eliminate supplement market availability [15]. Elysium Health developed the NRPT combination product (Basis), pairing nicotinamide riboside with pterostilbene at a dose of 50 mg pterostilbene per daily serving, and funded the Dellinger et al. (2017) clinical trial that established NAD⁺ elevation in healthy elderly adults [12].

3.5 Current research-clinical state

Pterostilbene has not entered pharmaceutical development for any indication. The compound is not the subject of an Investigational New Drug application at the United States Food and Drug Administration in publicly available registries. The current research state is one of extensive preclinical pharmacology across multiple therapeutic domains, a small number of human trials demonstrating safety and limited efficacy signals, and ongoing academic and industry interest in the compound as a bioavailability-optimized stilbenoid for longevity, neuroprotection, and metabolic health applications. The compound is available as a dietary supplement and as a research chemical without prescription.

4. Mechanism of Action

Pterostilbene is a multi-target polyphenol. Its principal molecular activities, characterized in cell culture systems and confirmed in rodent models, are SIRT1 activation, AMPK activation, Nrf2/Keap1 pathway induction, NF-kappaB/AP-1 transcriptional suppression, and modulation of the PI3K/Akt/mTOR axis. These activities converge on mitochondrial function, oxidative stress defense, metabolic regulation, anti-inflammatory gene expression, and cell survival and proliferation decisions.

4.1 SIRT1 activation and downstream signaling

Sirtuin 1 (SIRT1) is an NAD⁺-dependent protein deacetylase that regulates mitochondrial biogenesis, cellular stress resistance, insulin sensitivity, and inflammatory gene expression through deacetylation of downstream targets including PGC-1alpha, FOXO transcription factors, p53, and NF-kappaB p65 [16]. Pterostilbene activates SIRT1 in multiple cell types and in vivo, promoting PGC-1alpha deacetylation and consequent mitochondrial biogenesis. The SIRT1 activation by pterostilbene has been demonstrated to attenuate doxorubicin-induced cardiotoxicity through PGC-1alpha-mediated enhancement of mitochondrial function [17], to protect against oxidative stress-induced intestinal injury [18], and to ameliorate skeletal muscle ischemia-reperfusion injury [19].

The SIRT1-mediated mechanism is the molecular basis for the neuroprotective activity observed in amyloid-beta 25-35-induced cognitive deficit models, where pterostilbene treatment rescued spatial memory through SIRT1-dependent pathways that were abolished by the SIRT1 inhibitor EX-527 [20].

4.2 AMPK activation

AMP-activated protein kinase (AMPK) is a master regulator of cellular energy homeostasis. Pterostilbene activates AMPK through phosphorylation at Thr172, producing downstream effects including suppression of hepatic gluconeogenic gene expression (PEPCK, G6Pase), promotion of glucose transporter 4 (GLUT4) transloca-

tion to the plasma membrane, enhancement of fatty acid oxidation through phosphorylation of acetyl-CoA carboxylase, and inhibition of lipogenic gene expression through suppression of SREBP-1c [21, 22].

The AMPK activation contributes to the antidiabetic profile observed in rodent models. In fructose-induced diabetic rats, pterostilbene ameliorated glycemic control, insulin sensitivity, and hepatic oxidative stress through AMPK-dependent mechanisms [23]. In H4IIE hepatoma cells, pterostilbene suppressed hepatic gluconeogenic gene expression through AMPK activation with an efficacy comparable to metformin at equivalent concentrations [21].

4.3 Nrf2/Keap1 pathway activation

The nuclear factor erythroid 2-related factor 2 (Nrf2) pathway is the principal transcriptional regulator of the cellular antioxidant response. Under basal conditions, Nrf2 is sequestered in the cytoplasm by Kelch-like ECH-associated protein 1 (Keap1) and targeted for proteasomal degradation. Pterostilbene activates the Nrf2 pathway through at least three mechanisms: direct disruption of the Keap1-Nrf2 protein-protein interaction by binding to basic amino acid residues in the Keap1 kelch domain [24]; epigenetic derepression of the Nrf2 promoter through reduction of CpG island methylation [25]; and stimulation of histone acetylation at the Nrf2 promoter locus [25].

The downstream consequence is nuclear translocation of Nrf2, binding to antioxidant response elements in target gene promoters, and induction of phase II detoxification and antioxidant enzymes including heme oxygenase-1 (HO-1), NAD(P)H quinone dehydrogenase 1 (NQO1), superoxide dismutase (SOD), catalase (CAT), and glutathione S-transferase [24, 26]. The Nrf2-mediated antioxidant response is the molecular basis for the cytoprotective effects observed in models of oxidative damage, ferroptosis, and ischemia-reperfusion injury.

Li et al. (2020) demonstrated that pterostilbene induced Nrf2/HO-1 signaling and potentially regulated NF-kappaB and JNK-Akt/mTOR signaling in neonatal rat models of ischemic brain injury, establishing a mechanistic link between Nrf2 activation and neuroprotection [26].

4.4 NF-kappaB and AP-1 inhibition

Pterostilbene inhibits the transcriptional activity of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kappaB) and activating protein-1 (AP-1), two master regulators of inflammatory gene expression [27]. The inhibition is mediated in part through SIRT1-dependent deacetylation of the NF-kappaB p65 subunit and in part through AMPK-dependent phosphorylation events that suppress IkappaB kinase activity. The downstream consequence is reduced expression of pro-inflammatory mediators including inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), tumor necrosis factor alpha (TNF-alpha), interleukin-1 beta (IL-1beta), and interleukin-6 (IL-6).

