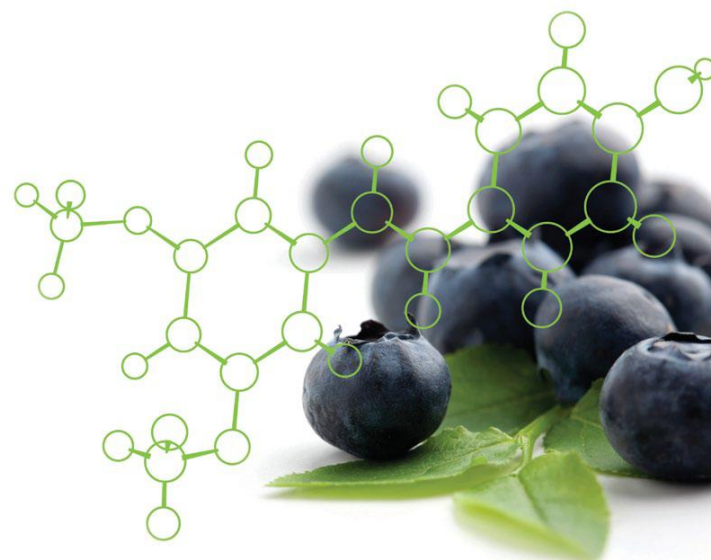


pTeroPure Pterostilbene: The Next Generation Resveratrol

Jeremy Bartos, PhD

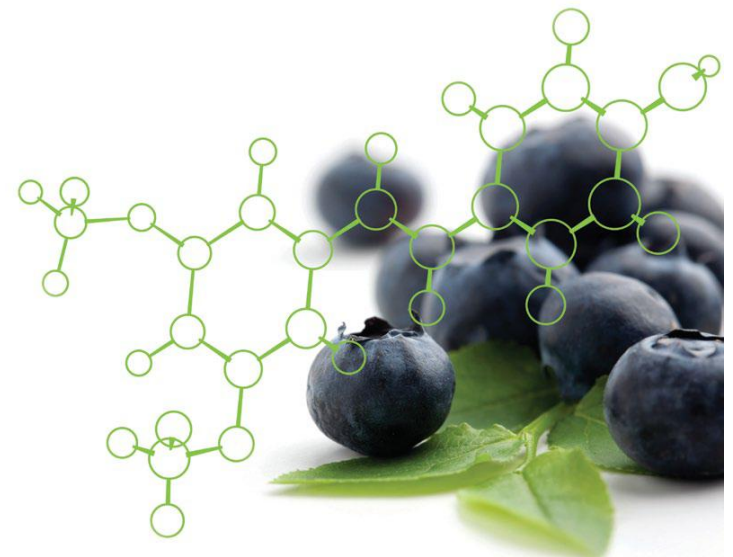
pTeroPure Ingredients Product Manager



Pterostilbene and Nutraceuticals: More than Just a Resveratrol Replacement

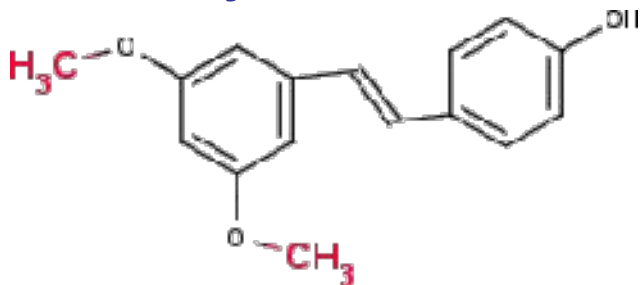
Potential markets for products containing Pterostilbene

- Anti-Aging
- Anti-Oxidant/Oxidative Stress
- Memory Improvement/Cognitive Enhancement
- Anti-Inflammatory
- Heart health
 - Cholesterol
 - Blood Pressure
 - Atherosclerosis
- Blood sugar control

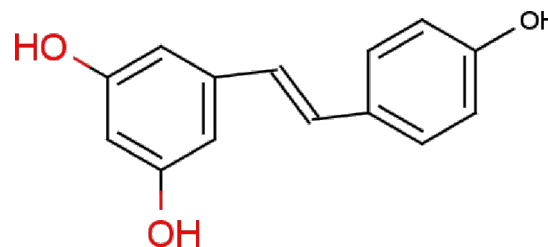


What is Pterostilbene?

- Methylated resveratrol



pterostilbene



resveratrol

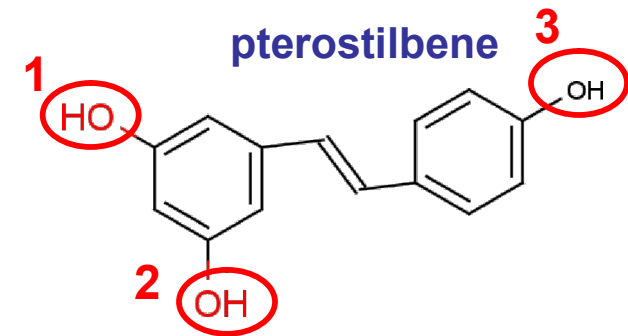
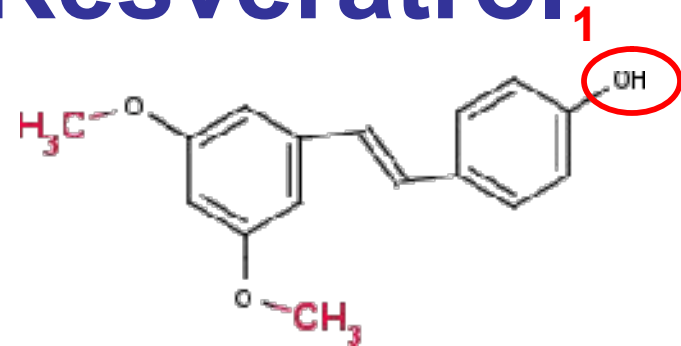
- Naturally found in small berries (blueberries, huckleberries, grapes, etc.)
- Phytoalexin (plant defense system); anti-fungal, anti-microbial



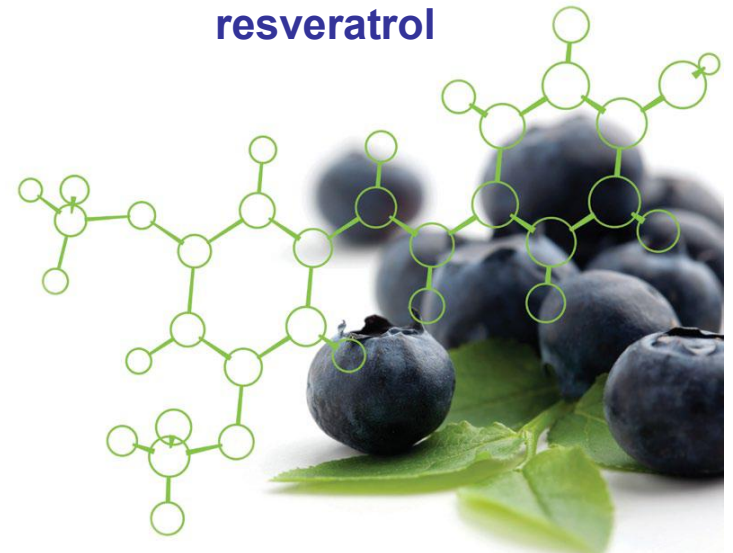
Pterostilbene vs. Resveratrol¹

Pterostilbene is:

- More lipophilic than resveratrol
 - higher potential for cellular uptake
- More bio-available than resveratrol
 - greatly improved oral adsorption
 - greater metabolic stability
- Longer half-life in the body than resveratrol
 - **resveratrol: ~14 minutes in blood**
(Asensi et al, Free Radic Biol Med, 33, 387, 2002)
 - **pterostilbene: ~ 105 minutes in blood**
(Remsberg et al, Phytother. Res. 22, 169, 2008)



resveratrol



Pterostilbene and Resveratrol Synergism

R Mikstacka, et al.; Plant Foods Hum Nutr. 65, 57 (2010)

Table 1 Combination index for LPO inhibition in human erythrocytes by mixtures of quercetin, *trans*-resveratrol and pterostilbene

Total concentration [μM] ^a	Combination index ^b		
	Quercetin + resveratrol	Quercetin + pterostilbene	Resveratrol + pterostilbene
2.5	0.57 \pm 0.15 ^c	2.86 \pm 0.50 X	0.45 \pm 0.10 ^c
5	0.65 \pm 0.21 ^c	0.90 \pm 0.11	0.46 \pm 0.18 ^c
10	0.90 \pm 0.46	1.27 \pm 0.30	0.65 \pm 0.11 ^c
20	1.06 \pm 0.37	1.43 \pm 0.40	0.53 \pm 0.12 ^c
40	0.95 \pm 0.59	1.70 \pm 0.67	0.82 \pm 0.13 ^c
60	0.80 \pm 0.16	1.66 \pm 0.41	0.89 \pm 0.06 ^c
80	1.04 \pm 0.23	1.75 \pm 0.61	1.18 \pm 0.06
100	1.29 \pm 0.24	1.41 \pm 0.56	1.47 \pm 0.02

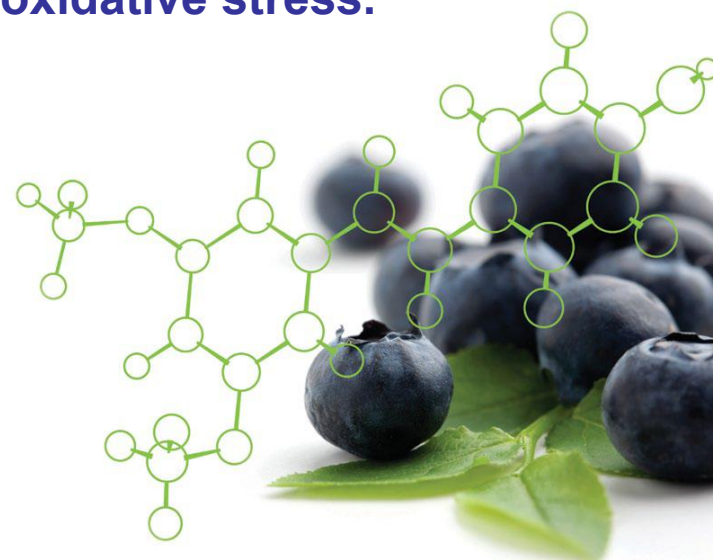
^a Molar ratio of polyphenols 1:1

^b Mean values of three independent experiments performed with different blood sample \pm SEM

^c CI<1; synergistic effect

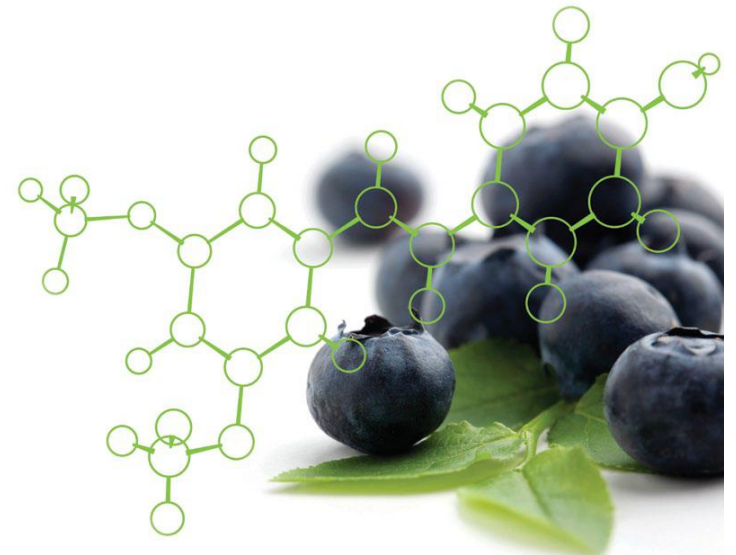
LPO = H₂O₂-induced lipid peroxidation

Conclusion: Pterostilbene and resveratrol act synergistically in protecting human erythrocytes from damage due to oxidative stress.



