PTEROSTILBENE++

The most efficient pterostilbene ingredient available on the market.

PTEROSTILBENE++ is the most potent pterostilbene ingredient available on the market. This extraordinary potency is due to the solid form in which it crystalized during its isolation. In some infrequent cases, two highly pure products can form a single crystal unlocking its healthy properties.
This is the case of PTEROSTILBENE++.

ACTIVE INGREDIENT	Pterostilbene
COFORMER	Picolinic acid
PURITY	>99.4%
PTEROSTILBENE CONTENT	68%

STILBENOID NATURAL PRODUCTS FAMILY

Resveratrol and **Pterostilbene** are both **natural stilbenoid compounds** present in many plants, with a very similar chemical structure. As a consequence, similar pharmacological activity has been described for both of them, including **analgesia, antiaging, antidiabetic, anti-inflammation, anti obesity, antioxidation, cholesterol lowering, neuroprotection**, and so on. Beyond these similarities, pharmacological activity of pterostilbene is usually stronger than that of resveratrol. This has been explained due to the **better bioavailability of pterostilbene**[1] (Wang, 2018).

To exert efficacy, these stilbenoids must be absorbed by the body and remain unaltered. **Resveratrol** is **rapidly metabolized**, rendering very low levels of unaltered resveratrol in blood after its intake. **Pterostilbene** is more resistant to these modifications, but due to its **low solubility,** the body absorbs a low fraction of the ingested product. It improves resveratrol… but not so much.

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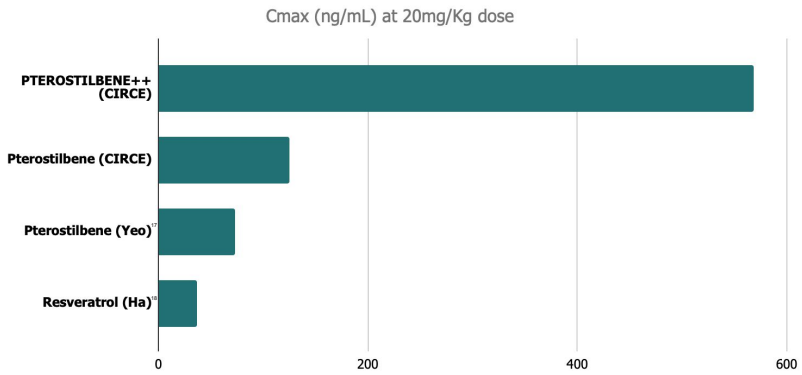
PTEROSTILBENE++ improves pterostilbene solubility more than 35 fold

→ Dissolution rate of pterostilbene vs cocrystal: 12 vs 427 nmol/min.

BUT DOES THIS TRANSLATE TO A BETTER BIOAVAILABILITY?

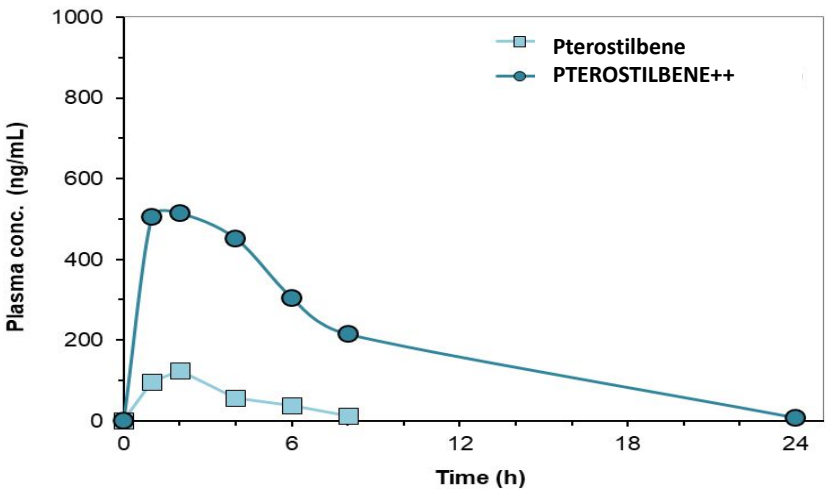
BIOAVAILABILITY STUDIES IN SPRAGUE-DAWLEY RATS, AT 20 MG/KG DOSE



The same amount of **PTEROSTILBENE++** achieves much higher levels in blood than pterostilbene or resveratrol, being the **most potent stilbenoid** on the market. A higher bioavailability has been related with superior pharmacological activity by many authors.

