Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Pterostilbene

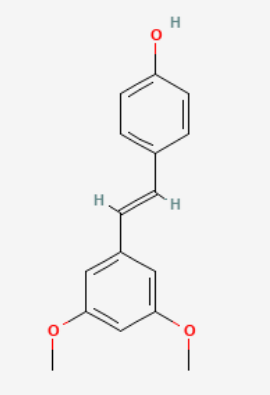
Evidence Summary

Pterostilbene is more bioavailable than resveratrol, but only a few clinical trials have tested it alone, so more evidence is needed. Pterostilbene may increase cholesterol levels and interact with some drugs.

Neuroprotective Benefit: Pterostilbene has higher bioavailability than resveratrol. Studies in rodent models suggest cognitive benefits through antioxidative and anti-inflammatory effects. However, no clinical trials have confirmed these effects in humans.

Aging and related health concerns: Clinical evidence is limited and mixed. Pterostilbene treatment may increase cholesterol levels but decrease blood pressure. So far, the promising preclinical data in various conditions have not been validated in humans.

Safety: Based on a few clinical trials testing pterostilbene alone, adverse events were uncommon. Pterostilbene treatment may increase total and LDL-cholesterol. Pterostilbene likely interacts with drugs/compounds metabolized by UGT1A9.

Availability: OTC	**Dose**: Clinical trials have typically tested a dose of 50 mg per day, orally.	**Chemical formula:** $C_{16}H_{16}O_3$ **MW**: 256.30  Source: PubChem
Half-life: not documented in humans; 1.7 hours in rats	**BBB**: penetrant in rodents	
Clinical trials: A clinical trial testing pterostilbene alone enrolled 80 participants.	**Observational studies**: none available	

What is it?

Pterostilbene is an anti-fungal agent naturally created by plants like red sandalwood, blueberries, and grapes. It is also a major phenolic compound of darakchasava, an herbal preparation used in traditional Indian Ayurvedic medicine. Pterostilbene and resveratrol are structurally very similar but pterostilbene has stronger anti-fungal properties, better bioavailability (up to 80% versus ~30% for resveratrol), and greater penetrance through the blood-brain barrier (Estrela 2013; Dutta et al., 2023; Qu et al., 2023). However, pterostilbene has low aqueous solubility.

Pterostilbene has emerged as a promising therapeutic for age-related conditions, including cardiovascular diseases, metabolic conditions, and cognitive decline. Based on predominantly preclinical data, pterostilbene's mechanisms of action include activation of Nrf2, the transcription factor that regulates antioxidant defenses, and activation of the AMPK/SIRT1/PGC-1α axis important for energy and mitochondrial homeostasis (Dutta et al., 2023; Qu et al., 2023).

Neuroprotective Benefit: Pterostilbene has higher bioavailability than resveratrol. Studies in rodent models suggest cognitive benefits through antioxidative and anti-inflammatory effects. However, no clinical trials have confirmed these effects in humans.

Types of evidence:

- 1 randomized controlled trial testing a combination therapy including pterostilbene in ALS patients
- Numerous laboratory studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function:

No studies have tested pterostilbene for the prevention of dementia or age-related cognitive decline in humans.

Human research to suggest benefits to patients with dementia:

No studies have tested pterostilbene treatment in patients with dementia.

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

Laboratory studies suggest that pterostilbene exerts neuroprotective effects through antioxidant effects, anti-inflammation, regulation of lipid metabolism, vascular smooth muscle cell proliferation, and improvement in synaptic function and neurogenesis (Qu et al., 2023). Evidence from rodent studies suggest that pterostilbene crosses the blood-brain barrier. No clinical trials have tested pterostilbene for neuroprotection in humans except for a small study in amyotrophic lateral sclerosis patients that tested a combination therapy including pterostilbene.