Pterostilbene and Your Health

- Cholesterol
- Diabetes
- Anti-Oxidant/Oxidative Stress (aging)
- Cognitive Decline
- Cancer



Pterostilbene and Cholesterol

PPAR α : involved in fatty acid and lipid catabolism; activation leads to decreased triglyceride and very low density lipoprotein (VLDL) synthesis

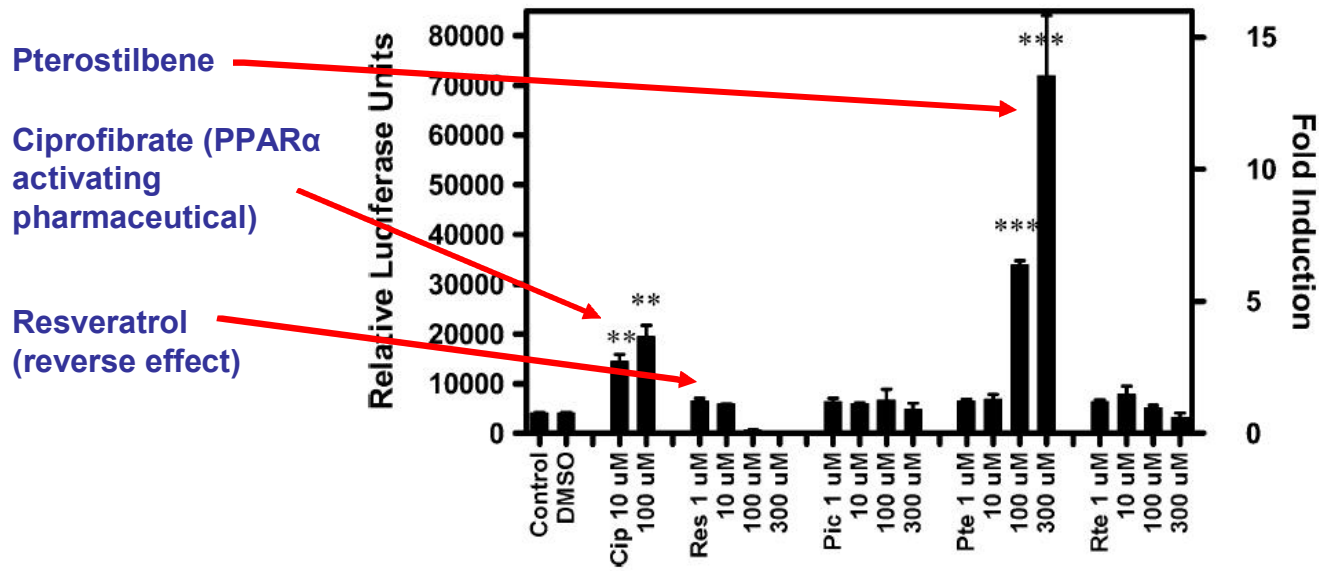
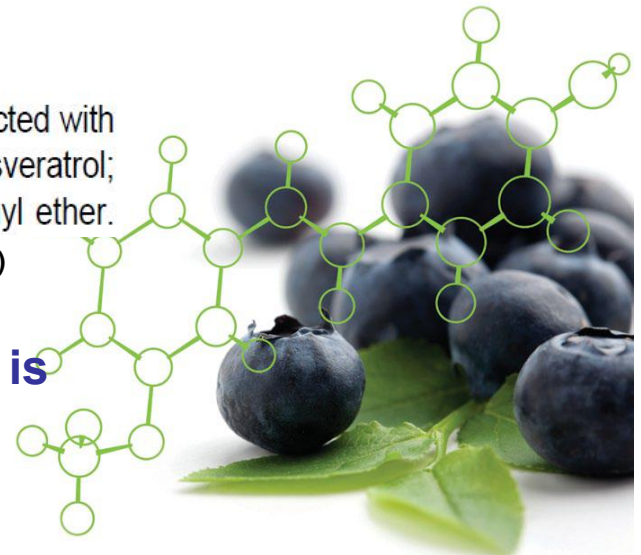


Figure 2. Effect of stilbenes on PPAR α in H4IIEC3 cells transfected with PPARE-AB LUC reporter gene plasmid. Cip, ciprofibrate; Res, resveratrol; Pic, piceatannol; Pte, pterostilbene; and Rte, resveratrol trimethyl ether.

A.M. Rimando, et al.; J. Agric. Food Chem. 53, 3403 (2005)

Conclusion: pterostilbene activates PPAR α , which lowers the bad LDL, even better than ciprofibrate, and is the only stilbene tested to do so.



Pterostilbene and Cholesterol

	<u>Control</u>	<u>Pterostilbene</u>
Plasma Lipoprotein Cholesterol (mg/dL)^b		
VLDL	99.3 ± 15.3	82.7 ± 15.7 (17% ↓)
LDL	320.9 ± 4.9	228.1 ± 4.2^c (29% ↓)
HDL	127.4 ± 1.1	137.0 ± 2.1 (7% ↑)
Total	547.6 ± 6.7	447.8 ± 5.6^c (18% ↓)
LDL/HDL ratio	2.6 ± 0.37	1.8 ± 0.39^c (31% ↓)
Plasma glucose (mg/dL)	216.5 ± 10.1	185.1 ± 8.7 (14% ↓)
Animals per group	10	8

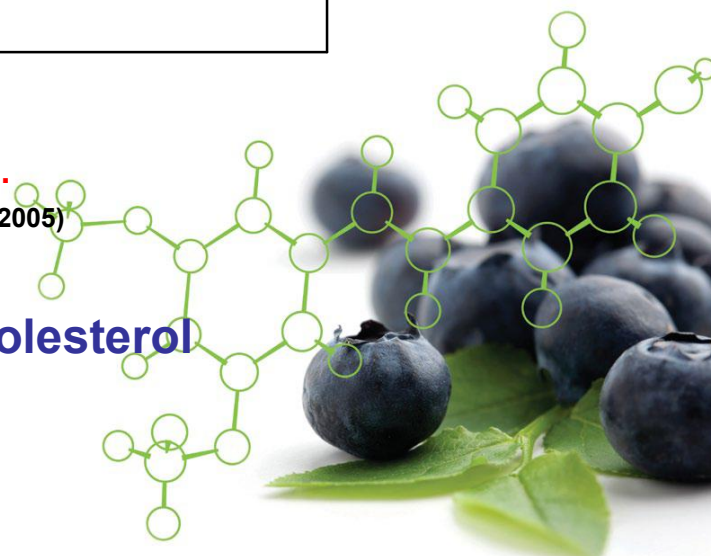


^aBased on a single dose of 25 mg/kg/day of diet for 21 days; pterostilbene intake is ~2.5 mg/kg BW.

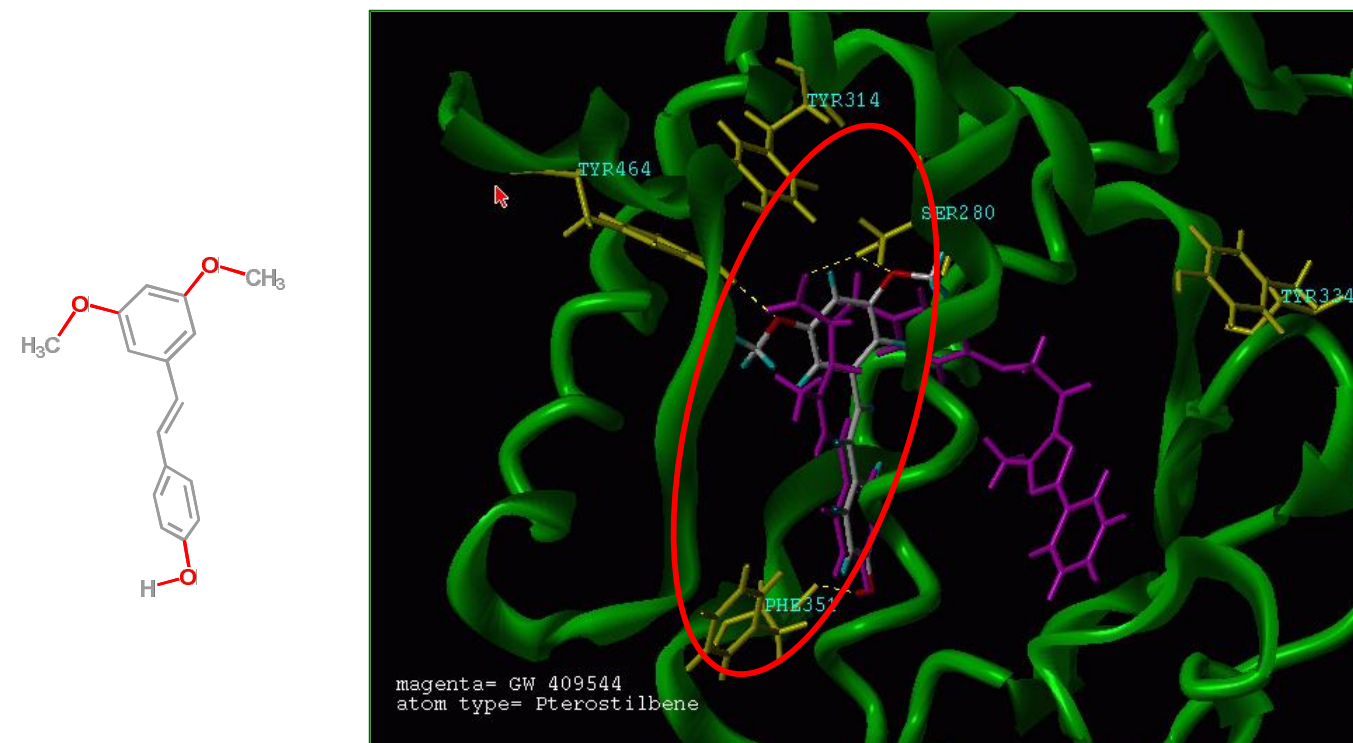
^bValues are the mean ± SEM. ^cSignificance at the P = 0.05 level.

Data from A.M. Rimando, et al.; J. Agric. Food Chem. 53, 3403 (2005)

Conclusion: pterostilbene raises the good HDL cholesterol and significantly lowers the bad LDL cholesterol



Docking of Pterostilbene in the PPAR α Ligand-Binding Domain



Mizuno et al., *Bioorg. Med. Chem.* 16:3800-3808, (2008)

Conclusion: Pterostilbene is an excellent fit in the hydrophobic binding cavity and overlaps that of GW409544, and has H-bond interactions with the **Tyr464**, **Ser280**, and **Phe351** that are involved in PPAR α activation.

Binding pose of pterostilbene inside PPAR α ligand binding domain, superimposed on the co-crystal structure of GW409544 (magenta).



Pterostilbene PPAR α Summary

- Among the stilbenes tested, **only** pterostilbene was a stimulant of PPAR α activity in hepatic cells *in vitro*.
- Plasma lipoprotein cholesterol and glucose lowering effects of pterostilbene in hypercholesterolemic hamsters are consistent with the *in vivo* lipid lowering actions previously reported for PPAR α agonists (e.g., fenofibrate).
- Pterostilbene had an excellent structural alignment for H-bond interactions with three key L-amino acids of the ligand binding domain involved in PPAR α activation.
- Pterostilbene is a unique **natural product** template as an PPAR α agonist.
- Pterostilbene could be a possible **alternative to fibrates** in the treatment of human cardiovascular-related diseases (dyslipidemias and atherosclerosis).