The convergence of SIRT1 activation and NF-kappaB suppression through the P-AMPK-alpha/SIRT1/PGC-1alpha/NF-kappaB/P38 signaling axis has been characterized in alveolar epithelial cell models of influenza A virus-induced acute lung injury, where pterostilbene reduced pro-inflammatory cytokine expression and attenuated tissue damage [28].

4.5 PI3K/Akt/mTOR pathway modulation

In oncology models, pterostilbene modulates the phosphatidylinositol 3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/Akt/mTOR) signaling cascade. The compound suppresses Akt phosphorylation in multiple cancer cell lines, leading to downstream inhibition of mTOR-dependent protein synthesis, cell cycle arrest (principally at G0/G1 and G2/M checkpoints), induction of apoptosis through caspase-3 and caspase-9 activation, and induction of autophagy [29, 30]. The dual induction of apoptosis and autophagy is a notable feature of the pterostilbene anticancer mechanism; pharmacological blockade of autophagy augments the growth-inhibitory effect, suggesting that autophagy serves a partially cytoprotective function in pterostilbene-treated cancer cells [30].

4.6 PPAR-alpha activation

Peroxisome proliferator-activated receptor alpha (PPAR-alpha) activation by pterostilbene has been characterized as a component of the neuroprotective and lipid-modulatory mechanisms. Chang et al. (2012) reported that pterostilbene, but not resveratrol at equivalent doses, upregulated PPAR-alpha expression in the brains of aging SAMP8 mice and that this upregulation was associated with modulation of

cellular stress markers and improvement in cognition-related behavioral endpoints [8]. PPAR-alpha activation promotes fatty acid oxidation, reduces triglyceride synthesis, and exerts anti-inflammatory effects in the central nervous system and in hepatocytes.

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

Pterostilbene is well absorbed from the gastrointestinal tract after oral administration. Oral bioavailability in Sprague-Dawley rats is approximately 67 percent at a 56 mg/kg dose (compared to approximately 30 percent for resveratrol at the same dose), reflecting the reduced susceptibility to first-pass conjugation [2]. Peak plasma concentration (C_{max}) values for pterostilbene are approximately 36-fold higher than those of resveratrol at equivalent oral doses. Time to peak plasma concentration is approximately 1 to 2 hours in rats.

Human pharmacokinetic data are limited. Physiologically-based pharmacokinetic modeling predicts human oral bioavailability of approximately 43 percent, with intestinal availability of approximately 13 percent and hepatic availability of approximately 72 percent [31]. The lower human bioavailability prediction relative to rat values is consistent with species differences in intestinal and hepatic conjugation enzyme activity. Despite this reduction, human bioavailability remains substantially higher than that of resveratrol.

5.2 Distribution

Pterostilbene has moderate to high volume of distribution, consistent with its lipophilic character (LogP approximately 3.4). The compound crosses the blood-brain barrier, a property demonstrated by direct measurement of brain tissue concentrations in rodent studies and by the central nervous system pharmacodynamic effects observed at oral doses in aging and Alzheimer's disease models [8]. The enhanced blood-brain barrier penetration relative to resveratrol is attributable to the greater lipophilicity and is a principal pharmacological advantage for neuroprotection applications.

Tissue distribution studies in rats have demonstrated accumulation in liver, kidney, and brain. Plasma protein binding has not been precisely characterized in published literature but is expected to be moderate to high based on the

lipophilicity.

5.3 Metabolism

Pterostilbene undergoes predominantly phase II metabolism. The principal metabolic pathways are glucuronidation (catalyzed by UDP-glucuronosyltransferases, principally UGT1A1, UGT1A6, UGT1A9, and UGT2B7), sulfation (catalyzed by sulfotransferases), and to a lesser extent mono-O-demethylation by cytochrome P450 enzymes [2, 7].

The critical pharmacokinetic advantage over resveratrol resides in the reduced efficiency of glucuronidation. Resveratrol, bearing three free hydroxyl groups, is rapidly and extensively glucuronidated by hepatic and intestinal UGTs, producing resveratrol-3-O-glucuronide and resveratrol-4'-O-glucuronide as major metabolites with very short plasma half-life. Pterostilbene, bearing only a single free hydroxyl group at the 4'-position, has substantially fewer sites available for conjugation, and the glucuronidation efficiency at the 4'-hydroxyl is lower than that of the resveratrol hydroxyls [7]. The result is reduced first-pass metabolism and longer plasma residence.

The plasma elimination half-life in rats is approximately 105 minutes for pterostilbene, compared to approximately 14 minutes for resveratrol [2]. The clearance rate of pterostilbene is significantly lower than that of resveratrol, consistent with the reduced conjugation efficiency.

Phase I metabolism contributes a minor fraction of total clearance. CYP-mediated O-demethylation at the 3- or 5-position can produce mono-desmethyl metabolites that are subsequently conjugated. The specific CYP isoforms responsible have not been comprehensively characterized, though CYP1A2 is implicated based on in vitro data.

5.4 Drug-metabolizing enzyme interactions

Pterostilbene inhibits several drug-metabolizing enzymes at pharmacologically relevant concentrations. Al-Shara et al. (2019) reported significant inhibition of CYP2C8 (IC₅₀ approximately 3.0 micromolar) and UGT1A6 (IC₅₀ approximately 15.1 micromolar) [32]. Separate studies have identified potent inhibition of CYP2C9 (IC₅₀

approximately 0.12 micromolar), suggesting that pterostilbene at supplement doses may produce clinically meaningful interactions with CYP2C9 substrates including warfarin and phenytoin [33].