Amyotrophic lateral sclerosis (ALS): In a double-blind randomized controlled trial of 32 patients with ALS (20 study completers), treatment with pterostilbene + nicotinamide riboside (NR)(1,200 mg; EH301, Elysium Health) for 4 months resulted in significant improvements in the ALS functional rating scale-revised (ALSFRS-R) score ($p<0.01$), pulmonary function, muscular strength, and in skeletal muscle/fat weight ratio compared to the placebo group (de la Rubia et al., 2019). Pterostilbene and NR (NAD+ precursor) are thought to work synergistically to increase NAD+ levels and promote sirtuin activity. In the clinical trial, there were some baseline imbalances between the pterostilbene + NR and placebo

groups; the Medical Research Council (MRC) grading scale index and surface electromyogram (EMG) measurements in the right tibia muscles were lower in the pterostilbene + NR group compared to the placebo group. With regards to ALSFRS-R score, patients in the placebo group had deteriorated significantly relative to their baseline measurements ($p < 0.05$), corresponding to a 3.0- and 5.5-point decline at the 2- and 4-month evaluation, respectively. Everyone in the placebo group except one patient showed disease progression. In contrast, the pterostilbene + NR group showed a significant improvement in ALSFRS-R score at the 2- and 4-month evaluation, corresponding to a 3.4- and 2.5-point improvement, respectively. Out of 10 patients treated with pterostilbene + NR, 7 showed improvement in the ALSFRS-R scores. With regards to the secondary outcome, MRC grading scale, pterostilbene + NR treatment for 2 months showed a significant improvement compared to placebo, despite the lower baseline index in the pterostilbene + NR group; the pterostilbene + NR group improved by 9.6 points while the placebo group declined by 10.0 points. This was also significant at 4 months, when the difference between pterostilbene + NR and placebo groups were 23.2 points ($p<0.01$).

Forced vital capacity (FVC) was significantly improved with pterostilbene + NR treatment relative to baseline ($p<0.05$) and relative to placebo ($p<0.01$)(de la Rubia et al., 2019). After 2 months of treatment, the pterostilbene + NR group had a 6.1% increase in FVC, while the placebo group experienced a 3.8% decline. After 4 months of treatment, there was a difference of 19.4% in FVC between pterostilbene + NR and placebo groups. Pterostilbene + NR treatment for 4 months also led to a significant increase in electrical activity within the right and left tibial muscles relative to baseline ($p<0.01$ for both) and significantly greater electrical activities in the left biceps, right and left triceps, and left tibial muscles compared to the placebo group. After 2 months of treatment, the pterostilbene + NR group had an increase in electrical activity in 5 out of 8 muscle groups. After 4 months of treatment, a significant pterostilbene + NR treatment effect (compared to placebo) was observed for the right and left triceps and the right and left tibial muscles ($p<0.01$ for all). Pterostilbene + NR treatment also resulted in a significant decrease in fat and a significant increase in skeletal muscle weights, which were opposite what was observed in the placebo group. These findings suggest that pterostilbene + NR treatment may improve muscular strength in ALS patients.

After the completion of the ALS trial, all participants were given the option to continue treatment on an open-label extension study, and all participants elected to continue taking pterostilbene + NR (de la Rubia et al., 2019). After 1-year post-randomization to pterostilbene + NR, patients did not show significant deterioration in the ALSFRS-R score or muscle function (measured by the MRC grading scale). Also, 6 of the 8 muscle groups investigated (using EMG) did not show deterioration. There was, however, an 11.5% reduction in FVC, suggesting some decline in pulmonary function, though this

reduction in FVC at 1-year is less than the reduction in FVC observed in the placebo group at 4 months (16.7% reduction).

Rodent models of cognitive dysfunction: Numerous studies have tested the effects of pterostilbene in various rodent models of cognitive dysfunction.

In a mouse model of Alzheimer's disease (APP/PS1 mice), pterostilbene treatment (10 or 40 mg/kg/day, intragastric) for 10 weeks enhanced learning and memory (measured by the Y-maze, novel object recognition, and Morris water maze) and reduced inflammation (Iba1 immunoreactivity, TNF-α , IL-1β, and IL-6 mRNA) and Aβ aggregation in the hippocampus (Xu et al., 2023).