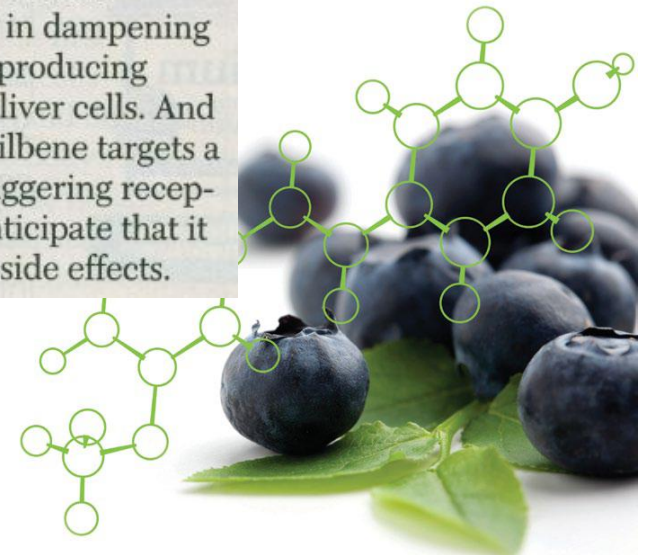


Pterostilbene in the news



Time, December 6, 2004

B
BLUEBERRIES
Pterostilbene may sound more like a spelling-bee stumper than a lifesaver, but if early studies prove correct, this compound, found in abundance in blueberries, could be the foundation of a natural remedy to reduce cholesterol. In head-to-head lab studies against a cholesterol-lowering drug, pterostilbene was just as active as the pharmaceutical in dampening the cholesterol-producing functions of rat liver cells. And because pterostilbene targets a specific lipid-triggering receptor, scientists anticipate that it will have fewer side effects.



Pterostilbene in the news

What America Eats New data proves our favorite foods aren't just good—they're good for us.

The Year's Best Food News

THE OLD ADAGE, "You are what you eat," may hold more promise than ever. Researchers reported this year that many common health problems—including obesity—can be eased by eating more of the foods you've always enjoyed.

True Blue Benefits
Blueberries—a good source of antioxidants—also may help break down cholesterol and fat, as studies on rat cells at the U.S. Department of Agriculture's laboratories in Oxford, Miss., found. **Pterostilbene**, a compound in the berries, may prove to be a potent weapon in the battle against heart disease.

Eat More (Soup), Weigh Less
A little soup before meals may be just what the weight-loss doctor ordered. In a recent study at Penn State, dieters who ate broth-based soups twice a day lost more weight and kept it off longer than those who went soupless or ate snack

Drink To Your Health
Two to four cups of coffee a day may lower the risk of liver disease, cancer, clogged arteries, Parkinson's disease, Alzheimer's and diabetes, according to a report presented recently at the New York Academy of Sciences. Coffee experts say that each cup is actually a complex mixture of active compounds, including healthful antioxidants.

Drizzle the Fatty Dressing
Sard lovers, don't limit yourself to fat-free dressing! A recent study at Iowa State indicates that significantly more carotenoids—those healthy compounds found in fruits and vegetables—are absorbed by the body when a reduced-fat dressing is used. When sard is enjoyed with a full-fat dressing, the health benefits may be even greater.

More Milk, Less Midriff?
Mom always said that milk builds strong bones and is a good source of vitamins, but did she know that drinking 24 ounces a day of low-fat or fat-free milk also may help you manage your weight? Better still, new research out of the University of Tennessee suggests that milk specifically triggers fat loss deep inside the stomach.

Breakfast Just Got Healthier
This fall, leading cereal companies gave their product lines a nutritional makeover. The revamped cereals are packed with whole grains and less sugar—yet still provide the same great taste.

—By Denise Webb

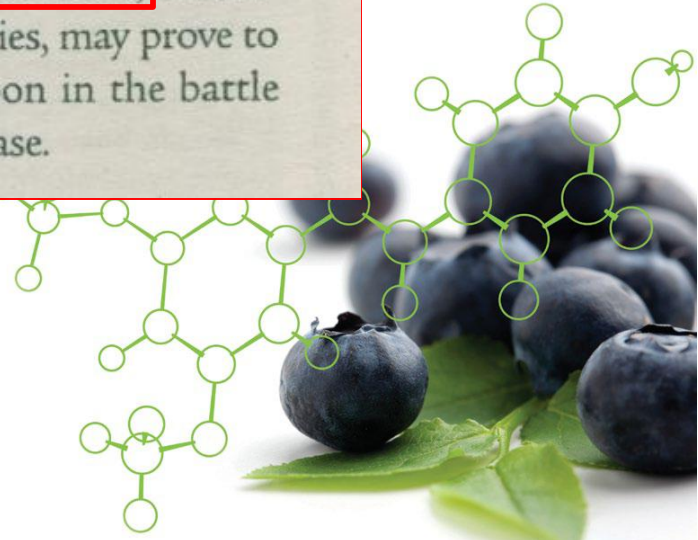

PAGE 24 • NOVEMBER 14, 2004 • PARADE

PAGE 23 • NOVEMBER 14, 2004 • PARADE

Parade, November 14, 2004

True Blue Benefits

Blueberries—a good source of antioxidants—also may help break down cholesterol and fat, as studies on rat cells at the U.S. Department of Agriculture's laboratories in Oxford, Miss., found. **Pterostilbene**, a compound in the berries, may prove to be a potent weapon in the battle against heart disease.



Pterostilbene and Diabetes

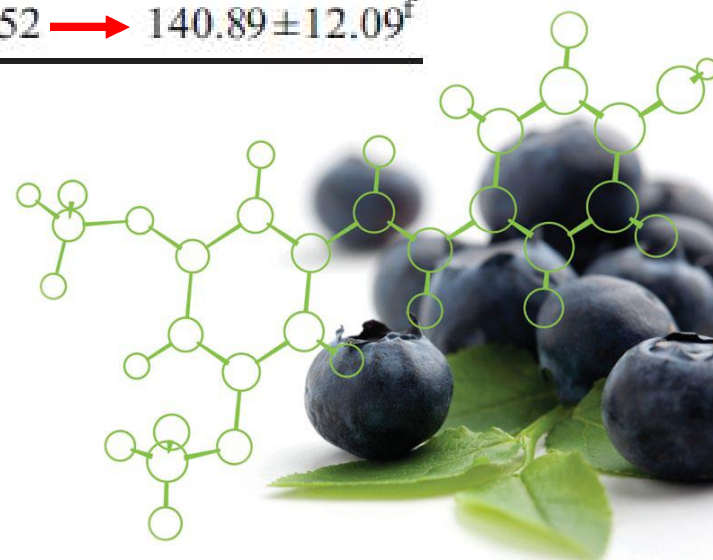
Table 1

Changes in the levels of glucose in normal and experimental rats for 2, 4 and 6 weeks

Groups	Glucose (mg/dl)	
	Day 0	6th week
Normal control	72.51 ± 6.96	74.50 ± 6.30 ^a
Normal + Pterostilbene (40 mg/kg)	80.48 ± 7.06	67.48 ± 6.67 ^a
Diabetic control	310.24 ± 27.07	394.19 ± 32.67 ^b
Diabetic + Pterostilbene (10 mg/kg)	292.21 ± 24.95	186.80 ± 15.66 ^c
Diabetic + Pterostilbene (20 mg/kg)	282.68 ± 24.24	165.16 ± 13.76 ^d
Diabetic + Pterostilbene (40 mg/kg)	279.58 ± 23.66	121.50 ± 10.84 ^e
Diabetic + Metformin (500 mg/kg)	288.49 ± 24.52	140.89 ± 12.09 ^f

L. Pari & M.A. Satheesh; Life Sci. 79, 641 (2006)

Conclusion: pterostilbene lowers blood glucose levels in diabetic rats better than pharmaceutical drug Metformin and at a much lower dose



Pterostilbene and Diabetes

Table 2
Changes in the levels of insulin
in normal and experimental rats

Groups	Insulin (μ U/ml)
Normal control	16.73 ± 1.41^a
Normal + Pterostilbene (40 mg/kg)	17.54 ± 1.53^a
Diabetic control	6.40 ± 0.56^b
Diabetic + Pterostilbene (40 mg/kg)	14.54 ± 1.53^c
Diabetic + Metformin (500 mg/kg)	11.48 ± 0.56^c

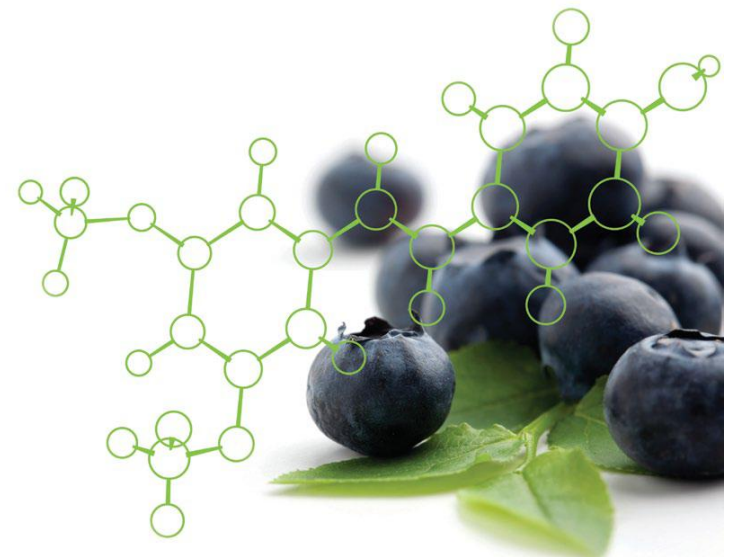
L. Pari & M.A. Satheesh; Life Sci. 79, 641 (2006)

Conclusion: pterostilbene raises insulin levels in diabetic rats, better than pharmaceutical drug Metformin and at a lower dose.

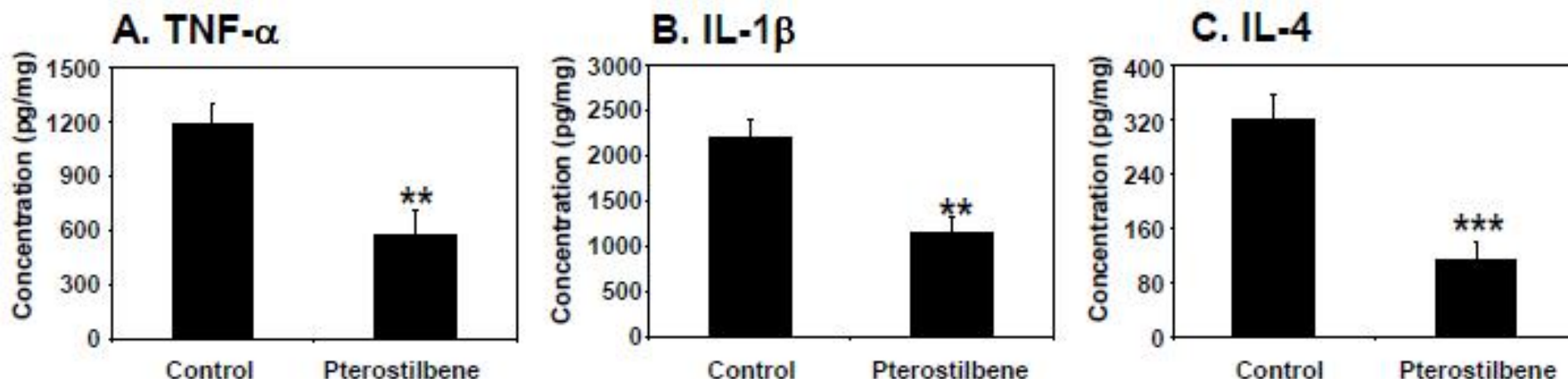


Pterostilbene and Anti-Aging

- **Anti-Inflammatory**
- **Anti-Oxidant/Oxidative Stress**
- **Memory Improvement**
- **Anti-Cancer**