Jiang et al. (2019) characterized potent noncompetitive inhibition of UGT1A9 by pterostilbene (IC₅₀ 0.92 micromolar, K_i 0.52 micromolar), and estimated that pterostilbene supplementation at 100 mg/day or higher may produce at least a 50 percent increase in the area under the curve of drugs predominantly cleared by UGT1A9, including propofol, mycophenolic acid, and certain nonsteroidal anti-inflammatory drugs [34].

5.5 Elimination

Renal excretion of conjugated metabolites (glucuronides and sulfates) is the principal elimination pathway. Less than 5 percent of an administered dose is excreted as unchanged pterostilbene in urine. Biliary excretion contributes a minor fraction. The elimination is therefore predominantly metabolic (phase II conjugation followed by renal clearance of conjugates).

5.6 Routes of administration

Oral administration is the standard route for both dietary supplement use and research applications. Pterostilbene is supplied as capsules or bulk powder for oral ingestion, typically at 50 to 250 mg per dose. Intraperitoneal and intravenous routes have been used in rodent pharmacology research. Topical formulations have been explored for dermatological applications. Nanoparticle and nanoemulsion formulations have been developed to further enhance bioavailability and tissue targeting [35].

6. Preclinical Pharmacology

6.1 Neuroprotection and cognitive enhancement

Pterostilbene has demonstrated neuroprotective activity in multiple rodent models of neurodegeneration and aging-related cognitive decline.

Chang et al. (2012) reported that low-dose pterostilbene (but not resveratrol at equivalent doses) was a potent neuromodulator in the SAMP8 accelerated aging mouse model, producing significant improvement in radial arm water maze performance, upregulation of PPAR-alpha expression, and positive modulation of markers of cellular stress, inflammation, and Alzheimer's disease pathology [8]. The study established that pterostilbene was more pharmacologically active than resveratrol in the central nervous system at equivalent oral doses, consistent with the superior blood-brain barrier penetration.

In amyloid-beta 25-35-induced cognitive deficit models in mice, pterostilbene rescued spatial memory through SIRT1-dependent mechanisms, with the neuroprotective effect abolished by concurrent administration of the SIRT1 inhibitor EX-527 [20]. In aluminum chloride-induced Alzheimer's disease models in rats, pterostilbene at 50 mg/kg and 100 mg/kg significantly increased spontaneous alternation percentage (by 35.7 percent and 42.9 percent, respectively) and discrimination index (by 79.7 percent and 83.4 percent, respectively) [36].

Pterostilbene ameliorated intracerebroventricular streptozotocin-induced memory decline in rats, with improvements on Morris water maze and novel object recognition tests associated with reduced oxidative stress, reduced acetylcholinesterase activity, and restored antioxidant enzyme levels [37].

In neonatal rat models of ischemic brain injury, pterostilbene reduced infarct volume, alleviated cerebral edema, decreased activated microglial cell counts, and suppressed eNOS and IL-1beta expression through Nrf2/HO-1 pathway induction [26].

6.2 Anticancer activity

Pterostilbene has demonstrated antiproliferative, pro-apoptotic, and anti-metastatic activity in cell culture and xenograft models across multiple cancer types.

In breast cancer, pterostilbene inhibited growth of MCF-7, MDA-MB-231, and other breast cancer cell lines through induction of apoptosis, cell cycle arrest, and inhibition of Wnt signaling [30, 38]. Wang et al. (2012) demonstrated that pterostilbene simultaneously induced apoptosis, cell cycle arrest, and cytoprotective autophagy in breast cancer cells, with blockade of autophagy augmenting the antiproliferative effect [30].

In colon cancer, pterostilbene and its derivative 3'-hydroxypterostilbene demonstrated potent anti-cancer effects in colon xenograft tumor models [39]. In lung cancer, pterostilbene activated endoplasmic reticulum stress pathways and induced apoptosis and autophagy through inhibition of AKT and JNK pathways and activation of ERK1/2 [40]. In prostate cancer, pterostilbene in combination with histone deacetylase inhibitors attenuated cancer progression through targeting of the MTA1/HIF-1 α signaling axis [41].

Pterostilbene enhanced chemosensitivity in pancreatic cancer cells and reversed cisplatin resistance in gastric and oral cancer cell lines through modulation of AKT signaling and suppression of multidrug resistance protein 1 [42, 43].

The anticancer mechanism involves convergent suppression of PI3K/Akt/mTOR, MAPK/ERK, JAK/STAT, and NF-kappaB signaling, with the net effect of inhibiting cell proliferation, promoting apoptosis, suppressing angiogenesis (through VEGF and MMP-9 downregulation), and inhibiting metastatic invasion [29].

6.3 Metabolic disease

In rodent models of type 2 diabetes and metabolic syndrome, pterostilbene has demonstrated antidiabetic and lipid-lowering activity. Pterostilbene ameliorated insulin sensitivity, glycemic control, and hepatic oxidative stress in fructose-induced diabetic rats [23]. In H4IIE hepatoma cells, pterostilbene activated AMPK and suppressed hepatic gluconeogenic gene expression, a mechanism parallel to metformin [21].

However, the metabolic disease evidence is not uniformly positive. Gomez et al. (2022) reported that pterostilbene failed to rescue insulin secretion and sensitivity in multiple murine models of diabetes (diet-induced obese mice and streptozotocin-induced diabetic mice), suggesting that the antidiabetic effects may be model-dependent and may not translate universally across species or disease severity [44].

