Resveratrol, a Polyphenolic Antioxidant, Present in Grape Skin, is Dose Dependent in Providing Health Benefits

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trans - resveratrol

cis - resveratrol
<table>
<thead>
<tr>
<th>Source</th>
<th>Resveratrol concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>100% Natural peanut butter</td>
<td>~0.65 μg/g</td>
</tr>
<tr>
<td>Bilberries</td>
<td>~16 ng/g</td>
</tr>
<tr>
<td>Blueberries</td>
<td>~32 ng/g</td>
</tr>
<tr>
<td>Boiled peanuts</td>
<td>~5.1 μg/g</td>
</tr>
<tr>
<td>Cranberry raw juice</td>
<td>~0.2 mg/L</td>
</tr>
<tr>
<td>Dry grape skin</td>
<td>~24.06 μg/g</td>
</tr>
<tr>
<td>Grapes</td>
<td>0.16–3.54 μg/g</td>
</tr>
<tr>
<td>Peanut butter</td>
<td>0.3–1.4 μg/g</td>
</tr>
<tr>
<td>Peanuts</td>
<td>0.02–1.92 μg/g</td>
</tr>
<tr>
<td>Pistachios</td>
<td>0.09–1.67 μg/g</td>
</tr>
<tr>
<td>Ports and sherries</td>
<td>&lt;0.1 mg/L</td>
</tr>
<tr>
<td>Ref grape juice</td>
<td>~0.50 mg/L</td>
</tr>
<tr>
<td>Red wines</td>
<td>0.1–14.3 mg/L</td>
</tr>
<tr>
<td>Roasted peanuts</td>
<td>~0.055 μg/g</td>
</tr>
<tr>
<td>White grape juice</td>
<td>~0.05 mg/L</td>
</tr>
<tr>
<td>White wines</td>
<td>&lt;0.1–2.1 mg/L</td>
</tr>
</tbody>
</table>
The French paradox
Effect of white wine, its components tyrosol and hydroxytyrosol, red wine, and resveratrol on the infarct size.

Dudley et al., J Agric Food Chem. 2008
Effect of white wine, its components tyrosol and hydroxytyrosol, red wine, and resveratrol on the infarct size.

Dudley et al., J Agric Food Chem. 2008
Dudley et al., J Agric Food Chem. 2008
Antitumor activity, Chemoprevention
Inhibits NF-κB activation, Proliferation,
Causes S-phase arrest, Induces apoptosis
of myeloid leukemia cells

Prevents prostate and
Pancreatic, gastric
and thyroid cancer

Anti-Aging

Cardioprotection

Protects from
Radiation injury

Protects cerebral
ischemic injury

Inhibited growth of
H. pylori

Reversible inhibition of herpes
simplex virus types 1 & 2 replication

Reduces platelet adhesion,
Monocyte adhesion
(anti-inflammatory response)

Prevents LDL oxidation

Protects lung from DNA
Damage and apoptosis

Neuroprotection
Molecular targets of Resveratrol

- COX/LOX
- STAT3
- Src
- TNF
- Akt
- PKC/PKD
- p56lck
- ERK 1/2, JNK, p38 MAPK
- PI3K/PKB
- FoxO
- AMPK
- Sirt1
- p53
- NFkB
- NO
- Ribonucleotide reductase
- Adenylyl cyclase
- Aromatase
- DNA polymerases α and δ
- Quinone reductase 2
- PGE2
- Bax/Bcl2
- eNOS
- iNOS
- PBEF
- Sirt1
Myocardial injury and ageing related diseases

RESVERATROL

Apoptosis

Anti-apoptotic resveratrol

Cancer prevention

RESVERATROL

Apoptosis

Pro-apoptotic resveratrol
Myocardial injury and ageing related diseases

Cancer prevention

Low dose of resveratrol was used

High dose of resveratrol was used

Health beneficiary effects of resveratrol are dose dependent or not?
High dose resveratrol promotes atherosclerosis in case of hypercholesterolemic rabbits

Sudan-IV stained rabbit aortas with atherosclerotic lesions appearing as darkened areas on a white aortic surface. Panel A) Arteries from control rabbits. Panel B) Arteries from resveratrol-treated rabbits.

Wilson et al., Life Sciences. 1996
**Effect of High Dose Resveratrol on Proliferation and Apoptosis in Endothelial and Tumor Cell Culture**

<table>
<thead>
<tr>
<th></th>
<th>Apoptosis</th>
<th>Mitosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>24 h</td>
<td>48 h</td>
</tr>
<tr>
<td>Control</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>0.1 µg/ml</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>1.0 µg/ml</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>10 µg/ml</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>100 µg/ml</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

Effect of resveratrol on the apoptotic and mitotic index of HUVEC Endothelial cell culture

<table>
<thead>
<tr>
<th></th>
<th>Apoptosis</th>
<th>Mitosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>24 h</td>
<td>48 h</td>
</tr>
<tr>
<td>Control</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>1 µg/ml</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>10 µg/ml</td>
<td>22</td>
<td>30</td>
</tr>
<tr>
<td>100 µg/ml</td>
<td>75</td>
<td>75</td>
</tr>
</tbody>
</table>

Effect of resveratrol on the apoptotic and mitotic index of HT-29 cell culture

<table>
<thead>
<tr>
<th></th>
<th>Apoptosis</th>
<th>Mitosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>24 h</td>
<td>48 h</td>
</tr>
<tr>
<td>Control</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>1 µg/ml</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>10 µg/ml</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>100 µg/ml</td>
<td>20</td>
<td>80</td>
</tr>
</tbody>
</table>

Effect of resveratrol on the apoptotic and mitotic index of HT-1080 human fibrosarcoma cell culture