In a different mouse model of Alzheimer's disease (intracerebroventricular injection of Aβ25-35), pterostilbene treatment (10, 20, or 40 mg/kg/day, intragastric) for 20 days alleviated cognitive dysfunction measured by the Y-maze, novel object recognition, and Morris water maze tests, while decreasing neuronal death and oxidative stress (activated Nrf2 pathway, increased SOD, and decreased MDA) in the hippocampus and cortex (Xu et al., 2021). In a related study using the same mouse model of Alzheimer's disease, pterostilbene treatment (40 mg/kg/day, intragastric) showed greater benefits than resveratrol treatment (40 mg/kg/day) in cognitive function measured by the novel object recognition, Y-maze, and Morris water maze tests (Zhu et al., 2022). Pterostilbene treatment upregulated sirtuin-1 (SIRT1, an NAD+-dependent enzyme), Nrf2 (transcription factor that regulates antioxidant pathways), and SOD (antioxidant enzyme), and inhibited mitochondria-dependent apoptosis (decreased Bax, increased Bcl2/Bax). Pterostilbene treatment also significantly increased neuronal (NeuN) and synaptic (PSD-95 and SYN-1) proteins.

In a mouse model of vascular dementia (bilateral common carotid artery occlusion to mimic chronic cerebral hypoperfusion), pterostilbene treatment (10 or 40 mg/kg) for 13 days attenuated working memory impairment measured by the Y-maze and Morris water maze tests and reduced hippocampal neuronal death, inflammation (iNOS and IL-1β mRNA), and microglial activation (reduced TLR4/NFkB-mediated inflammation through increased TLR4 ubiquitination)(Xu et al., 2022).

In a rat model of memory decline (induced by streptozotocin), pterostilbene treatment (10, 30, or 50 mg/kg, orally) for 13 days significantly improved memory, measured by Morris water maze and novel object recognition tests (Naik et al., 2017). Pterostilbene treatment also improved overall brain antioxidant parameters (increased catalase, SOD, GSH levels, lowered nitrites, lipid peroxides, and

carbonylated proteins). Gene expression studies suggested increased mitochondrial biogenesis (increased PPAR-α and PGC1-α) and decreased inflammation (decreased TNF-α, IL-6).

In a mouse model of accelerated aging (SAMP8), pterostilbene treatment (120 mg/kg of diet) for 2 months, but not resveratrol treatment (120 mg/kg of diet), improved cognitive function as measured by the radial arm water maze, and improved markers of oxidative stress (restored MnSOD), Alzheimer's-like pathology (decreased p-tau), and increased PPAR-α activity. In this model, neither pterostilbene nor resveratrol activated SIRT1 (Chang et al., 2012).

In a study in aged rats, pterostilbene treatment (0.004% or 0.016% in diet) for 12-13 weeks reversed cognitive aging measured by the Morris water maze (Joseph et al., 2008).

APOE4 interactions: Not known.

Aging and related health concerns: Clinical evidence is limited and mixed. Pterostilbene treatment may increase cholesterol levels but decrease blood pressure. So far, the promising preclinical data in various conditions have not been validated in humans.

Types of evidence:

- 1 randomized controlled trial testing pterostilbene
- 5 randomized controlled trial testing a combination therapy including pterostilbene
- Numerous laboratory studies

Cardiovascular diseases: UNCLEAR

In a double-blind randomized controlled trial that enrolled 80 people with high total or LDL cholesterol, pterostilbene treatment (50 mg or 125 mg twice daily) for 6-8 weeks significantly increased LDL cholesterol (17.1 mg/dL; p=0.001), though when pterostilbene treatment (50 mg twice daily) was combined with grape extract (100 mg twice daily), this increase was attenuated (Riche et al., 2014). High-dose pterostilbene treatment (125 mg twice daily) for 6-8 weeks significantly reduced systolic (by 7.8 mmHg; p<0.01) and diastolic blood pressure (by 7.3 mmHg; p<0.001). Participants not on cholesterol medication (n=51) exhibited minor weight loss with pterostilbene (-0.62 kg/m^2; p=0.012). No significant changes were seen in triglyceride levels or atherosclerotic cardiovascular disease risk scores with pterostilbene treatment. There was also no significant change in body mass index.

In a double-blind randomized, placebo-controlled clinical study in 120 healthy individuals between the ages of 60 to 80 years, pterostilbene + NR treatment (regular dose: 50 mg pterostilbene, 250 mg NR, daily; Basis, Elysium Health) over 8 weeks resulted in an increase in total cholesterol with the regular dose pterostilbene + NR on day 30 (by 3%) and day 60 (by 3.5%), compared to placebo (Dellinger et al, 2017). The increase in cholesterol was more pronounced in people with higher BMI (overweight category, 25-32). Larger increases in total cholesterol and LDL cholesterol were observed in the double dose pterostilbene + NR group (100 mg pterostilbene, 500 mg NR, daily).