In nonalcoholic fatty liver disease models, pterostilbene and its derivative 3'-hydroxypterostilbene ameliorated hepatic steatosis through synergistic modulation of gut microbiota and the SIRT1/AMPK signaling pathway [45].

6.4 Cardiovascular protection

Pterostilbene has demonstrated cardioprotective activity in preclinical models. The compound attenuated doxorubicin-induced cardiotoxicity through AMPK and SIRT1 cascade activation and PGC-1 α -mediated enhancement of mitochondrial function [17]. Anti-atherosclerotic effects have been reported through NF- κ B-mediated suppression of vascular inflammation and through improvement of endothelial function.

6.5 Anti-inflammatory activity

Beyond the NF- κ B and AP-1 inhibition detailed in the mechanism section, pterostilbene has demonstrated anti-inflammatory activity in models of colitis, acute lung injury, myocardial ischemia, and ocular inflammation [27, 28]. The anti-inflammatory mechanism involves suppression of pro-inflammatory cytokine production, inhibition of leukocyte recruitment, and promotion of anti-inflammatory M2 macrophage polarization.

7. Clinical Evidence Base

7.1 Metabolic parameters trial (Riche et al., 2014)

The principal clinical trial of pterostilbene as a single agent is the Riche et al. (2014) randomized, double-blind, placebo-controlled trial conducted at the University of Mississippi Medical Center [10, 11]. The trial enrolled 80 adults with hypercholesterolemia (LDL cholesterol 100 to 190 mg/dL, not on lipid-lowering therapy) and randomized them to four arms: placebo, pterostilbene 50 mg twice daily, pterostilbene 125 mg twice daily, or pterostilbene 50 mg twice daily plus grape extract 100 mg twice daily, for 6 to 8 weeks.

Blood pressure: Pterostilbene at 125 mg twice daily (250 mg/day) significantly reduced systolic blood pressure by 7.8 mmHg ($p < 0.01$) and diastolic blood pressure by 7.3 mmHg ($p < 0.001$) compared to placebo. The lower dose (100 mg/day) did not produce significant blood pressure reduction [10].

Lipids: Pterostilbene monotherapy at both 100 mg/day and 250 mg/day significantly increased LDL cholesterol by 17.1 mg/dL ($p = 0.001$) compared to placebo. The combination of pterostilbene 100 mg/day with grape extract 200 mg/day attenuated but did not fully abolish this LDL increase [10, 15].

Safety: No adverse drug reactions on hepatic function tests (ALT, AST, alkaline phosphatase), renal function tests (creatinine, BUN), or glucose markers were observed. No statistically significant self-reported adverse events or major adverse events occurred. A 3.6 percent reduction in serum bicarbonate was observed in the high-dose group ($p = 0.02$) [11].

Body weight: Pterostilbene at 250 mg/day produced a significant reduction in body weight of 0.78 kg ($p = 0.02$) compared to placebo [10].

7.2 Safety analysis (Riche et al., 2013)

A concurrent safety analysis from the same trial population confirmed that pterostilbene was generally safe for human use at doses up to 250 mg/day [11]. The analysis evaluated hepatotoxicity, nephrotoxicity, and glucotoxicity biomarkers and found no clinically significant perturbations.

7.3 NRPT trials (Dellinger et al., 2017 and subsequent)

The Dellinger et al. (2017) trial evaluated the combination of nicotinamide riboside (NR, 250 mg) and pterostilbene (PT, 50 mg) at recommended (NRPT 1X: 250 mg NR + 50 mg PT) and double doses (NRPT 2X: 500 mg NR + 100 mg PT) in a randomized, double-blind, placebo-controlled study of 120 healthy adults aged 60 to 80 years for 8 weeks [12]. Whole blood NAD⁺ levels increased by approximately 40 percent in the NRPT 1X group and approximately 90 percent in the NRPT 2X group after 4 weeks compared to placebo, with the elevation sustained through 8 weeks. The compound was well tolerated in both dose groups.

Dellinger et al. (2022) extended the NRPT program to nonalcoholic fatty liver disease in a 6-month randomized, double-blind, placebo-controlled trial of 111 adults [13]. The NRPT 1X group showed time-dependent decreases in circulating alanine aminotransferase (ALT) and gamma-glutamyltransferase (GGT) that were significant versus placebo, along with a significant decrease in circulating ceramide 14:0.

Simic et al. (2020) evaluated NRPT in acute kidney injury in a dose-escalation safety study, demonstrating safety and NAD⁺ elevation in this population [14].

Lapatto et al. (2023) evaluated NRPT supplementation in experimental muscle injury in elderly individuals in a randomized placebo-controlled trial, contributing additional safety data but failing to demonstrate significant benefit on the primary muscle injury endpoint [46].

7.4 Antioxidant and anti-inflammatory human evidence

Small human studies have evaluated pterostilbene-containing formulations for antioxidant and anti-inflammatory endpoints. A double-blind, randomized, placebo-controlled crossover trial in 96 elderly adults using a combination supplement containing pterostilbene demonstrated significant reductions in serum nitric oxide, C-reactive protein, and improvement in total antioxidant capacity [47]. However, the multi-ingredient design of such formulations limits attribution of effects specifically to pterostilbene.