"Comparison pharmacokinetics of resveratrol and pterostilbene in animals revealed that pterostilbene exhibited a superior pharmacokinetic profile than that of resveratrol, which could be a good explanation of why in vitro and/or in vivo pharmacological activities of pterostilbene are usually found to be superior than that of resveratrol."
(Wang et al. 2018, Metabolism and pharmacokinetics of resveratrol and pterostilbene)

CIRCE SCIENTIFIC COMPARATIVE BIOAVAILABILITY STUDY IN SPRAGUE-DAWLEY RATS



20mg/kg of PTEROSTILBENE++, containing 68% of pterostilbene, **achieves much higher levels in blood than 20mg/kg of regular pterostilbene**.

This may lead to improved activity, and to a dose reduction to achieve equivalent blood levels. **A dose reduction will also generate free volume to include additional ingredients on the capsule, if desired.**

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PTEROSTILBENE DESCRIBED HEALTHY ACTIVITIES DESCRIBED IN SCIENTIFIC LITERATURE

Pterostilbene is an emerging antioxidant that is attracting a lot of attention since evidences suggest that it may be helpful in a long list of human diseases which include neurological, cardiovascular, metabolic, and hematologic disorders. In addition, it has been reported that it can play a relevant role in cancer.

AGEING

Pterostilbene is a potent free radical scavenger that reduces oxidative stress[2]. Two recent clinical trials showed its **sun protection**, **skin brightening** and **anti aging** effect. Some evidence even suggests that pterostilbene may mimic the effects[3] of calorie restriction, a practice that has been shown to **increase life span**[4] and help prevent age-related disorders.

BRAIN

Pterostilbene is thought to offer neuroprotective benefits due to its antioxidant activity, which helps **prevent oxidative stress** in the brain, improves cognitive function and **reduce the risk of Alzheimer's disease**. Regular consumption of blueberries, the most potent natural source of pterostilbene, has also been associated with slower rates of cognitive decline[13].

CANCER

Pterostilbene shows[5] anti-cancer benefits in a few different ways: by altering the cell cycle, inducing apoptosis (or cell death), and inhibiting metastasis. In vitro and in vivo[6] studies suggest that pterostilbene may offer **protection against breast cancer[7], coloncancer[8], pancreatic cancer[9], and prostate cancer[10] cells**. Estrela et al. clearly state "taking into account the limitations of bioavailability, it appears reasonable to suggest that clinical studies on cancer prevention should first focus on skin and colon cancers[11]". Thus, an increased bioavailability can clearly broaden potential pterostilbene applications in cancer (among other conditions).

HEART

Pterostilbene (125 mg) twice a day showed significant **reductions in blood pressure** in human clinical trial compared to the placebo group[14].

SUGAR

Supplementation with pterostilbene **lowers blood glucose levels** in preclinical models, which suggests that this antioxidant may play a role in protecting against diabetes and improving insulin sensitivity[15].

In addition to the clinical trials already performed with pterostilbene (reduction of blood pressure, sun protection, skin brightening, antiaging…) there are many ongoing human trials in different conditions (hysterectomy in endometrial cancer; muscle regeneration, ALS, acute kidney injury, trauma, menopause, exercise performance…) with pterostilbene as only treatment, combined with other ingredient, or as an aid.

These described effects have not been evaluated or validated by FDA, EFSA or any other competent authority. This product is not intended to cure, prevent, diagnose or treat any disease.