In a double-blind randomized placebo-controlled crossover trial in 96 elderly people, a combination treatment of resveratrol (25 mg/capsule), pterostilbene (25 mg/capsule), quercetin (50 mg/capsule), δ-tocotrienol (25 mg/capsule), and nicotinic acid (25 mg/capsule) (taken 2 capsules after breakfast and 2 capsules after dinner) for 6 weeks significantly reduced serum nitric oxide, C-reactive protein, γ-glutamyl-transferase (γ-GT) activity, and improved total antioxidant capacity (Qureshi et al., 2013). In people who were hypercholesterolemic, total cholesterol, LDL-cholesterol, and triglycerides were also decreased significantly compared to baseline values, without affecting HDL-cholesterol.

Because these clinical studies included compounds other than pterostilbene, it is not possible to tease apart the specific effects of pterostilbene.

In a rat model of atherosclerosis (high-fat, high glucose, and high cholesterol diet), pterostilbene treatment reduced inflammatory response, attenuated atherogenesis, reduced aortic plaque size, reduced macrophage infiltration, and suppressed oxidative stress and apoptosis of vascular arterial walls (Tang et al., 2019). In cultured human endothelial cells, pterostilbene administration promoted antioxidant pathways by increasing Nrf2 expression and activation. In a different rat model of atherosclerosis (induced by endothelial injury of the iliac arteries), pterostilbene treatment (10 mg/kg/day, orally) reduced atherogenesis, aortic plaques, macrophage infiltration, and apoptosis of vascular arterial walls, while decreasing total cholesterol, LDL-cholesterol, HDL-cholesterol, inflammatory markers (TNF-α, IL-1, and IL-6) and oxidative stress (increased SOD, catalase, and HO-1, decreased MDA and MPO)(Xiong et al., 2020). Pterostilbene regulated endothelial cell apoptosis by regulating the Nrf2-mediated TLR-4/MyD88/NFkB pathway.

Stroke: POTENTIAL BENEFIT BASED ON RODENT STUDIES
No studies have tested pterostilbene treatment in human stroke patients.

In a mouse model of ischemic stroke (middle cerebral artery occlusion-reperfusion), pterostilbene treatment (5 or 10 mg/kg) started 1 hour after occlusion and immediately after reperfusion significantly decreased infarct volume, brain edema, neuronal apoptosis, and neurological dysfunction (Liu et al., 2019). Pterostilbene treatment decreased oxidation (ROS, MDA) and inflammatory mediators (TNF-α, IL-1β, and IL-6), and increased antioxidant defenses (SOD, glutathione peroxidase), by inhibiting phosphorylation and nuclear translocation of NFkB. In a rat model of ischemia (middle cerebral artery occlusion-reperfusion), pterostilbene treatment decreased neurological scores, brain water content (edema), and infarct volume (Liu et al., 2020). These effects of pterostilbene were related to decreased reactive oxygen species and inhibition of the NF-kB-mediated inflammatory pathway in microglia. In the same rat model of cerebral ischemia, pterostilbene treatment (15, 30, or 60 mg/kg/day, oral gavage) started one day after reperfusion and continued for up to 14 days reduced cerebral infarct volume, improved neurological deficits, increased cerebral microcirculation, and improved blood-brain barrier integrity by inhibiting the expression of MMP-9 and the degradation of the extracellular basement membrane (Yang et al., 2023).

In a mouse model of hemorrhagic stroke (subarachnoid hemorrhage), pterostilbene treatment (10 mg/kg, intraperitoneally, at 0.5 and 2 hours after hemorrhage induction) reduced subarachnoid hemorrhage score, neurological score, and brain water content (Liu et al., 2017). Pterostilbene treatment also reduced NLRP3 inflammasome activation, alleviated oxidative stress (increased SOD, decreased MDA, 3NT, 8OHdG), and reduced neuronal apoptosis.