Pterostilbene and Anti-Inflammation

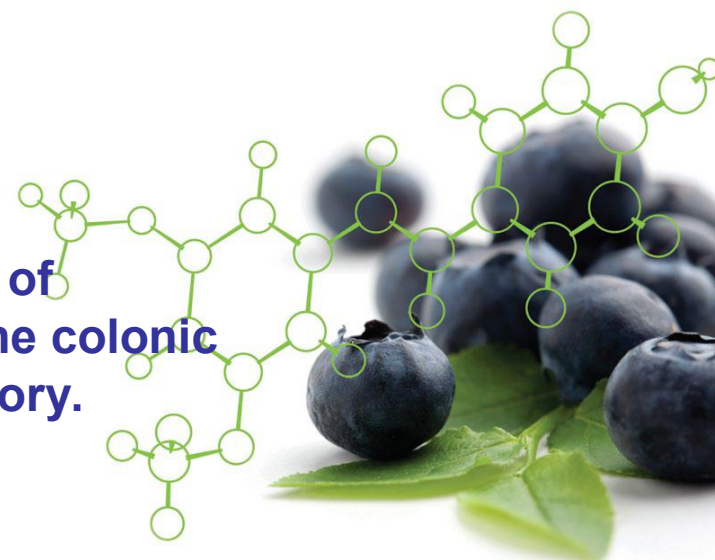


Paul et al. Carcinogenesis. 31, 1272 (2010)

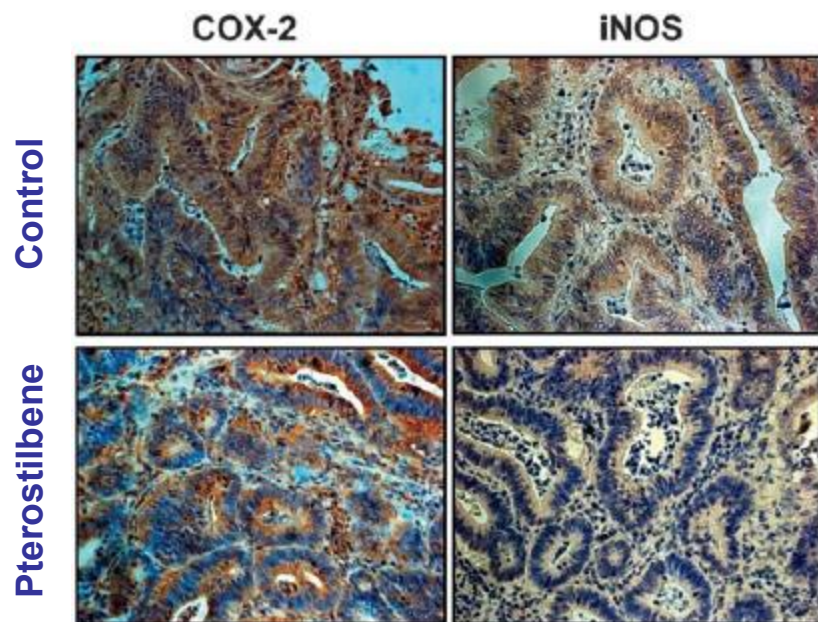
The mucosa samples were randomly selected from each group, homogenized and assayed by ELISA for the different cytokines. n = 12 in control group; n = 6 in pterostilbene group

p<0.01, *p<0.005.

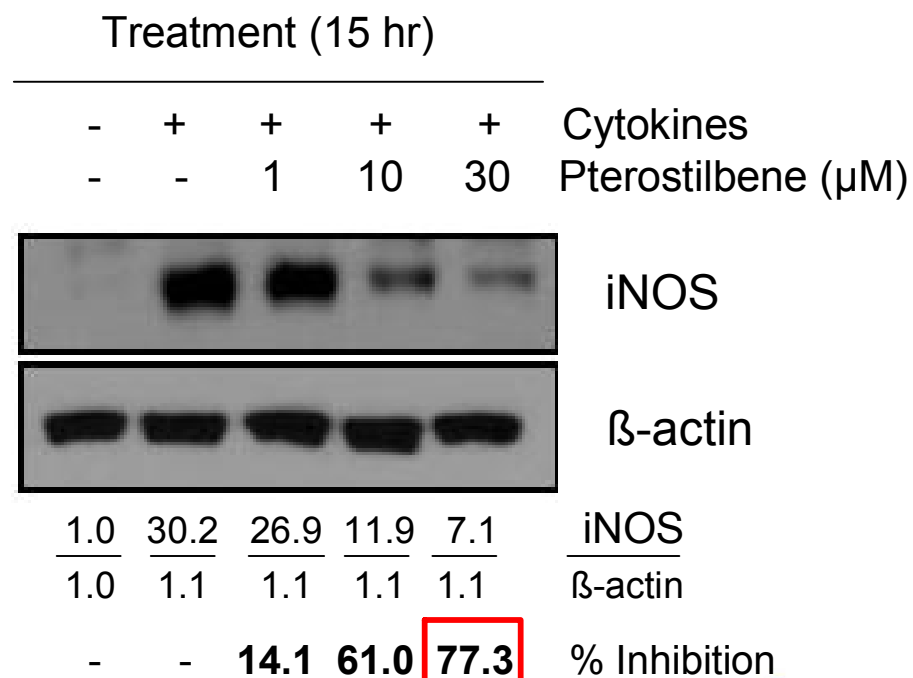
Conclusion: Pterostilbene lowered the production of inflammatory cytokines TNF- α , IL-1 β and IL-4 in the colonic mucosa of rats and thus acts as an anti-inflammatory.



Pterostilbene and Anti-Inflammation

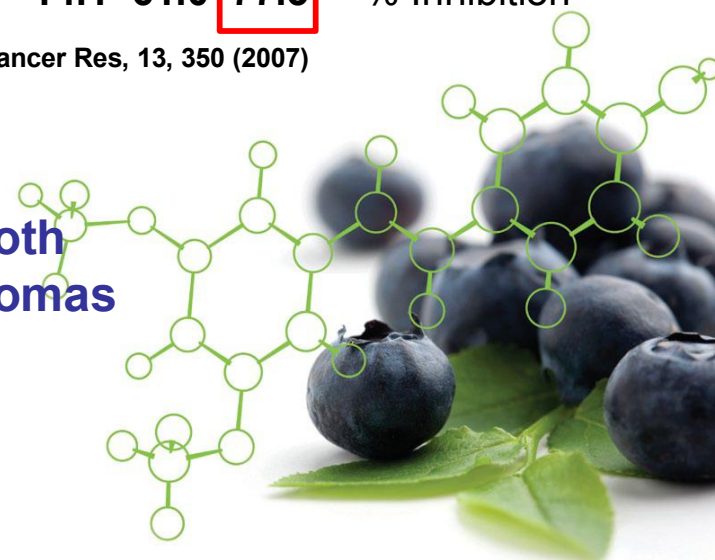


The colon tumor sections were incubated with the respective antibodies. Representative sections are shown. **Control cells (no pterostilbene) had heavier brown staining.**
Paul et al. Carcinogenesis. 31, 1272 (2010)



Suh et al., Clin. Cancer Res, 13, 350 (2007)

Conclusion: Pterostilbene was shown to reduce both iNOS and COX-2 expression in colon adenocarcinomas and dose-dependently inhibit iNOS expression in human colon cancer cells



Pterostilbene as an Anti-Oxidant

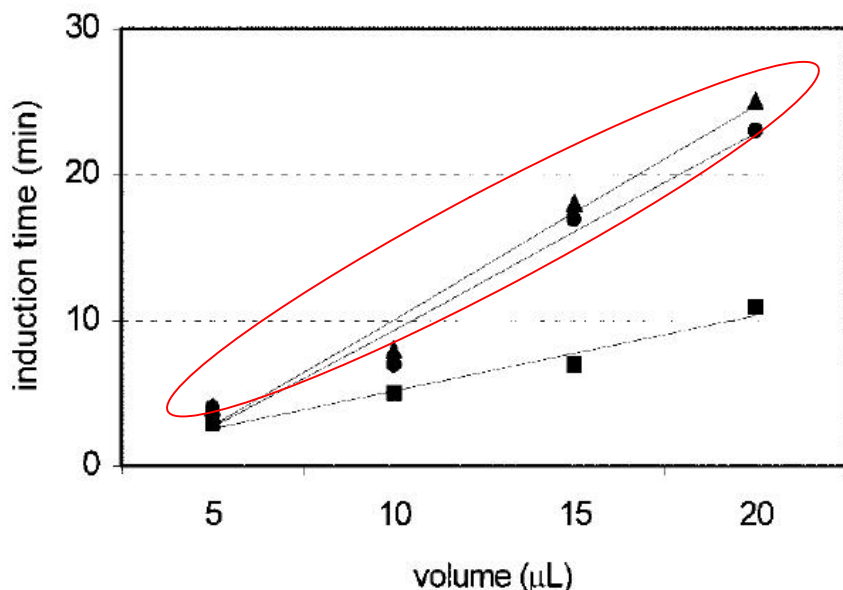


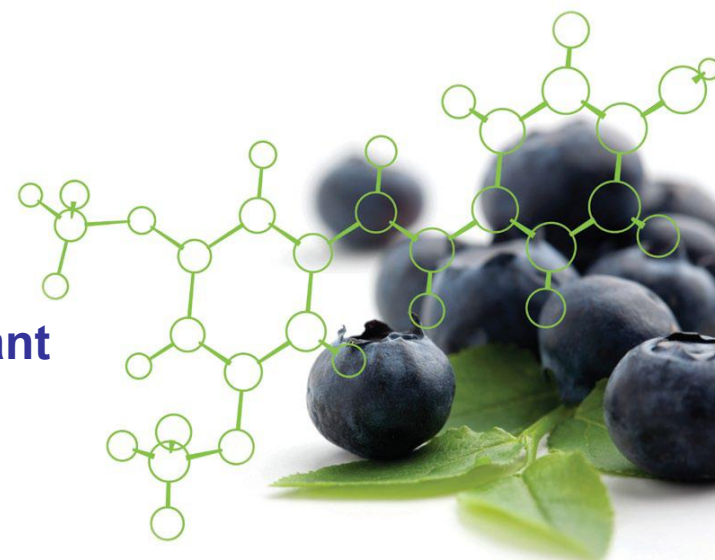
Table 1. Total Reactive Antioxidant Potential (TRAP) Expressed in μM Trolox Equivalents

sample	TRAP (μM)
Trolox	144 ± 16
pterostilbene	237 ± 58
resveratrol	253 ± 53

Figure 3. Induction time (min) as a function of the concentration of Trolox (150 μM initial concentration) (■), pterostilbene (●), and resveratrol (▲) (150 μM initial concentration).