7.5 Limitations of the clinical evidence

The human clinical evidence base for pterostilbene is limited by small sample sizes, short treatment durations, absence of clinical endpoint trials (no trials have evaluated hard endpoints such as cardiovascular events, cancer incidence, or dementia diagnosis), and the confounding effects of multi-ingredient formulations in several trials. No Phase 3 registration trials have been conducted. The compound has not been evaluated in an Investigational New Drug framework. Investigators should interpret the existing clinical data as preliminary safety and biomarker evidence rather than as definitive efficacy data.

8. Sourcing and Quality Verification

Pterostilbene is available from multiple sources across a range of purity and quality grades.

Dietary supplement grade: Multiple supplement manufacturers supply pterostilbene in capsule or powder form, typically at 50 to 150 mg per capsule. Supplement-grade material is generally produced by extraction from *Pterocarpus marsupium* heartwood or by chemical synthesis, with purity specifications varying by manufacturer. The supplement market was historically dominated by ChromaDex's pTeroPure branded ingredient; following ChromaDex's cessation of new pterostilbene orders in 2019, alternative suppliers have filled the market [15].

Research-grade chemical: Multiple chemical suppliers (Sigma-Aldrich, Cayman Chemical, Tocris, MedChemExpress, Selleckchem, Santa Cruz Biotechnology, Abcam) supply pterostilbene at greater than 97 percent purity by HPLC. Supply is in milligram to gram quantities. Pricing is moderate, in the range of \$20 to \$100 per gram at the time of monograph preparation.

Analytical verification: Investigators should confirm compound identity and purity on every research-grade lot through:

- High-performance liquid chromatography area-percent purity (greater than 97 percent recommended for research applications).
- Mass spectrometry confirmation of molecular weight (257.12 for the protonated molecule $[M+H]^+$, 256.11 for the molecular ion).
- Nuclear magnetic resonance spectroscopy confirmation of the trans-stilbene geometry and substitution pattern.
- Assessment of the trans/cis isomer ratio by HPLC or NMR (greater than 95 percent trans-isomer).
- Residual solvent analysis for compounds produced by chemical synthesis.

Third-party analytical laboratories (Janoshik Analytical, Anabolic Lab, others) provide independent confirmation of vendor certificates of analysis. Lot-to-lot variability in both supplement-grade and research-grade pterostilbene has been reported,

and on-receipt analytical confirmation is appropriate for any investigation where dose-response precision is important.

9. Reconstitution and Handling

Pterostilbene is supplied as a crystalline powder. For oral administration in research settings, the compound can be administered directly in capsule form, suspended in vehicle (typically 0.5 percent carboxymethylcellulose, olive oil, or polyethylene glycol 400 for rodent studies), or dissolved in ethanol or dimethyl sulfoxide for in vitro applications.

Stock solutions: For cell culture work, stock solutions are typically prepared at 10 to 100 mM in dimethyl sulfoxide (DMSO). Final DMSO concentration in cell culture medium should not exceed 0.1 percent (v/v) to avoid solvent cytotoxicity. Aqueous solubility is very low (less than 1 mg/mL); co-solvent systems or cyclodextrin complexation may be used to improve aqueous formulations [48].

Storage: The solid compound should be stored at minus 20 degrees Celsius, protected from light and moisture, under inert atmosphere (nitrogen or argon) for long-term stability. Under these conditions, stability exceeds 24 months. At room temperature in dry, dark conditions, stability is adequate for weeks to months. DMSO stock solutions should be stored at minus 20 degrees Celsius and are stable for at least 6 months. Aqueous solutions should be prepared fresh or used within 24 hours.

Light sensitivity: Pterostilbene undergoes photoisomerization from the active trans-isomer to the less active cis-isomer on exposure to ultraviolet light. Solutions and solid material should be protected from direct sunlight and from fluorescent lighting during preparation and storage. Amber glass vials or aluminum foil wrapping is appropriate.

Oxidation sensitivity: The compound is moderately sensitive to oxidation on prolonged exposure to air. Storage under inert gas headspace and minimization of air exposure during handling are recommended for long-term storage of bulk material.

10. Stack Interaction Considerations

Investigators combining pterostilbene with other research substances or dietary supplements should consider enzyme-level interactions, pharmacodynamic interactions, and target-level synergies and antagonisms.

CYP2C9 substrates: Pterostilbene inhibits CYP2C9 with an IC₅₀ of approximately 0.12 micromolar [33]. Concurrent use with CYP2C9 substrates (warfarin, phenytoin, losartan, celecoxib, fluvastatin, tolbutamide) may increase exposure to these drugs. Investigators and research participants using warfarin should exercise particular caution, as the interaction may elevate anticoagulant effect and bleeding risk.

CYP2C8 substrates: Pterostilbene inhibits CYP2C8 with an IC₅₀ of approximately 3.0 micromolar [32]. Concurrent use with CYP2C8 substrates (paclitaxel, repaglinide, amodiaquine, cerivastatin) may increase substrate exposure.

UGT1A9 substrates: Pterostilbene is a potent noncompetitive inhibitor of UGT1A9 (IC₅₀ 0.92 micromolar, K_i 0.52 micromolar) [34]. Concurrent use with UGT1A9-cleared drugs (propofol, mycophenolic acid, dapagliflozin, certain NSAIDs) at pterostilbene doses of 100 mg/day or higher may produce clinically meaningful increases in substrate exposure.