Diabetes and metabolic conditions: POTENTIAL BENEFIT BASED ON RODENT STUDIES
No studies have tested pterostilbene treatment in diabetes or metabolic diseases in humans. In rodent models of diabetes, pterostilbene treatment improved glucose homeostasis, enhanced peripheral utilization of glucose, inhibited oxidative stress and inflammation (regulated NFkB signal pathway), improved renal damage, and reduced lipid peroxidation (reviewed in Nagarajan et al., 2022; Dutta et al., 2023). These effects have not been confirmed in people with diabetes.

In a mouse model of obesity (induced by a Western diet), pterostilbene treatment for 16 weeks significantly reduced body weight gain and inguinal adipose tissue weight, while activating the SIRT1/PGC-1α/SIRT3 pathway to enhance mitochondrial biogenesis (increased NRF1 and TFAM) and thermogenesis (increased PRDM16 and UCP1)(Koh et al., 2023).

Muscle/physical performance: MIXED FINDINGS

In a double-blind randomized, placebo-controlled clinical study in 120 healthy individuals between the ages of 60 to 80 years, pterostilbene + NR treatment (regular dose: 50 mg pterostilbene, 250 mg NR, daily, or double dose: 100 mg pterostilbene, 500 mg NR, daily; Basis, Elysium Health) over 8 weeks significantly increased whole blood NAD+ levels (Dellinger et al, 2017). The double dose (but not the regular dose) pterostilbene + NR treatment improved mobility, measured by the 6-minute walk test and 30-second chair test.

In a randomized controlled trial of 32 old people (aged 55-80) subjected to experimental muscle injury, treatment with pterostilbene + NR (100 mg pterostilbene, 500 mg NR, twice daily, orally; Basis, Elysium Health) started 14 days before injury and continued until 30 days after injury did not significantly alter muscle stem cell content, proliferation, cell size, muscle fiber area, central nuclei, or embryonic myosin heavy chain (a protein expressed during muscle development)(Jensen et al., 2022). Whole-blood NAD+ levels were increased after pterostilbene + NR treatment, but skeletal muscle NAD+ levels were not. Functional recovery, measured as maximal voluntary contractions (MVC) and rate of force development (RFD) of the quadriceps femoris muscle, were decreased after injury but unaffected by the pterostilbene + NR treatment. Thus, pterostilbene + NR treatment did not improve recruitment of the muscle stem cell pool or promote skeletal muscle regeneration after injury.

Cancer: POTENTIAL BENEFIT BASED ON RODENT STUDIES
No studies have tested pterostilbene treatment in human cancer patients. Laboratory studies have documented inhibitory effects of pterostilbene against various cancers including stomach, skin, lung, liver, breast, colon, pancreas, oral, lymph, cervical, endometrial, prostate, leukemia, and myeloma, through inhibition of cancer cell proliferation and migration, induction of S-phase arrest of cancer cell cycle, and apoptosis of cancer cells (reviewed in Obrador et al., 2021; Nagarajan et al., 2022; Surien et al., 2023; Qu et al., 2023). These effects have not been confirmed in humans.

Neuropathy: POTENTIAL BENEFIT BASED ON RODENT STUDIES
No studies have tested pterostilbene treatment in people with neuropathy. In a rat model of peripheral neuropathy (oxaliplatin-induced), pterostilbene treatment (40 mg/kg/day, orally) for 5 weeks alleviated behavioral and motor impairments along with restoration of histopathological changes (Abd-Elmawla et al., 2023). Pterostilbene treatment also significantly attenuated sciatic nerve inflammatory markers (p38 MAPK, JNK, ERK1/2, NFkB, COX-2, PGE2, TNF-α, and interleukins levels), apoptotic markers (decreased caspase-3 and Bax, increased Bcl-2), and improved oxidative stress markers (decreased MDA, increased total antioxidant capacity). Coadministration of pterostilbene with celecoxib (30 mg/kg/day, orally) showed further relief of neuropathic pain.