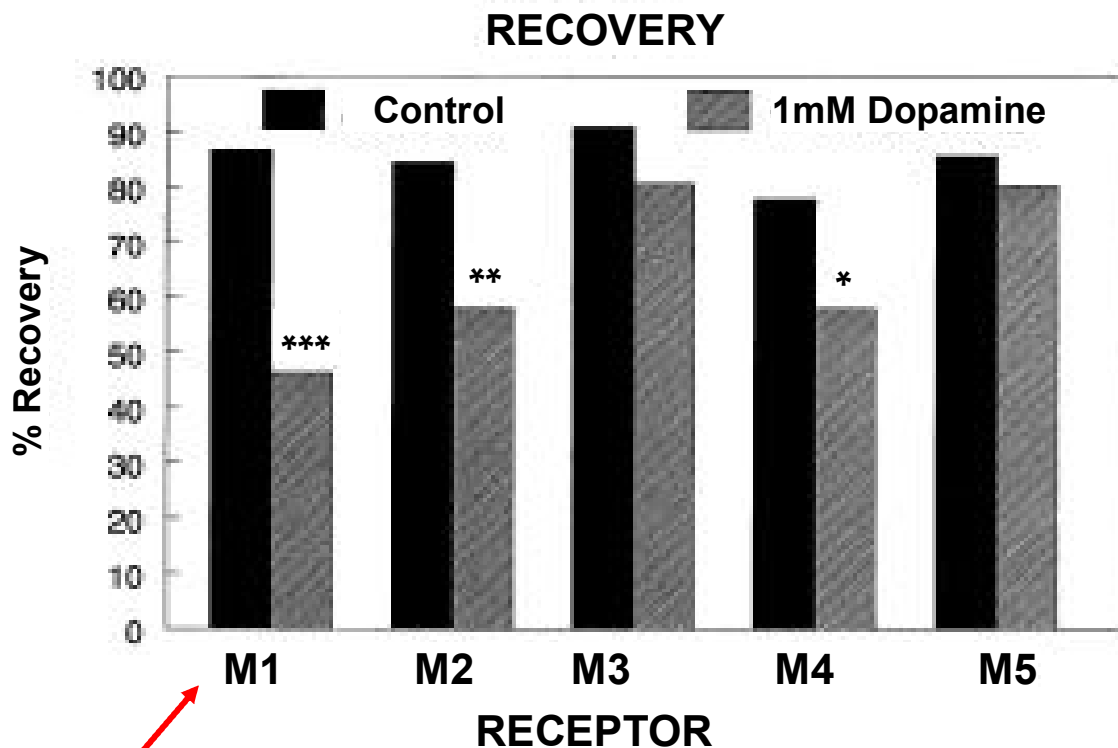
A.M. Rimando, et al.; J. Agric. Food Chem. 50, 3453 (2002)

Conclusion: pterostilbene has the same anti-oxidant potential as resveratrol



Pterostilbene and Oxidative Stress

Measuring Oxidative Stress



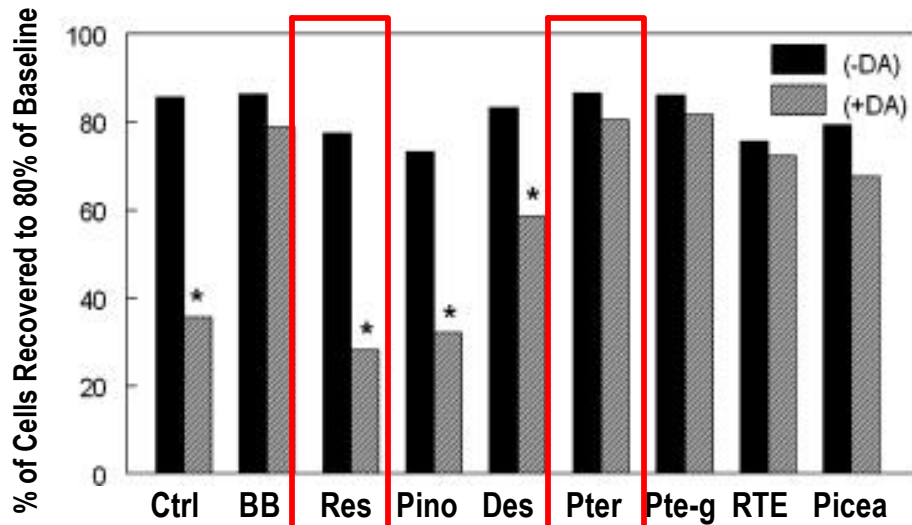
Percent of cells showing **Recovery** to oxotremorine-induced Ca^{2+} influx; * $p < .05$, ** $p < .01$, *** $p < .001$.

Joseph et al. Free Rad. Biol. Med. 32:153-161, (2002)

Conclusion: Muscarinic receptor subtype 1 was the most sensitive to oxidative stress.

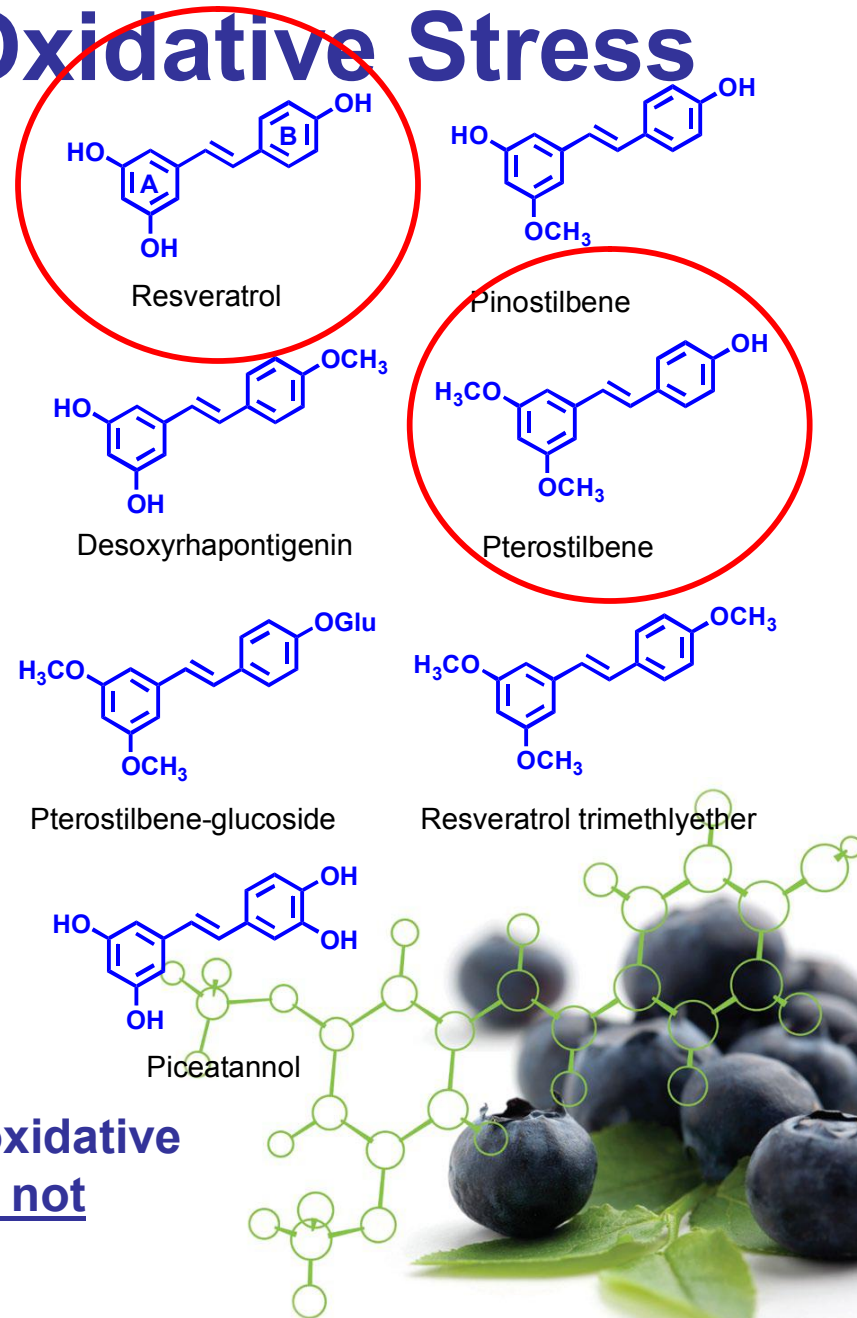


Pterostilbene and Oxidative Stress



Mean Ca^{2+} recovery in M1-transfected COS-7 cells, control and treated with the stilbenes, following 0 (-DA) or 1 mM DA (+DA) treatment. *Difference in recovery between non-DA-treated and DA-treated cells for each treatment ($p < 0.001$).

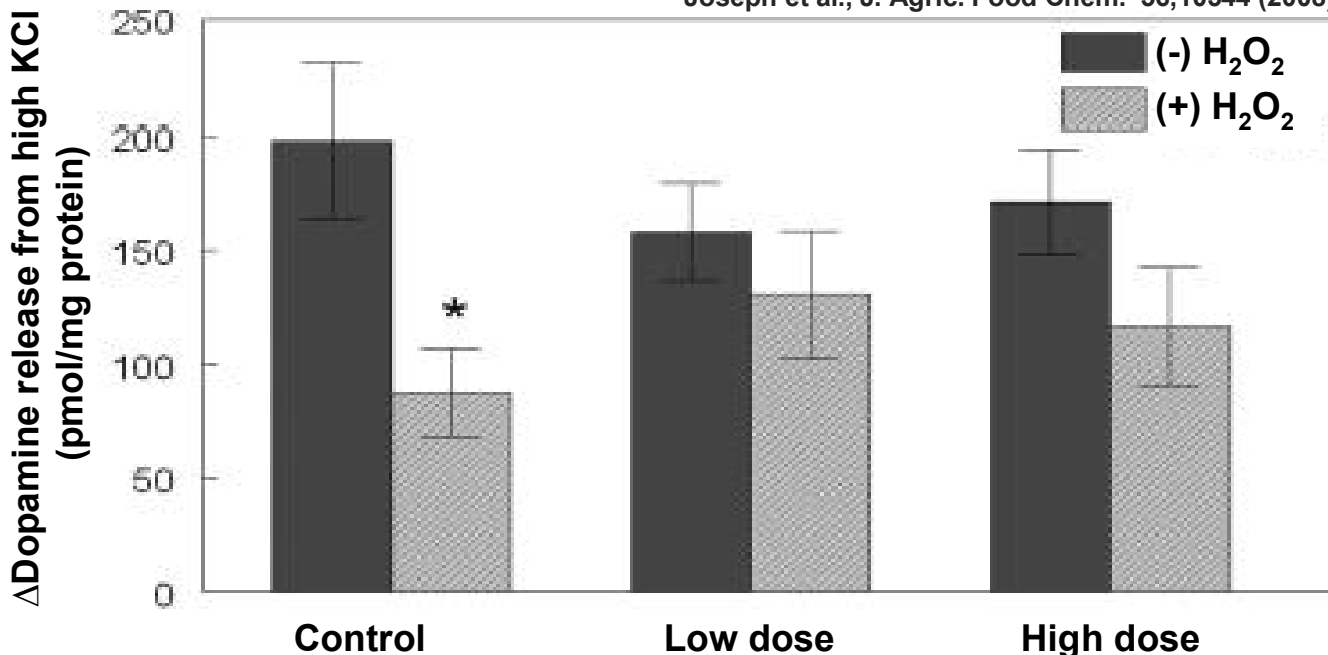
Joseph et al., J. Agric. Food Chem. 56:10544-10551 (2008)



Conclusion: Pterostilbene protects against oxidative stress in COS-7 cell assay; Resveratrol does not

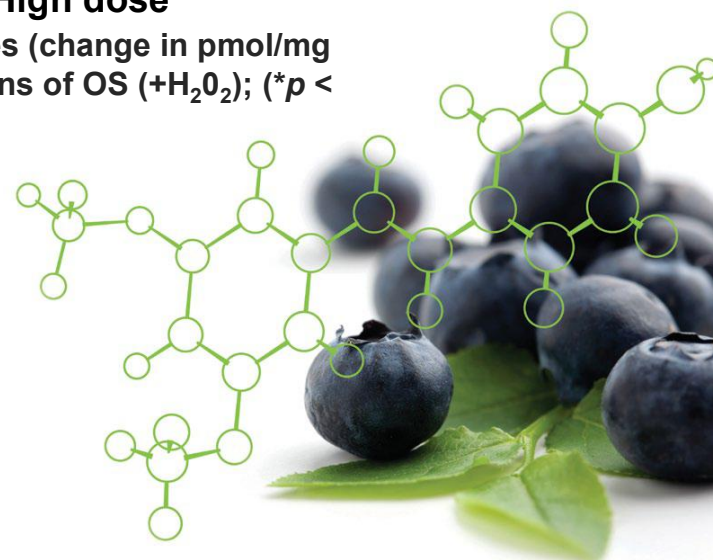
Pterostilbene and Oxidative Stress

Joseph et al., J. Agric. Food Chem. 56,10544 (2008)



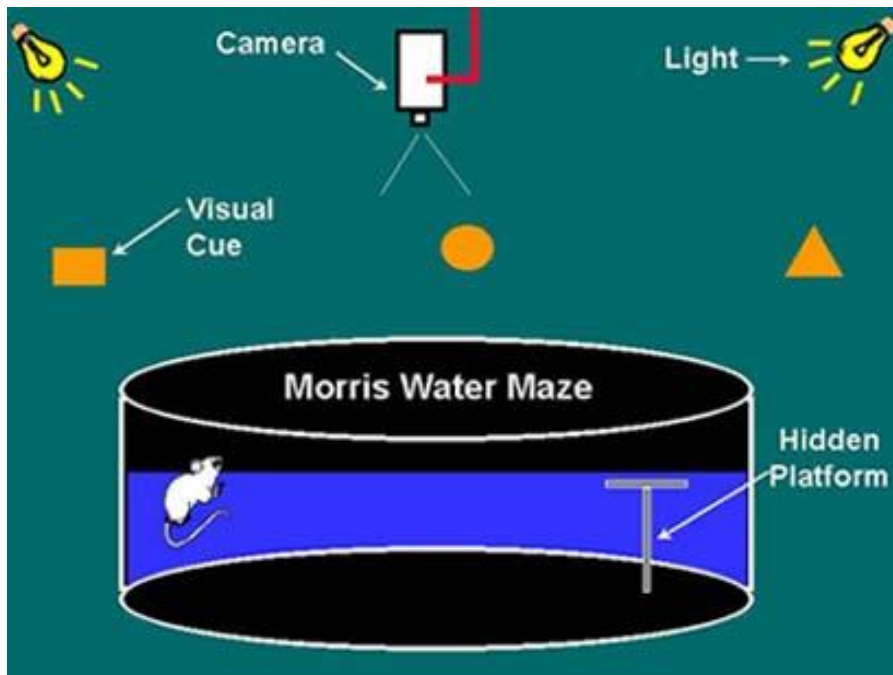
Oxotremorine enhancement of Dopamine release from striatal slices (change in pmol/mg protein, mean \pm SEM) under basal levels (-H₂O₂) and under conditions of OS (+H₂O₂); (* p < 0.01).