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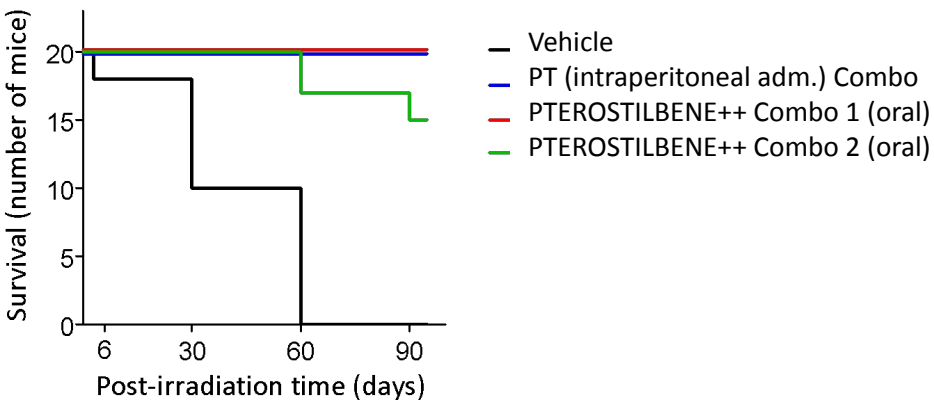
Pterostilbene is generally safe for use in humans at doses up to 250mg per day. Pterostilbene is well-tolerated at a twice daily dosing frequency. (Riche et al. 2013, Analysis of Safety from a Human Clinical Trial with Pterostilbene")

PTEROSTILBENE++ ACTIVITY



Obrador et al. recently described[16] a pterostilbene-based combination exerting a **high protection against lethal γ radiation in mice**. However, this effect can be observed when pterostilbene bioavailability was increased to achieve relevant levels in blood. Obrador used a pterostilbene phosphate disodium salt, intraperitoneally administered, to increase pterostilbene bioavailability.

When Obrador reproduced the same experiment with PTEROSTILBENE++, orally administered, it was able to exert the same level of protective activity. This proves that **PTEROSTILBENE++, in addition to its confirmed ability to increase bioavailability, also maintains the expected activity.**

PTEROSTILBENE HAS MANY APPLICATION AREAS

Our products bring significant improvements and benefits to the longevity healthcare sector.

Product application is broad and can be also used in the sport and pet industries.

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At CIRCE Scientific, by applying our proprietary Crystal Engineering Technology, we aim to dramatically optimize the known health benefits of recognized nutraceutical ingredients in order to offer to our customer premium ingredients for the development of innovative nutraceutical products in emerging health and longevity markets.

CIRCE Scientific's qualified team leads the development of new ingredients, its patent protection, transfer to industrial plant and regulatory development to provide innovative and safe ingredients.

PTEROSTILBENE++ is produced at a cGMP plant holding relevant certifications, audited by globally respected bodies, and sent worldwide from our Barcelona warehouse (SPAIN).

REFERENCES:

[1]Wang P, Sang S. Metabolism and pharmacokinetics of resveratrol and pterostilbene. Biofactors. 2018 Jan;44(1):16-25. doi: 10.1002/biof.1410. Epub 2018 Jan 8. PMID: 29315886

[2]Remsberg CM, Yáñez JA, Ohgami Y, Vega-Villa KR, Rimando AM, Davies NM. Pharmacometrics of pterostilbene: preclinical pharmacokinetics and metabolism, anticancer, antiinflammatory, antioxidant and analgesic activity. *Phytother Res*. 2008;22(2):169-179. doi:10.1002/ptr.2277

[3]Majeed, Muhammed & Majeed, Shaheen & Jain, Renuka & Mundkur, Lakshmi & Rajalakshmi, H. & Lad, Prachi & Neupane, Prakriti. (2020). An Open-Label Single-Arm, Monocentric Study Assessing the Efficacy and Safety of Natural Pterostilbene (Pterocarpus marsupium) for Skin Brightening and Antiaging Effects. Clinical, Cosmetic and Investigational Dermatology. Volume 13. 105-116. 10.2147/CCID.S238358; Majeed, Muhammed & Majeed, Shaheen & Jain, Renuka & Mundkur, Lakshmi & Rajalakshmi, H. & Lad, Prachi & Neupane, Prakriti. (2020). A Randomized Study to Determine the Sun Protection Factor of Natural Pterostilbene from Pterocarpus Marsupium. Cosmetics. 7. 16. 10.3390/cosmetics7010016.