Liver disease: LITTLE BENEFIT

In a double-blind randomized controlled trial of 111 patients with non-alcoholic fatty liver disease (NAFLD), treatment with pterostilbene + NR (50 mg pterostilbene and 250 mg NR, 100 mg pterostilbene and 500 mg NR, daily) for 6 months did not significantly alter the primary endpoint of hepatic fat fraction compared to placebo (Dellinger et al., 2023). Of prespecified secondary outcomes, the lower-dose pterostilbene + NR (50 mg/250 mg) resulted in a decrease in liver enzymes ALT and GGT and the toxic lipid ceramide 14:0 when compared to placebo. No effects were observed with the higher-dose pterostilbene + NR (100 mg/500 mg). Total cholesterol, triglycerides, and LDL levels were not significantly altered after 6 months of pterostilbene + NR treatment.

In a mouse model of acute liver injury (LPS-D-Gal-induced), pterostilbene treatment (40 mg/kg) reduced inflammatory infiltration, inflammation markers (TNF-α, IL-6, and IL-1β), hemorrhage, dissociation of the hepatic cord, oxidative stress, and liver enzymes (ALT and AST levels)(Liu et al., 2021). Pterostilbene treatment inhibited the pro-inflammatory NFkB signaling pathway while promoting the antioxidant Nrf2/HO-1 signaling pathway.

Kidney disease: UNKNOWN

In a double-blind randomized controlled trial of 24 hospitalized patients with acute kidney injury, treatment with escalating doses of pterostilbene + NR (50/250 mg, 100/500 mg, 150/750 mg, and 200/1,000 mg; twice daily for 2 days at each dose; Basis, Elysium) showed a trend for increase in blood NAD+ levels but only the dose of 100 mg pterostilbene and 500 mg NR taken twice daily for 2 days resulted in a significant increase in NAD+ levels (by 47%)(Simic et al., 2020). Across all doses, pterostilbene + NR increased NAD+ levels by 37% at 48 hours (p=0.002). However, there was a wide interindividual variability in NAD+ levels posttreatment. In contrast, placebo-treated patients showed a 50% reduction in whole-blood NAD+ levels at 48 hours compared to baseline.

Safety: Based on a few clinical trials testing pterostilbene alone, adverse events were uncommon. Pterostilbene treatment may increase total and LDL-cholesterol. Pterostilbene likely interacts with drugs/compounds metabolized by UGT1A9.

Types of evidence:

- 2 randomized controlled trials testing pterostilbene
- 5 randomized controlled trials testing combination therapy that included pterostilbene

- Numerous laboratory studies

Data from human clinical trials: In a double-blind randomized controlled trial that enrolled 80 people with high total or LDL cholesterol, pterostilbene treatment (50 mg or 125 mg twice daily) for 6-8 weeks did not result in any adverse drug reactions on liver, kidney, or glucose markers based on biochemical analyses (Riche et al., 2013). The majority (91.3%) of participants completed the trial. Among the participants receiving pterostilbene (total of 60 people), 2 people were lost to follow up and 2 people withdrew from the trial. One withdrawal was due to a loss of the trial medication bottle and the other withdrawal was due to worsening of cholesterol from an outside laboratory. There were no major adverse events. There was a 3.6% reduction in bicarbonate in the high-dose pterostilbene group versus placebo (p=0.02) and a similar trend seen with low-dose pterostilbene. The decrease in bicarbonate could indicate an acidic effect of pterostilbene in the blood (phenols are acidic). The combination of grape extract and low-dose pterostilbene decreased blood urea nitrogen (BUN) by 7.1% from baseline, but this reduction was not significant when compared to placebo. There were no other significant effects on electrolyte markers. Complete blood count, urinalysis, and electrocardiogram were not performed in this trial.