Nicotinamide riboside: The NRPT combination (nicotinamide riboside plus pterostilbene) is the most extensively studied pterostilbene stack in clinical trials. The combination produces synergistic NAD⁺ elevation in humans [12]. Pterostilbene's SIRT1 activation may enhance the utilization of the NAD⁺ pool elevated by nicotinamide riboside, providing a pharmacological rationale for the combination.

Resveratrol: Co-administration with resveratrol produces additive effects on shared targets (SIRT1, AMPK, Nrf2). No pharmacokinetic antagonism has been reported. The combination is pharmacologically rational but may be redundant given the overlapping mechanism; pterostilbene alone at appropriate doses may achieve the pharmacodynamic effects of both compounds given its superior bioavailability.

Lipid-lowering agents: Given the observed LDL cholesterol increase with pterostilbene monotherapy in humans [10], concurrent use with statins, PCSK9 inhibitors, ezetimibe, or other lipid-lowering agents should be considered. The grape extract co-administration attenuated the LDL increase in the Riche trial, suggesting that concurrent polyphenol administration may mitigate this effect.

Anticoagulants and antiplatelet agents: Beyond the CYP2C9-mediated interaction with warfarin, pterostilbene has demonstrated antiplatelet activity in preclinical models. Concurrent use with anticoagulants, antiplatelet agents, or other compounds with hemorrhagic potential warrants monitoring.

Chemotherapeutic agents: Preclinical evidence supports synergistic activity of pterostilbene with cisplatin, doxorubicin, and 5-fluorouracil [42, 43]. Investigators exploring pterostilbene as a chemosensitizer should be aware of the potential for altered chemotherapy pharmacokinetics through UGT and CYP inhibition.

11. Adverse Events and Safety

11.1 Human safety data

The Riche et al. (2013, 2014) trial provides the most comprehensive human safety data for pterostilbene monotherapy [10, 11]. At doses of 100 mg/day and 250 mg/day for 6 to 8 weeks in 80 hypercholesterolemic adults:

- No adverse drug reactions on hepatic function markers (ALT, AST, alkaline phosphatase).
- No adverse drug reactions on renal function markers (creatinine, BUN).
- No adverse drug reactions on glucose markers (fasting blood glucose, HbA1c).
- No statistically significant self-reported adverse events compared to placebo.
- No major adverse events (hospitalizations, serious illness, death) in any treatment group.

The NRPT trials (Dellinger et al., 2017; Simic et al., 2020; Dellinger et al., 2022; Lapatto et al., 2023) have reported safety of the nicotinamide riboside plus pterostilbene combination across healthy elderly adults, acute kidney injury patients, non-alcoholic fatty liver disease patients, and elderly muscle injury subjects [12, 13, 14, 46].

11.2 LDL cholesterol elevation

The principal metabolic safety signal is the increase in LDL cholesterol observed with pterostilbene monotherapy. In the Riche et al. (2014) trial, pterostilbene at both 100 mg/day and 250 mg/day produced a mean LDL increase of 17.1 mg/dL ($p = 0.001$) compared to placebo [10]. This increase was attenuated when pterostilbene was co-administered with grape extract but was not fully abolished. The mechanism is not fully characterized but may involve PCSK9/HNF1-alpha/SREBP2/LDLR signaling modulation, as suggested by in vitro studies in HL-1 cardiomyocytes [49].

ChromaDex ceased new pterostilbene orders in 2019, citing the LDL data as a basis for the commercial decision [15]. The clinical significance of the LDL increase depends on the baseline cardiovascular risk of the individual and the duration of

exposure; short-term use at moderate doses may not produce clinically meaningful cardiovascular risk elevation, but chronic high-dose use in individuals with existing dyslipidemia warrants lipid monitoring.

11.3 Serum bicarbonate reduction

The Riche et al. (2014) trial reported a 3.6 percent reduction in serum bicarbonate in the high-dose pterostilbene group (250 mg/day) compared to placebo ($p = 0.02$) [10]. The clinical significance is uncertain; mild metabolic acidosis is a theoretical concern but has not been confirmed in longer-duration studies.

11.4 Preclinical safety

Preclinical toxicology studies in rodents have not identified dose-limiting toxicity at doses up to 3000 mg/kg in acute toxicity studies. Subchronic 28-day and 90-day toxicity studies in rats at doses up to 300 mg/kg/day have not identified target organ toxicity. Genotoxicity assays (Ames test, chromosomal aberration test, micronucleus test) have been negative. The compound is not classified as carcinogenic, mutagenic, or teratogenic based on available preclinical data.

11.5 Drug interaction risk

As detailed in the stack interaction section, pterostilbene inhibits CYP2C9, CYP2C8, and UGT1A9 at concentrations achievable with supplement dosing [32, 33, 34]. The drug interaction risk is the most important safety consideration for individuals taking concurrent medications, particularly warfarin, phenytoin, and UGT1A9-cleared drugs.

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five stilbenoid and polyphenol compounds against pterostilbene, evaluated against five competency standards: novelty, effect size, promising potential (current clinical state and trajectory), side-effect profile, and overall validation. The five comparators were selected as the principal compounds that share mechanism, structural class, or research positioning with pterostilbene, with priority on those that have produced material clinical evidence.

12.1 Resveratrol (trans-3,5,4'-trihydroxystilbene)

Mechanism: SIRT1 activation, AMPK activation, Nrf2 induction, NF-kappaB inhibition. The target profile is essentially identical to pterostilbene; the two compounds share the same pharmacological class and the same downstream signaling effects. The structural difference is the presence of three free hydroxyl groups in resveratrol (compared to one hydroxyl and two methoxy groups in pterostilbene), which determines the pharmacokinetic divergence [1].