Conclusion: Pterostilbene protected against the decrease in dopamine release following oxidative stressor.



Pterostilbene and Cognitive Function

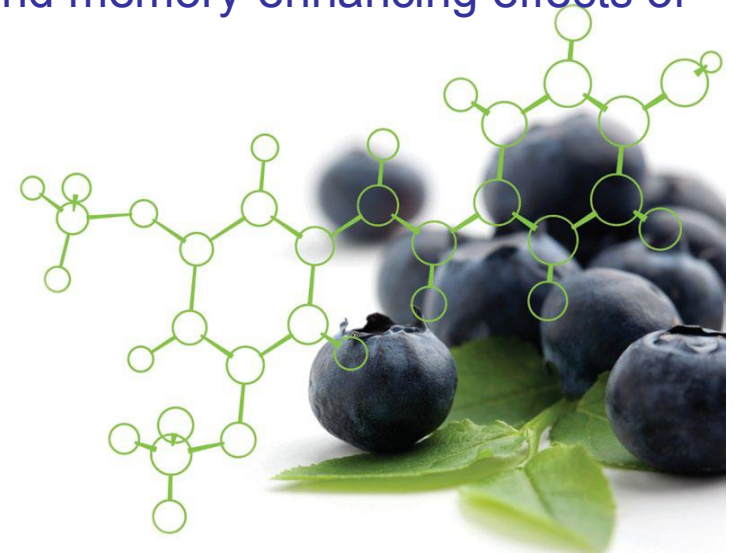
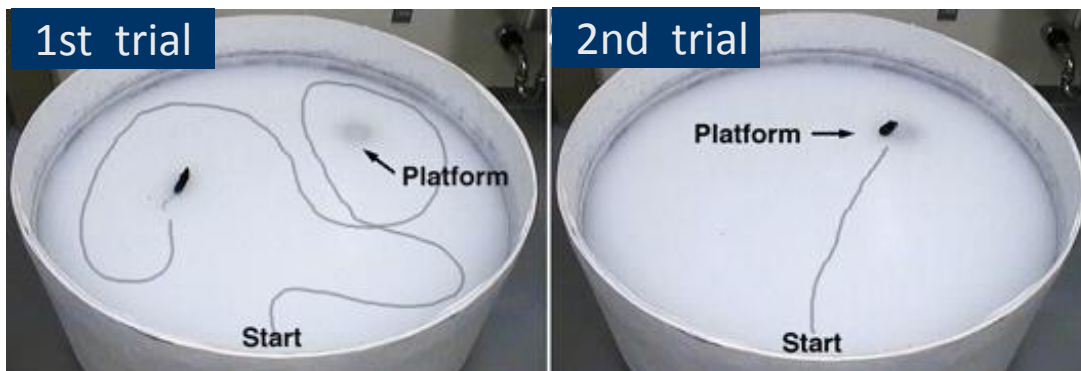
Morris Water Maze Test



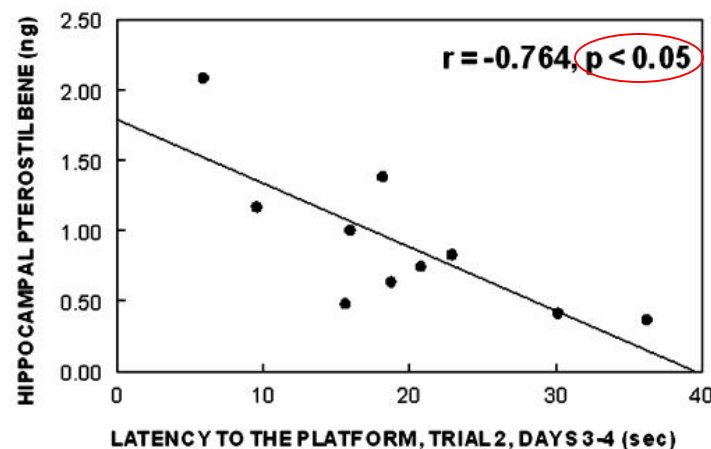
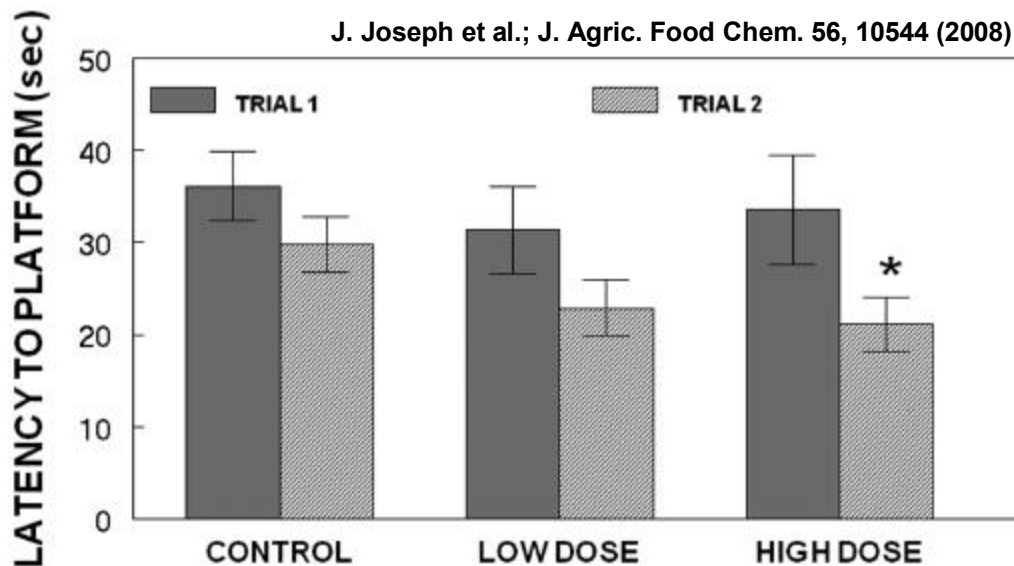
<http://www.mcg.edu/Core/Labs/sabc/Morriswatermaze.htm>

Description: The Morris Water Maze test involves placing the rodent in a pool of water where it must use external visual cues to remember the location of a hidden platform just below the water's surface.

Purpose: The MWM test measures spatial learning and memory. This is one of the most popular tasks in behavioral neuroscience and is sensitive to both the amnesic and memory-enhancing effects of drugs.



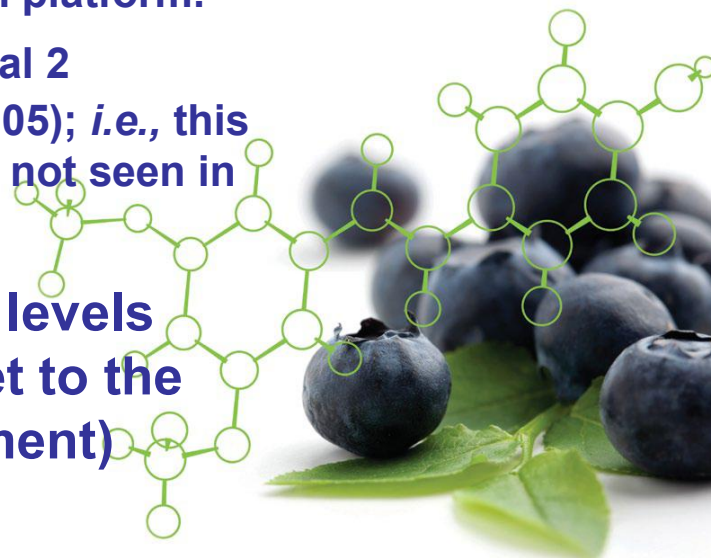
Pterostilbene and Cognitive Function



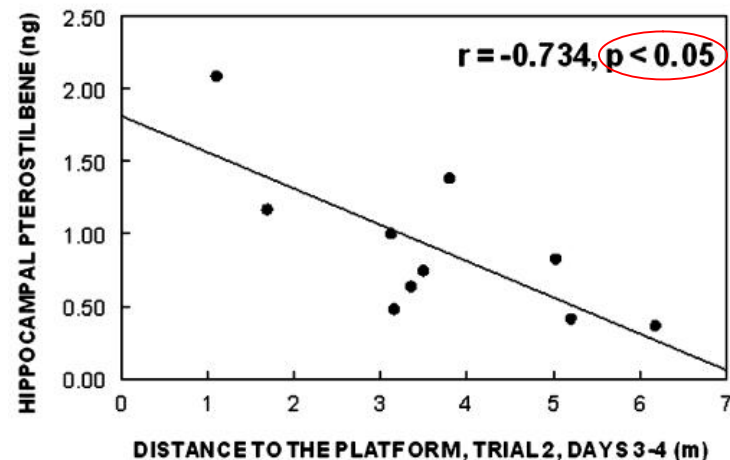
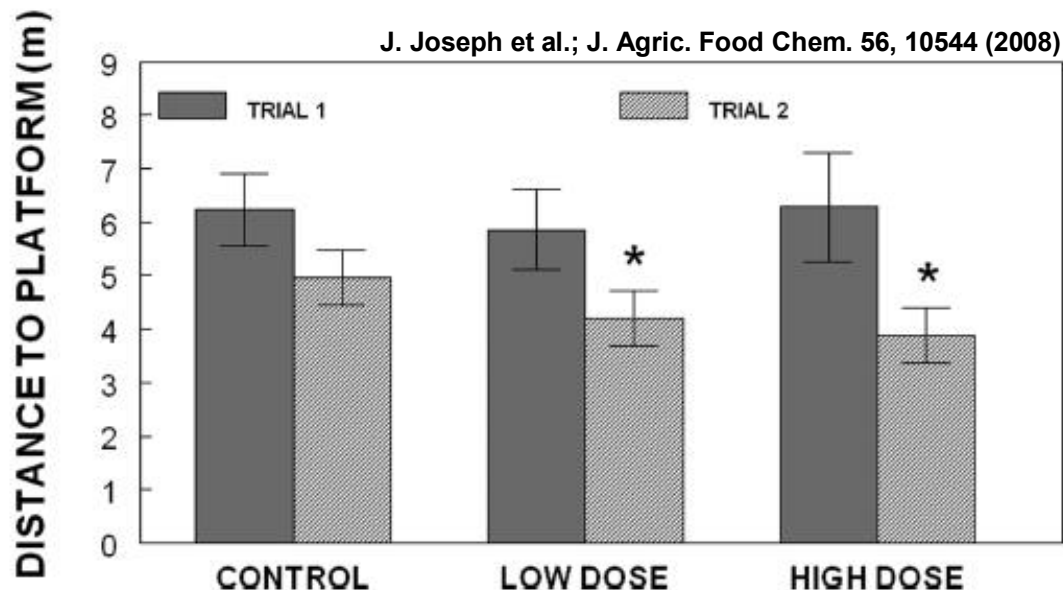
MWM performance assessed as **latency** to find the hidden platform.