In a double-blind randomized controlled trial of 60 healthy adults, treatment with *P. marsupium* extract containing 90% pterostilbene (200 mg per day) for 2 months was well-tolerated (Majeed et al., 2023). Hematological, lipid (total-, LDL-, and VLDL-cholesterol, triglycerides), glycemic (fasting blood sugar, glycosylated hemoglobin percentages), thyroid profiles, liver functions (AST, ALT, GGT), and renal functions (urea, uric acid, creatinine, glomerular filtration rate, sodium, potassium, and chloride levels) remained within the normal range in all participants, and no significant differences were observed between the *P. marsupium* and placebo groups. Blood pressure, pulse rate, body weight, body mass index, and electrocardiogram did not reveal any significant differences between the *P. marsupium* and placebo groups at the beginning and end of the study. Urine analysis outcomes including color, appearance, pH, specific gravity, protein, glucose, ketone bodies, bilirubin, nitrites, urobilinogen, and microscopic parameters, were within the normal reference range and were comparable between *P. marsupium* and placebo groups at all time points. No serious adverse events were observed in any participant throughout the study duration. Three participants in the placebo group reported mild adverse events of fever and fatigue, which were mild and resolved; no participants in the *P. marsupium* group reported any adverse events. With regards to oxidative stress markers, the antioxidant glutathione was 128.25 ± 28.32 nM/mL and 132.46 ± 25.55 nM/mL, respectively, in the *P. marsupium* and placebo groups at the first visit, and 142.28 ± 39.46 nM/mL and 134.45 ± 34.42 nM/mL respectively, at the final visit. The mean change from baseline to final visit in the *P. marsupium* group was 14.41

(11.3% increase from baseline), numerically higher than in the placebo arm. The oxidative stress marker malondialdehyde remained unchanged at the final visit compared to baseline values in both the *P. marsupium* and placebo groups. The antioxidant enzyme, SOD, decreased in both the *P. marsupium* and placebo groups at the end of the study.

In a double-blind randomized, placebo-controlled clinical study in 120 healthy individuals between the ages of 60 to 80 years, pterostilbene + NR treatment (regular dose: 50 mg pterostilbene, 250 mg NR, daily, or double dose: 100 mg pterostilbene, 500 mg NR, daily; Basis, Elysium Health) over 8 weeks was well tolerated with no serious adverse events (Dellinger et al, 2017). There were no significant differences in the incidence of adverse events across treatment groups. There was one adverse event mild in intensity possibly related to the pterostilbene + NR at the regular dose (nausea) and 5 adverse events possibly related to the double dose pterostilbene + NR (moderate fatigue, mild headache, moderate dyspepsia, moderate abdominal discomfort, and diarrhea), and one adverse event possibly related to the placebo product (pruritus). Whole blood NAD+ levels increased at the regular dose (by ~40%) and with double the regular dose (by ~90%) at 4 weeks. Levels were maintained with the regular dose over 8 weeks. In the double dose, levels were initially higher after four weeks (by ~90%) and returned to levels seen with the regular dose (~55%) after 8 weeks. There were no changes in liver function tests except a significant decrease was observed in alanine transaminase in the regular dose pterostilbene + NR group, suggesting improvement in liver function. There were no changes in blood pressure or hematology and clinical chemistry parameters. There was an increase in total cholesterol with the regular dose pterostilbene + NR on day 30 (by 3%) and day 60 (by 3.5%), compared to placebo. The increase in cholesterol was more pronounced in people with higher BMI (overweight category, 25-32). Larger increases in total cholesterol and LDL cholesterol were observed in the double dose pterostilbene + NR group. The double dose pterostilbene + NR group showed improvements in mobility, measured by the 6-minute walk test and 30-second chair test.

In a randomized controlled trial of 32 old people (aged 55-80) subjected to experimental muscle injury, treatment with pterostilbene and NR (100 mg pterostilbene, 500 mg NR, twice daily, orally; Basis, Elysium Health) started 14 days before injury and continued until 30 days after injury was well-tolerated (Jensen et al., 2022). Two participants in the placebo group reported constipation. Transient reflux and transient loose stools were reported by one subject each in the pterostilbene + NR group. These adverse events were all mild in severity. Blood biochemistry showed no difference between treatment and placebo after 14 days.

In a double-blind randomized controlled trial of 32 patients with ALS (20 study completers), treatment with pterostilbene + NR (1,200 mg; Elysium Health) for 4 months did not result in any adverse events attributed to the investigational product (de la Rubia et al., 2019). Adverse events including mild headache, moderate dyspepsia, and moderate diarrhea were reported by 4 participants in the placebo group and 5 participants of the pterostilbene + NR group.

In a double-blind randomized controlled trial of 111 patients with non-alcoholic fatty liver disease (NAFLD), treatment with pterostilbene + NR (50 mg pterostilbene and 250 mg NR, or 100 mg pterostilbene and 500 mg NR, daily) for 6 months resulted in adverse events that were mostly gastrointestinal issues (Dellinger et al., 2022). There were no severe adverse events.