*Szende et al., Experimental And Molecular Medicine 2000*
Effect of resveratrol on the proliferation of HUVEC human endothelial cells

Effect of Reserveratol on the proliferation of HT-29 human colon carcinoma cells

Szende et al., Experimental And Molecular Medicine 2000
## Resveratrol Associated Renal Toxicity is Dose Dependent

### Histologic Changes in the Kidneys of Rats Administered Resveratrol Orally for 4 Weeks

<table>
<thead>
<tr>
<th>Dose mg/kg bwt/day</th>
<th>0</th>
<th>300</th>
<th>1000</th>
<th>3000</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>F</td>
<td>M</td>
<td>F</td>
</tr>
<tr>
<td>Kidney lesion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tubule dilatation</td>
<td>0/20</td>
<td>0/20</td>
<td>0/20</td>
<td>0/19</td>
</tr>
<tr>
<td>Papillary necrosis</td>
<td>0/20</td>
<td>0/20</td>
<td>0/20</td>
<td>0/19</td>
</tr>
<tr>
<td>Ulceration, pelvic epithelium</td>
<td>0/20</td>
<td>0/20</td>
<td>0/20</td>
<td>0/19</td>
</tr>
<tr>
<td>Inflammation, acute pelvic</td>
<td>0/20</td>
<td>0/20</td>
<td>0/20</td>
<td>0/19</td>
</tr>
<tr>
<td>Inflammation, acute pelvic adventitia</td>
<td>0/20</td>
<td>0/20</td>
<td>0/20</td>
<td>0/19</td>
</tr>
<tr>
<td>Glomerular necrosis</td>
<td>0/20</td>
<td>0/20</td>
<td>0/20</td>
<td>0/19</td>
</tr>
<tr>
<td>Papillary fibrosis</td>
<td>0/20</td>
<td>0/20</td>
<td>0/20</td>
<td>0/19</td>
</tr>
<tr>
<td>Hyperplasia, pelvic epithelium</td>
<td>0/20</td>
<td>0/20</td>
<td>2/20 (0.20)</td>
<td>0/19</td>
</tr>
<tr>
<td>Nephropathy</td>
<td>11/20 (0.65)</td>
<td>8/20 (0.50)</td>
<td>12/20 (0.60)</td>
<td>6/19 (0.32)</td>
</tr>
</tbody>
</table>

*Values represent incidence (mean group severity score).*

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Crowell et al., Toxicological Sciences. 2004
Influence of resveratrol (RSV) concentration on the viability of HEK 293 cells before and after UV irradiation.
Dumazet et al. (2002) showed that at higher dose resveratrol inhibits the growth and induces apoptosis in case of both normal and leukemic hematopoietic cells.

Zhou et al., (2003) showed that in human esophageal carcinoma cells, resveratrol induces apoptosis when used in high concentration (100 mM) and this high dose of resveratrol also downregulated Bcl2 protein expression and upregulated Bax protein expression.

Signorelli et al., (2005) showed that in androgen-sensitive prostate cancer cells, resveratrol had a proliferative activity at a low dose (5 µM), whereas it had a pro-apoptotic activity at a high dose (15 µM or higher).
Jang et al., (2006) showed that low concentration (5µM), resveratrol appears to increase cell proliferation, whereas apoptosis is induced in various cancer cells at 15 µM or higher concentration.

Kyungmin et al. (2006) showed that 100 µM resveratrol induced apoptosis by cleavage of caspase 3 and resveratrol has an inhibitory effect on cell migration.

Howitz et al. (2003) showed that the photoprotective effect of resveratrol from radiation induced apoptosis in HEK 293 cells was reversed at concentrations greater than 50 µM.
Dose-response curve of the effects of resveratrol on myocardial performance

Das et al., J Pharmacol Exp Ther. 2006
Dose-response curve of the effects of resveratrol on myocardial performance

Das et al., J Pharmacol Exp Ther. 2006
Dose-response curve of the effects of resveratrol on myocardial infarction and cardiomyocyte apoptosis.

Das et al., J Pharmacol Exp Ther. 2006
Isolated Working Heart Model of Ischemia-Reperfusion

Control
- 2 h 45 min Perfusion with KHB

I/R
- 15' 30' Ischemia
- 2 h Reperfusion

Resveratrol Treated
- 15' 30' Ischemia
- 2 h Reperfusion

Infarct size
Apoptosis
Biochemical and Molecular Biological Studies
Dudley et al., Journal of Nutritional Biochemistry. 2008
Dudley et al., Journal of Nutritional Biochemistry. 2008
Dudley et al., Journal of Nutritional Biochemistry. 2008
Effects of high and low doses of resveratrol on the myocardial infarct size

Dudley et al., Journal of Nutritional Biochemistry. 2008
Effects of high and low doses of resveratrol on the myocardial infarct size

Cardiomyocyte apoptosis (%)

- Control I/R
- 2.5mg/kg
- 5 mg/kg
- 25 mg/kg
- 50 mg/kg

Dudley et al., Journal of Nutritional Biochemistry. 2008
Effects of high and low doses of resveratrol on mRNA transcript of some redox genes

Dudley et al., Journal of Nutritional Biochemistry. 2008
Effects of high and low doses of resveratrol on Ref1 protein induction

Dudley et al., Journal of Nutritional Biochemistry. 2008
Effects of high and low doses of resveratrol on survival signal

Dudley et al., Journal of Nutritional Biochemistry. 2008
• Resveratrol is good for health but the health benefit of resveratrol is dose dependent.

• Low doses resveratrol protects from different types of diseases such as cardiovascular, ageing etc.

• High doses resveratrol can be detrimental for normal tissue but it can be used in cancer prevention.