* Indicates a significant difference between Trial 1 and Trial 2 performance for the high dose pterostilbene group ($p < 0.05$); *i.e.*, this group had **improved working memory**. Improvement was not seen in the control rats.

Conclusion: an increase in brain pterostilbene levels leads to a decrease in the amount of time to get to the platform between two trials (memory improvement)



Pterostilbene and Cognitive Function



MWM performance assessed as **distance** to find the hidden platform.

* Indicates a difference between Trial 1 and Trial 2 performance for the low and high dose pterostilbene groups ($p < 0.05$); *i.e.*, these groups had **improved working memory**. This improvement was not seen in the control rats.

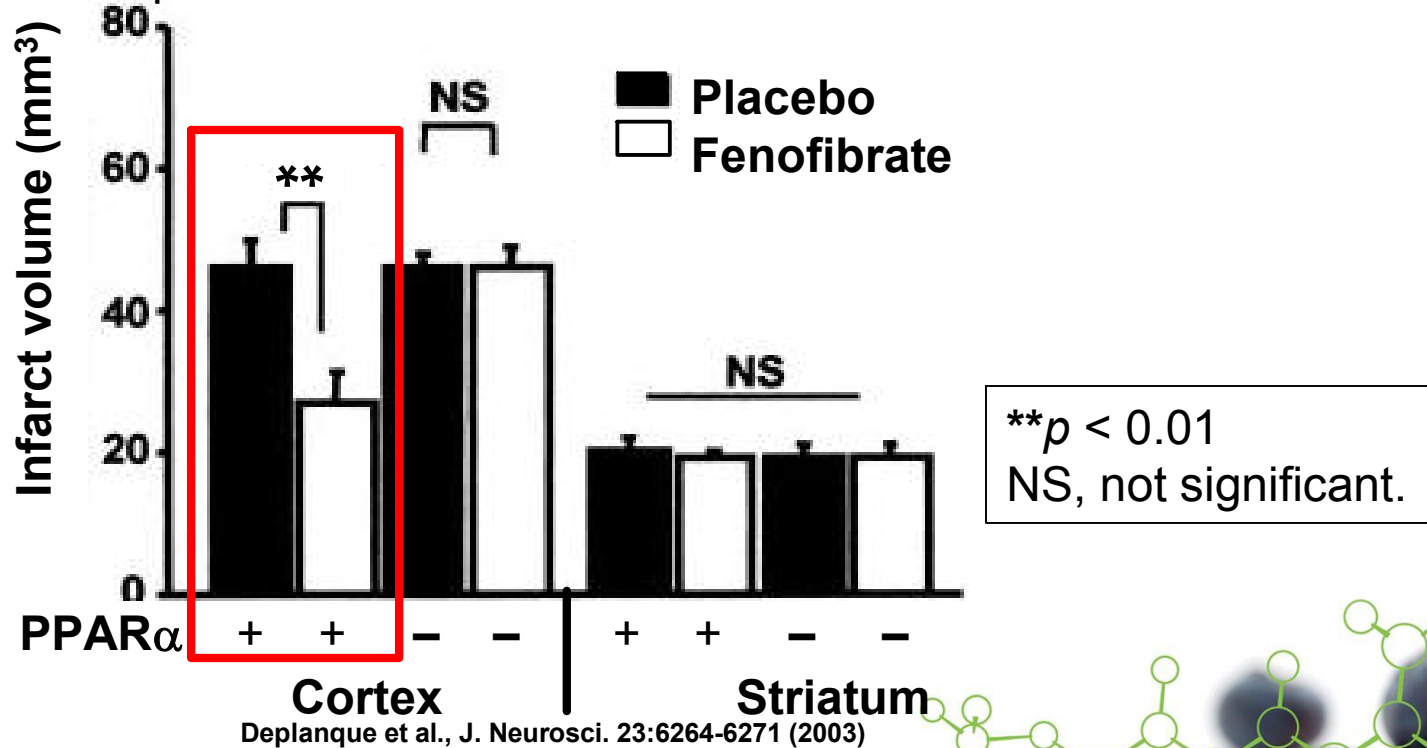
Conclusion: an increase in brain pterostilbene levels leads to a decrease in the distance travelled between two trials (memory improvement)



Pterostilbene and Cognitive Function

More than just modulating metabolic pathways (as seen in cholesterol lowering), PPAR α is able to regulate oxidative as well as inflammatory pathways.

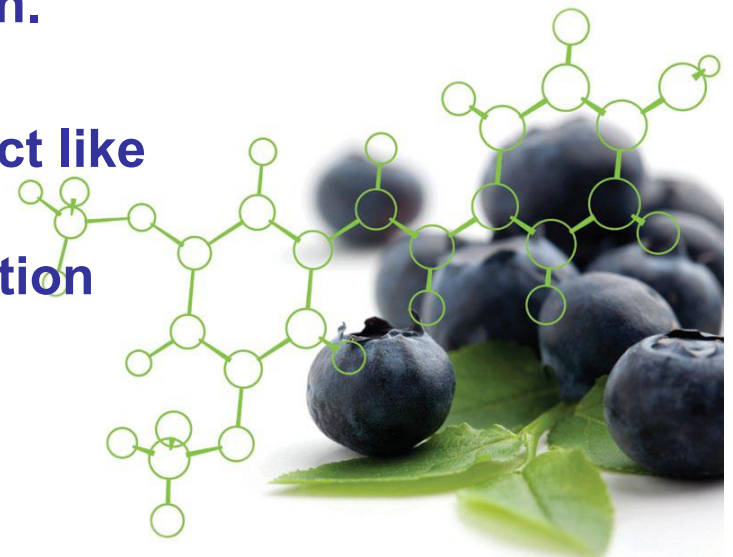
The neuroprotective effect of fenofibrate in SV129 mice.



Conclusion: The neuroprotective effect of fenofibrate was not seen in PPAR α -deficient mice, so fenofibrate induced neuroprotection via PPAR α activation in cortical areas of the brain (hippocampus). As a PPAR α agonist, pterostilbene should induce the same effect.

Pterostilbene and Anti-Aging Summary

- Of all stilbenes tested, pterostilbene demonstrated the best protection against oxidative stress in M1-transfected COS-7 cells.
- Pterostilbene reversed cognition decreases in old rats, likely due to protection from oxidative stress.
- Levels of pterostilbene in the hippocampus positively correlated with animal behavior and cognitive function.
- As a PPAR α agonist, pterostilbene may act like fenofibrate by activating PPAR α in the hippocampus, contributing to neuroprotection from oxidative stress.



Pterostilbene and Cancer

Pterostilbene has shown anti-cancer activity in several different solid tumors

Melanoma (inhibits metastasis)

Ferrer et al, Neoplasia 7, 37 (2005)

Colorectal Cancer (suppresses premalignant lesion formation and invasion)

N. Suh et al; Clin. Cancer Res. **13**, 350 (2007); S. Paul et al; Carcinogenesis **31**, 1272 (2010)

Gastric Carcinoma (induces cell cycle arrest and apoptosis)

M.H. Pan, et al.; J. Agric. Food Chem. **55**, 7777 (2007)

Breast Cancer (inhibits metastasis and induces apoptosis)

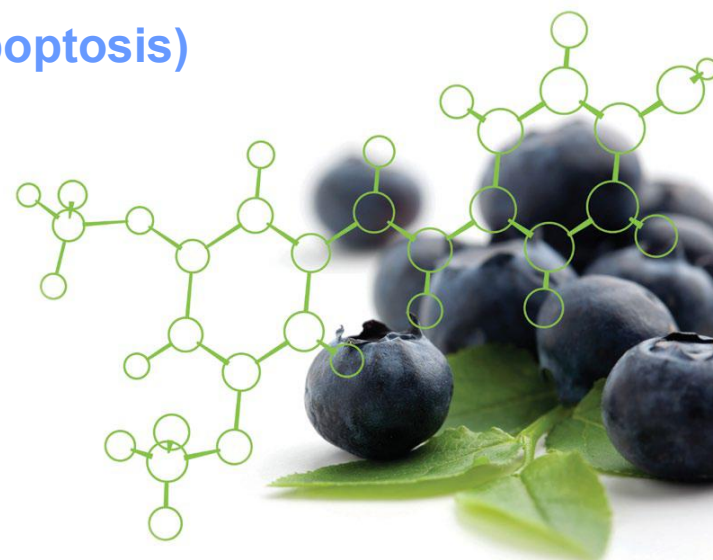
M. Pan et al; Evid. Based Complement Alternat. Med. **7**, (2009)

Hepatocellular Carcinoma (inhibits metastasis)

M.H. Pan et al; Carcinogenesis. **30**, 1234 (2009)

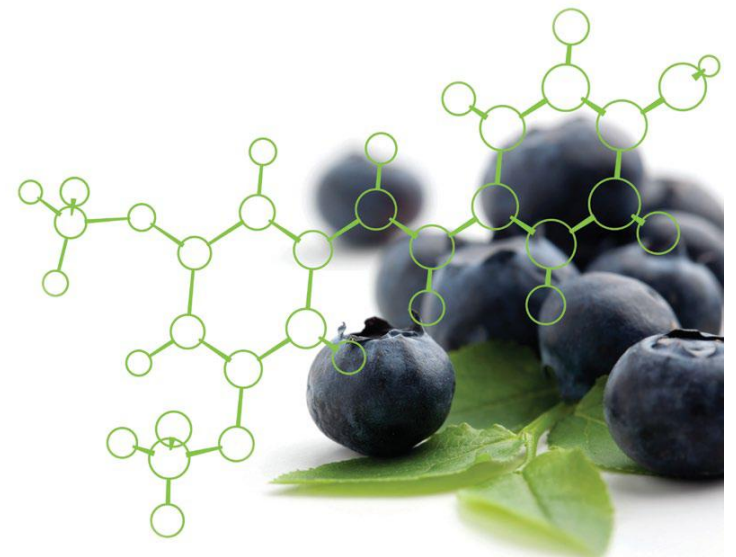
Lung Cancer (induces apoptosis)

J.G. Schneider et al.; J. Surg. Res. **161**, 18 (2010)



Summary: The Diverse Biological Activities of Pterostilbene

- Analgesic
- Antioxidant
- Anti-diabetic
- Anti-inflammatory
- Cancer chemopreventive
- Cytotoxic
- Hypolipidemic
- Cognitive function improvement
- Anti-microbial



Pterostilbene Dosage

Human dose translation from animal studies is based on body surface area (BSA)

HED = human equivalent dose

Formula for Dose Translation Based on BSA

$$\text{HED (mg/kg)} = \text{Animal dose (mg/kg)} \text{ multiplied by } \frac{\text{Animal } K_m}{\text{Human } K_m}$$

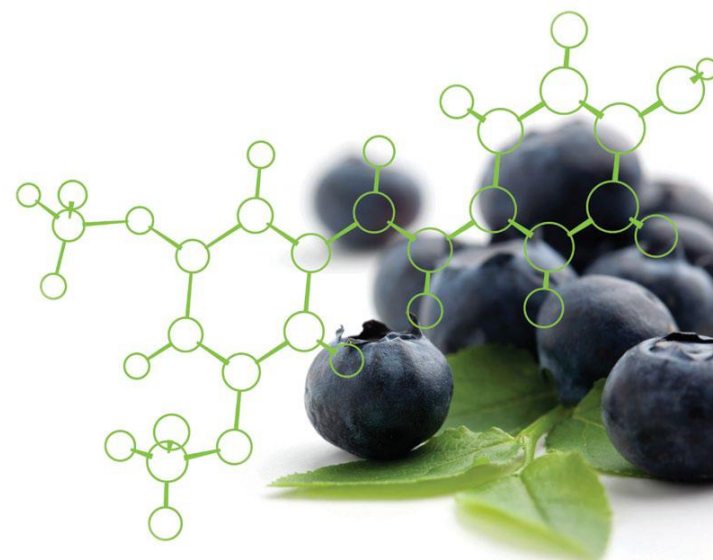
TABLE 1. Conversion of animal doses to HED based on BSA

Species	Weight (kg)	BSA (m ²)	<i>K_m</i> factor
Human			
Adult	60	1.6	37
Child	20	0.8	25
Baboon	12	0.6	20
Dog	10	0.5	20
Monkey	3	0.24	12
Rabbit	1.8	0.15	12
Guinea pig	0.4	0.05	8
Rat	0.15	0.025	6
Hamster	0.08	0.02	5
Mouse	0.02	0.007	3

Values based on data from FDA Draft Guidelines (7). To convert dose in mg/kg to dose in mg/m², multiply by *K_m* value.