Novelty: Low. Resveratrol is the original and most extensively studied stilbenoid. Its pharmacology has been characterized in thousands of publications since the early 1990s. Pterostilbene offers novelty principally through superior pharmacokinetics rather than through novel mechanism.

Effect size: Preclinical effect sizes for resveratrol are broadly similar to pterostilbene on shared targets, but the lower bioavailability (approximately 20 percent oral, 14-minute plasma half-life) limits achievable plasma concentrations at practical oral doses [2]. Human clinical trials of resveratrol have produced inconsistent results, with meta-analyses showing modest effects on metabolic parameters at doses of 150 to 1000 mg/day. The Chang et al. (2012) head-to-head comparison in SAMP8 mice demonstrated that pterostilbene, but not resveratrol at equivalent doses, produced significant neuromodulatory effects [8].

Promising potential: Moderate. Resveratrol has a substantially larger human clinical trial database than pterostilbene (dozens of randomized trials across cardiovascular, metabolic, oncology, and neurological endpoints) but has not produced a definitive positive Phase 3 outcome in any indication. The compound is widely available as a dietary supplement.

Side-effect profile: Resveratrol is generally well tolerated at doses up to 1000 mg/day. Gastrointestinal symptoms (diarrhea, nausea) are the most common adverse events at higher doses. Resveratrol interacts with CYP enzymes (CYP1A2, CYP2C9, CYP2D6, CYP3A4) and may produce drug interactions at high doses. The LDL cholesterol elevation reported with pterostilbene has not been consistently observed with resveratrol.

Overall validation: Moderate to high as a research tool; low as a clinical intervention. The extensive preclinical literature and the large number of human trials provide substantial mechanistic validation, but the pharmacokinetic limitations and the inconsistent clinical trial results reduce the translational confidence.

Comparison to pterostilbene: Resveratrol and pterostilbene are structurally and mechanistically closely related. Pterostilbene has the advantages of superior oral bioavailability, longer plasma half-life, enhanced blood-brain barrier penetration, and demonstrated superiority in head-to-head preclinical comparisons. Resveratrol has the advantages of a larger clinical evidence base, wider commercial availability, and absence of the LDL cholesterol signal. For research applications requiring reliable plasma concentrations, pterostilbene is the preferred stilbenoid.

12.2 Piceatannol (trans-3,4,3',5'-tetrahydroxystilbene)

Mechanism: SIRT1 activation, AMPK activation, Nrf2 induction, NF-kappaB inhibition, and additional Syk kinase inhibition and antiadipogenic activity [50]. Piceatannol is a hydroxylated stilbenoid (bearing four hydroxyl groups compared to three for resveratrol) with additional molecular targets not shared by pterostilbene or resveratrol.

Novelty: Moderate. The Syk kinase inhibition and antiadipogenic mechanisms distinguish piceatannol from the other stilbenoids and provide a differentiated pharmacological profile.

Effect size: Preclinical effect sizes on shared SIRT1/AMPK targets are comparable to resveratrol and pterostilbene. The antiadipogenic effect (inhibition of adipocyte differentiation) has been demonstrated in cell culture and rodent models.

Promising potential: Low. Human clinical evidence is minimal. The compound is available as a research chemical but not as a widely marketed dietary supplement. No randomized clinical trials of piceatannol monotherapy have been published at the time of monograph preparation.

Side-effect profile: Preclinical safety data suggest tolerability comparable to resveratrol. Human safety data are absent.

Overall validation: Low to moderate. The compound has a growing preclinical literature but essentially no clinical validation.

Comparison to pterostilbene: Piceatannol shares the stilbenoid mechanism with pterostilbene but has inferior pharmacokinetic properties (four hydroxyl groups subject to rapid conjugation), substantially less clinical evidence, and less commercial availability. The Syk kinase inhibition is a differentiating feature but has not been clinically validated. Pterostilbene is the more advanced and better characterized compound for most research applications.

12.3 Oxyresveratrol (trans-2,3',4,5'-tetrahydroxystilbene)

Mechanism: Tyrosinase inhibition, antioxidant activity, NF-kappaB inhibition, neuroprotective activity [51]. Oxyresveratrol is a tetrahydroxylated stilbenoid found in mulberry (*Morus alba*) with a distinct substitution pattern and a prominent mechanism of tyrosinase inhibition that is not shared by pterostilbene or resveratrol.

Novelty: Moderate. The potent tyrosinase inhibition (IC50 in the low-micromolar range) positions oxyresveratrol uniquely in the stilbenoid class for dermatological and depigmentation applications.

Effect size: Preclinical effect sizes for antioxidant and neuroprotective endpoints are modest. The tyrosinase inhibition is potent and well-characterized.

Promising potential: Low to moderate. Limited human clinical evidence exists, principally in dermatological applications. The compound is not widely available as a dietary supplement.

Side-effect profile: Preclinical safety data are limited. Human safety data are minimal.

Overall validation: Low. The compound is principally a preclinical research tool with a differentiated mechanism (tyrosinase inhibition) but minimal clinical translation.

Comparison to pterostilbene: Oxyresveratrol occupies a different niche (dermatological and depigmentation applications) than pterostilbene (metabolic, neuroprotective, and longevity applications). Direct comparison is limited by the divergent research trajectories. Pterostilbene has substantially more clinical evidence and broader pharmacological characterization.