[4]Alcaín FJ, Villalba JM. Sirtuin activators. *Expert Opin Ther Pat*. 2009;19(4):403-414. doi:10.1517/13543770902762893

[5]McCormack D. et al. Pterostilbene and cancer: current review. *J Surg Res*. 2012;173(2):e53-e61. doi:10.1016/j.jss.2011.09.054

[6]Obrador E., Salvador-Palmer R., Jihad-Jebbar A., López-Blanch, R., Dellinger, T., Dellinger R. & Estrela J. (2021). Pterostilbene in Cancer Therapy. Antioxidants. 10. 492. 10.3390/antiox10030492

[7]Moon D, McCormack D, McDonald D, McFadden D. Pterostilbene induces mitochondrially derived apoptosis in breast cancer cells in vitro. *J Surg Res*. 2013;180(2):208-215. doi:10.1016/j.jss.2012.04.027

[8]Nutakul W, Sobers HS, Qiu P, et al. Inhibitory effects of resveratrol and pterostilbene on human colon cancer cells: a side-by-side comparison. *J Agric Food Chem*. 2011;59(20):10964-10970. doi:10.1021/jf202846b

[9]McCormack DE, Mannal P, McDonald D, Tighe S, Hanson J, McFadden D. Genomic analysis of pterostilbene predicts its antiproliferative effects against pancreatic cancer in vitro and in vivo. *J Gastrointest Surg*. 2012;16(6):1136-1143. doi:10.1007/s11605-012-1869-7

[10]Lin VC, Tsai YC, Lin JN, et al. Activation of AMPK by pterostilbene suppresses lipogenesis and cell-cycle progression in p53 positive and negative human prostate cancer cells. J Agric Food Chem. 2012;60(25):6399-6407. doi:10.1021/jf301499e

[11]Estrela JM, Ortega A, Mena S, Rodriguez ML, Asensi M. Pterostilbene: Biomedical applications. Crit Rev Clin Lab Sci. 2013 May-Jun;50(3):65-78. doi: 10.3109/10408363.2013.805182. Epub 2013 Jul 1. PMID: 23808710.

[12]Chang J, Rimando A, Pallas M, et al. Low-dose pterostilbene, but not resveratrol, is a potent neuromodulator in aging and Alzheimer's disease. Neurobiol Aging. 2012;33(9):2062-2071. doi:10.1016/j.neurobiolaging.2011.08.015

[13]Devore EE, Kang JH, Breteler MM, Grodstein F. Dietary intakes of berries and flavonoids in relation to cognitive decline. Ann Neurol. 2012;72(1):135-143. doi:10.1002/ana.23594

[14]Riche D, Riche K, Blackshear C, McEwen C, Sherman J, Wofford M, Griswold M, (2014). Pterostilbene on Metabolic Parameters: A Randomized, Double-Blind, and Placebo-Controlled Trial. Evidence-based complementary and alternative medicine : eCAM. 2014. 459165. 10.1155/2014/459165

[15]Manickam M, Ramanathan M, Jahromi MA, Chansouria JP, Ray AB. Antihyperglycemic activity of phenolics from Pterocarpus marsupium. J Nat Prod. 1997;60(6):609-610. doi:10.1021/np9607013; Pari L, Satheesh MA. Effect of pterostilbene on hepatic key enzymes of glucose metabolism in streptozotocin- and nicotinamide-induced diabetic rats. Life Sci. 2006;79(7):641-645. doi:10.1016/j.lfs.2006.02.036; Amarnath Satheesh M, Pari L. The antioxidant role of pterostilbene in streptozotocin-nicotinamide-induced type 2 diabetes mellitus in Wistar rats. J Pharm Pharmacol. 2006;58(11):1483-1490. doi:10.1211/jpp.58.11.0009

[16]Obrador E, Salvador-Palmer R, , Pellicer B, López-Blanch R, , Sirerol JA, Villaescusa J, Montoro A, Dellinger R, Estrela J (2022). Combination of natural polyphenols with a precursor of NAD+ and a TLR2/6 ligand lipopeptide protects mice against lethal γ radiation. Journal of Advanced Research. 10.1016/j.jare.2022.05.005.

[17]Yeo SC, Ho PC, Lin HS (2013) Pharmacokinetics of pterostilbene in Sprague-Dawley rats: the impacts of aqueous solubility, fasting, dose escalation, and dosing route on Bioavailability. Mol Nutr Food Res. 57(6):1015-1025

[18]Ha ES, Choi DH, Baek IH, Park H, Kim MS. Enhanced Oral Bioavailability of Resveratrol by Using Neutralized Eudragit E Solid Dispersion Prepared via Spray Drying. Antioxidants (Basel). 2021 Jan 11;10(1):90