Reagan-Shaw et al.; FASEB J. 22(3):659-61 (2008)

Figure 1. Formula for dose translation based on BSA.



Pterostilbene Dosage

Cholesterol paper (A.M. Rimando, et al.; J. Agric. Food Chem. 53, 3403; 2005)

hamsters: 2.5 mg/kg = 0.337 mg/kg for humans
= **24.6 mg** for a 160 pound person

Diabetes paper (L. Pari & M.A. Satheesh; Life Sci. 79, 641; 2006)

rats: 10 - 40 mg/kg = 1.62 - 6.48 mg/kg for humans
= **117.8 - 471.3 mg** for a 160 pound person

Cognitive Function paper (J. Joseph et al.; J. Agric. Food Chem. 56, 10544; 2008)

rats: 2.5 - 10 mg/kg = 0.41 - 1.62 mg/kg for humans
= **29.8 - 117.8 mg** for a 160 pound person

Recommended dose: 50-150 mg per day



Pterostilbene Toxicity

28-day subchronic toxicity study in mice

Doses/day (mg/kg of body weight): 30, 300, 3000

- HED for a 154 pound person = **125 mg/day, 1.25 g/day, 12.5 g/day, respectively**

Table 4. Urinary Balance in Male and Female Swiss Mice Treated Orally with the Highest Dose Administrated of Pterostilbene

	male		female	
	control	P3	control	P3
specific weight ($\times 10^3$)	1.007 \pm 2.8	1.011 \pm 2.5	1.01 \pm 2.5	1.01 \pm 2.5
pH	8.2 \pm 0.5	6.5 \pm 0.6	8.2 \pm 0.9	6.5 \pm 0.6
leukocytes μL^{-1}	negative	negative	negative	negative
nitrite	negative	negative	negative	negative
protein (g L $^{-1}$)	0.2	0.3	0.15	0.15
glucose	normal	normal	normal	normal
ketones	negative	negative	negative	negative
urobilinogen	normal	normal	normal	normal
bilirubin	negative	negative	negative	negative
blood/hemoglobin (erythrocytes μL^{-1})	ca. 11	ca. 25	ca. 10	ca. 23

3. RESULTS

After daily oral administration of either of the doses tested for the 28 days period, there were no deaths. No evident treatment-related effect was observed on behavior. Clinical chemistry and hematological and histopathological analyses revealed that oral intake of high doses of t-PTER and QUER is safe, since this is not associated with significant local or systemic toxicity.

M.J. Ruiz et al.; J. Agric. Food Chem. 57, 3180 (2009)



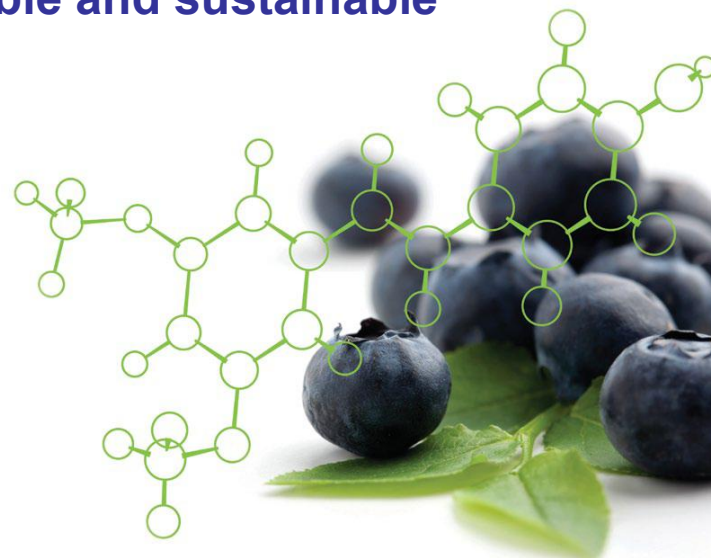
Pterostilbene: Extract vs. pTeroPure

Extracted material

- Low purity (5-25%)
 - contains unknown chemicals other than pterostilbene (GMP compliance)
 - difficult to achieve a clinically relevant dose in a small capsule
- Typically extracted from *Pterocarpus marsupium* tree (the levels found in blueberries and other small fruits are too low to be considered a commercially viable source).
 - non-renewable resource
 - endangered species

pTeroPure

- High purity (99+%)
 - contains pterostilbene only
 - easy to achieve a clinically relevant dose in a small capsule
- Chemical starting material is renewable and sustainable



pTeroPure pterostilbene clinical studies

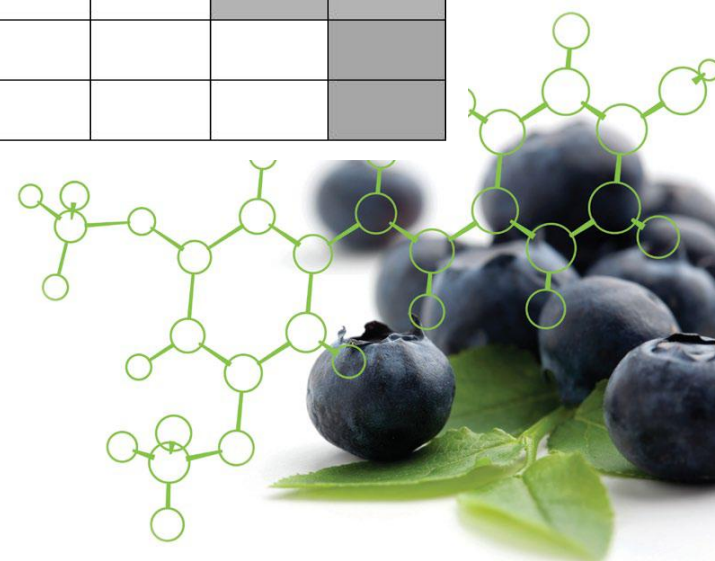
First Human Clinical Study Utilizing Pterostilbene:

- ChromaDex in collaboration with the University of Mississippi
- Primary Endpoint: Cholesterol
- Secondary Endpoints: Blood Pressure and Oxidative Stress Markers
- 4 Arms with 20 people per arm = 80 total participants
 - 100mg pterostilbene + 200mg Shanstar grape extract/day
 - 100mg pterostilbene/day
 - 250mg pterostilbene/day
 - placebo



pTeroPure pterostilbene clinical studies

Month	Jun/Jul 10	Aug/Sep 10	Oct/Nov 10	Dec/Jan 10/11	Feb/Mar 11	Apr/May 11	Jun/Jul 11	Aug/Sep 11	Oct/Nov 11	Dec/Jan 11/12
Timeline										
IRB Approval										
Patient Recruitment/ Enrollment										
Data Collection										
Planned Interim Analysis										
Data Analysis										
Manuscript Preparation										
Results Presentation										
Submission of Final Report										
Submission of Manuscript										

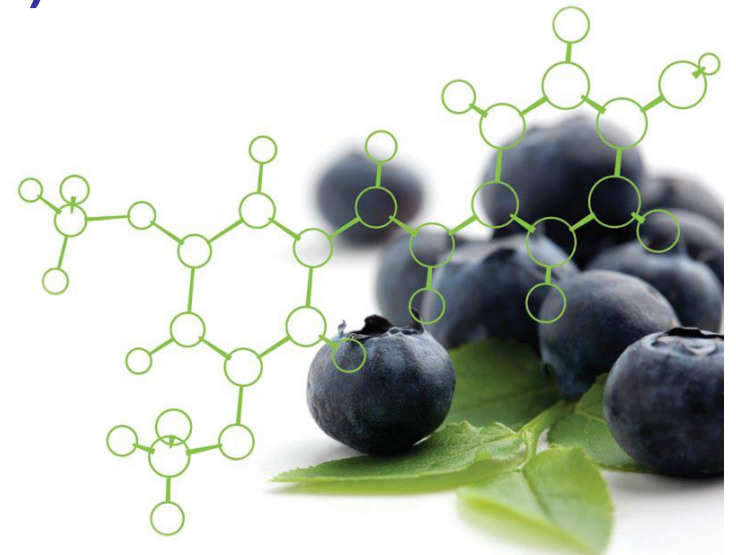


pTeroPure Pterostilbene GRAS Status

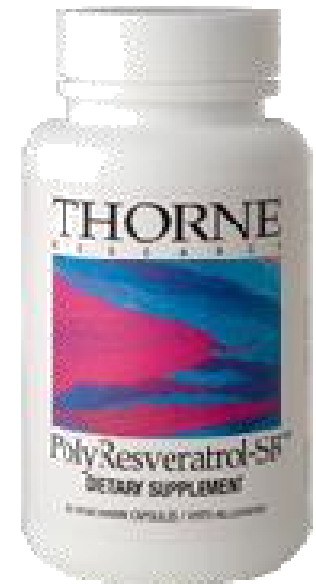
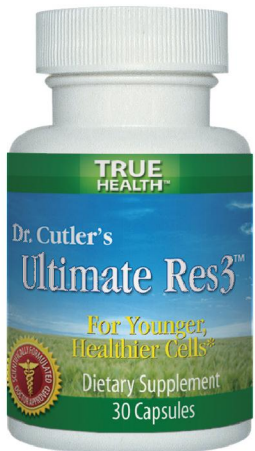


**GRAS self-affirmation for pTeroPure
Pterostilbene in collaboration with AIBMR**

**Anticipated completion next year (can vary
based on current FDA timeline for GRAS
review and notification)**



Current pTeroPure Pterostilbene Products on the Market



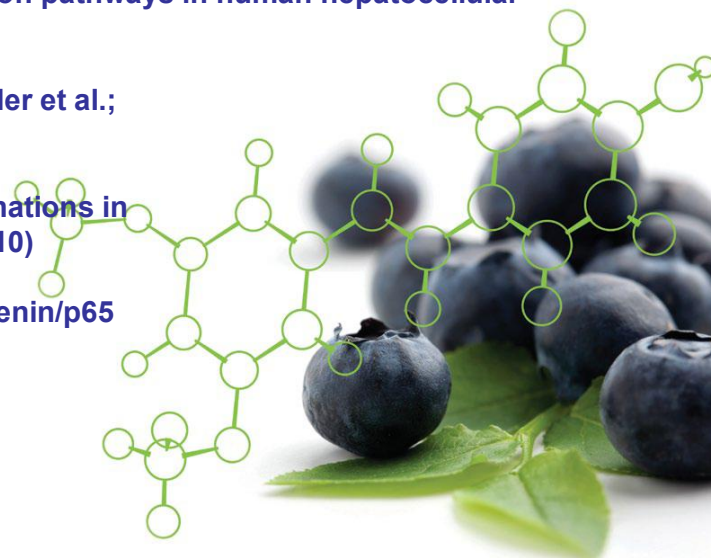
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Thank you!

pTeroPure Pterostilbene The Next Generation Resveratrol

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