In a double-blind randomized controlled trial of 24 hospitalized patients with acute kidney injury, treatment with escalating doses of pterostilbene + NR (50/250 mg, 100/500 mg, 150/750 mg, and 200/1,000 mg; twice daily for 2 days at each dose; Basis, Elysium) was well-tolerated and did not alter any safety laboratory tests, including creatinine, estimated glomerular filtration rate (eGFR), electrolytes, liver function tests (ALT, AST, ALP), and blood counts (Simic et al., 2020). Three out of 20 patients receiving pterostilbene + NR at the two lower doses reported minor gastrointestinal side effects (bloating and gas, indigestion with upper abdominal discomfort). No side effects were reported with placebo or with the two higher doses of pterostilbene + NR. There were no serious adverse events in this study.

Data from preclinical studies: In mice, pterostilbene treatment even at high doses (up to 3000 mg/kg/day) for up to 4 weeks did not result in significant alterations in food or water consumption, body weight, organ weight, clinical signs, biochemical measures, and histopathological assessments (Ruiz et al., 2009).

Drug interactions: Pterostilbene is a broad-spectrum inhibitor of human UDP-glucuronosyltransferases (UGT) enzymes (Jiang et al., 2020). Pterostilbene potently inhibits HLM, UGT1A6, UGT1A9, UGT2B7, and UGT2B15, and moderately inhibits UGT1A1, UGT1A3, UGT1A8, and UGT2B4. Based on a quantitative prediction study, coadministration of pterostilbene at 100 mg/day or higher doses may result in at least a 50% increase in the area under the curve (AUC) of drugs predominantly cleared by UGT1A9. Thus, precautions and dose adjustments may be required when considering the use of pterostilbene while also taking other supplements or drugs metabolized by UGT1A9 (e.g., furosemide, mycophenolic acid, phenylbutazone, propofol, raloxifene, retigabine, sulfinpyrazone)(Knights et al., 2013). Pterostilbene has also been reported to strongly inhibit drug-metabolizing enzymes, CYP3A4, CYP2C19, CYP1A1, CYP1A2,

and CYP1B1, which may contribute to potential drug-supplement interactions and toxicity (Hyrsova et al., 2019).

Sources and dosing:

Pterostilbene is available as a supplement from numerous companies. Elysium's Basis has been tested in several clinical trials and contains a combination of 50 mg of pterostilbene with 250 mg nicotinamide riboside (NAD+ precursor) per serving. Pterostilbene is present in some foods including blueberries (9.9-15.1 µg/kg)(Qu et al., 2023). Although pterostilbene has higher oral availability (up to 80%) compared to resveratrol (~30%), it has low aqueous solubility of about 21 mg/ml (Bethune et al., 2011; Dutta et al., 2023). Administration of pterostilbene with or subsequent to a meal promotes bile production and increases its aqueous solubility.

Research underway:

Based on ClinicalTrials.gov, there are 4 ongoing clinical trials testing pterostilbene, two in amyotrophic lateral sclerosis patients (combined with nicotinamide), one in endometrial cancer patients, and one testing the oral bioavailability of a new formulation of pterostilbene.

Due to low aqueous solubility of pterostilbene, innovative formulations have been studied, including cocrystals, prodrugs, nanoemulsions, lipid-based encapsulation, and others (Liu et al., 2020; Bofill et al., 2021; Zou et al., 2021; Liu et al., 2024).

Search terms:

Pubmed, Google: pterostilbene

- + clinical trial, + meta-analysis, + Alzheimer, + dementia, + APOE4

Websites visited for pterostilbene:

- Clinicaltrials.gov
- NIH RePORTER
- Examine.com
- Geroprotectors.org (0)
- Drugs.com (0)
- WebMD.com (0)
- PubChem

- DrugBank.ca
- Labdoor.com (0)
- ConsumerLab.com

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If you have suggestions for drugs, drugs-in-development, supplements, nutraceuticals, or food/drink with neuroprotective properties that warrant in-depth reviews by ADDF's Aging and Alzheimer's Prevention Program, please contact INFO@alzdiscovery.org. To view our official ratings, visit Cognitive Vitality's Rating page.