12.4 Honokiol (3',5-di(prop-2-en-1-yl)[1,1'-biphenyl]-2,4'-diol)

Mechanism: SIRT3 activation, AMPK activation, NF-kappaB inhibition, PPAR-gamma modulation, anti-angiogenic activity, and antitumor activity through multiple pathways [52]. Honokiol is a neolignan (not a stilbenoid) from Magnolia bark with a partially overlapping pharmacological profile but a distinct structural class and distinct molecular targets.

Novelty: Moderate to high. The SIRT3 (rather than SIRT1) activation and the PPAR-gamma modulation distinguish honokiol from the stilbenoid class. The compound has a traditional medicine history (Magnolia bark is used in traditional Chinese and Japanese medicine).

Effect size: Preclinical effect sizes in oncology models are substantial, with honokiol demonstrating antiproliferative activity across multiple cancer cell lines and xenograft models. Anti-anxiety and neuroprotective effects have been reported in rodent behavioral models.

Promising potential: Low to moderate. Human clinical evidence is limited to small studies of Magnolia bark extract rather than isolated honokiol. The compound is available as a dietary supplement (principally in Magnolia bark extract formulations) and as a research chemical.

Side-effect profile: Generally well tolerated in preclinical studies. Magnolia bark extract has a long history of use in traditional medicine without significant reported adverse events. Isolated honokiol human safety data are limited.

Overall validation: Moderate as a preclinical research tool; low as a clinically validated intervention. The compound has a substantial preclinical literature in oncology and neuroprotection but minimal controlled clinical evidence.

Comparison to pterostilbene: Honokiol and pterostilbene share the pleiotropic polyphenol profile (antioxidant, anti-inflammatory, anticancer, neuroprotective) but differ in structural class, molecular targets, and clinical evidence. Pterostilbene has more controlled clinical trial evidence and a more precisely characterized pharmacokinetic profile. Honokiol offers differentiated mechanism (SIRT3, PPAR-gamma) that may complement pterostilbene in combination research.

12.5 Fisetin (3,3',4',7-tetrahydroxyflavone)

Mechanism: SIRT1 activation, senolytic activity (selective clearance of senescent cells), Nrf2 activation, NF-kappaB inhibition, PI3K/Akt inhibition [53]. Fisetin is a flavonol (not a stilbenoid) found in strawberries, apples, and onions. Its distinguishing pharmacological feature is senolytic activity demonstrated by the Kirkland laboratory at Mayo Clinic, positioning fisetin uniquely in the longevity and aging research space.

Novelty: High. The senolytic mechanism (selective induction of apoptosis in senescent cells while sparing non-senescent cells) is mechanistically distinct from the stilbenoid pharmacology and is supported by a growing body of preclinical and early clinical evidence. The Yousefzadeh et al. (2018) study in aging mice demonstrated that fisetin extended healthspan and reduced senescence biomarkers [53].

Effect size: Preclinical senolytic effect sizes in aged mice are substantial. The AFFIRMM trial and other ongoing fisetin trials are evaluating clinical senolytic endpoints.

Promising potential: Moderate to high. Fisetin is the subject of multiple active clinical trials (NCT03675724, NCT04210986, and others) evaluating senolytic activity in aging, osteoarthritis, frailty, and COVID-19 recovery. The clinical trajectory is more advanced and more focused than that of pterostilbene.

Side-effect profile: Fisetin is generally well tolerated in early clinical trials. Bioavailability is poor (similar to resveratrol); novel formulations are under development.

Overall validation: Moderate. The senolytic mechanism is well-supported pre-clinically and is under active clinical investigation. The compound shares some pharmacological overlap with pterostilbene (SIRT1, Nrf2, NF-kappaB) but is differentiated by the senolytic mechanism.

Comparison to pterostilbene: Fisetin and pterostilbene share pleiotropic polyphenol pharmacology but occupy different research niches. Fisetin is positioned primarily as a senolytic agent; pterostilbene is positioned primarily as a bioavailability-optimized stilbenoid for metabolic, neuroprotective, and longevity applications. Fisetin has a more active clinical trial program. Pterostilbene has superior bioavailability among the naturally occurring polyphenols. The two compounds are mechanistically complementary and could be studied in combination for synergistic aging and senescence endpoints.

12.6 Comparator summary

The five comparators occupy distinct positions relative to pterostilbene. **Resveratrol** is the closest structural and mechanistic analog but is pharmacokinetically inferior; pterostilbene provides the same pharmacology with better drug-like properties. **Piceatannol** adds Syk kinase inhibition but has poor pharmacokinetics and minimal clinical evidence. **Oxyresveratrol** is differentiated by tyrosinase inhibition for dermatological applications but has limited clinical translation. **Honokiol** offers complementary mechanism (SIRT3, PPAR-gamma) from a different structural class with a traditional medicine history but limited clinical evidence. **Fisetin** is the most differentiated comparator through its senolytic mechanism and has the most active clinical trial program among the comparators.

Pterostilbene occupies a unique position in this landscape as the bioavailability-optimized stilbenoid with the best balance of preclinical breadth, human safety data, pharmacokinetic characterization, and commercial availability. Its principal limitations are the modest clinical evidence base (no Phase 3 trials, no clinical endpoint studies), the LDL cholesterol safety signal, and the absence of pharmaceutical regulatory approval. Investigators selecting among these compounds for research applications should consider pterostilbene when reliable oral bioavailability and blood-brain barrier penetration are priorities, fisetin when senolytic activity is the primary research question, and resveratrol when alignment with the largest human clinical evidence base is desired.

13. References

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