RESVERATROL
"Scientific Evidence in Health and Disease"

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La cuarta edad

En el último Congreso Argentino de Salud, llevado a cabo a fines del 2011, se ha llegado a la conclusión que los avances médicos y las nuevas tecnologías, que han extendido la vida humana, obligaron a crear la categoría de "cuarta edad" para las personas que superan los 80 años.

Según estimaciones del Centro Latinoamericano de Demografía (Celaade) para 2020 en Argentina los mayores de 65 años serán alrededor de 5.225.000.

La extensión de la vida más allá de los 90 años exige un replanteo de las estructuras y los recursos tanto en el ámbito médico como en el social.

En la Argentina ya viven 3.487 habitantes mayores de 100 años y esa tendencia se acentuará en los próximos años, planteando un desafío para los sistemas de salud, ya que la vejez demanda mayor atención médica y, en consecuencia, mayores gastos.

El envejecimiento poblacional es un fenómeno que se da con claridad en Europa y que se está trasladando a América Latina.

Hacia los 80 años es frecuente que se manifiesten varios padecimientos simultáneamente o en un breve lapso, lo que produce en la persona un grave cambio físico, psiquico y emocional.

Si bien no hace mucho se marcaba ese umbral en los 55 años, ahora se puede hablar de una denominada "cuarta edad", que es cuando realmente empieza el envejecimiento.
Evidence-Based Medicine

- Users' guides to the medical literature. II. How to use an article about therapy or prevention. A. Are the results of the study valid? Evidence-Based Medicine Working Group. Guyatt GH, Sackett DL, Cook DJ. JAMA. 1993 Dec 1;270(21): 2598-601

- Department of Medicine, McMaster University, Hamilton, Ontario, Canada.

- Globalise the evidence, localise the decisión
  John Eisemberg (1999)
  AHCPR (Agency for Health Care Policy and Research)
Resveratrol

3,5,4’-trans-trihidroxiestilbeno

bioactive constituent, non-nutritional food

Molecular Weight 228.24328 [g/mol]
Calorie Restriction = Resveratrol


- Jang M et al 1997 Cancer Chemopreventive Activity of Resveratrol, a Natural Product Derived from Grapes Science 10 January Vol. 275 no. 5297 pp. 218-220

  In the case of middle-aged men from eastern France, a moderate daily intake of wine (22-32 g of alcohol) was associated with a lower risk of death due to CVDs (40%), cancer (22%), other causes (42%), and all causes (33%).
Calorie Restriction

Resveratrol and health – N° of Papers and trials

Sirt1 inhibits resistin expression in aortic stenosis.
   PMID: 22433735 [PubMed - in process]
   Related citations

Reactive oxygen species facilitate translocation of hormone sensitive lipase to the lipid droplet during lipolysis in human differentiated adipocytes.
2. Krawczyk SA, Haller JF, Ferrante T, Zoeller RA, Corley BE.
   PMID: 22433722 [PubMed - in process]
   Related citations

Resveratrol inhibits paraquat-induced oxidative stress and fibrogenic response by activating the Nrf2 pathway.
   J Pharmacol Exp Ther. 2012 Apr 4. [Epub ahead of print]
   PMID: 22493042 [PubMed - as supplied by publisher]
   Related citations

Endoplasmic reticulum stress in retinal vascular degeneration: protective role of resveratrol.
   PMID: 22491413 [PubMed - as supplied by publisher]
   Related citations

Flavonoids and structurally related 4-chromenones inhibit carbonic anhydrases by a different mechanism of action.
   J Med Chem. 2012 Apr 5. [Epub ahead of print]
   PMID: 22491078 [PubMed - as supplied by publisher]
   Related citations

Free Full Text (1150) Review (630)
Calorie Restriction = Resveratrol

- Increased quality and span of life
- Reduced oxidative stress
- Reduced risk of cancer
- Reduced neurodegenerative disorders
- Reduced autoimmune disease
- Reduced cardiovascular disease
- Reduced Type II diabetes mellitus
### Resveratrol content of selected fruits and vegetables

<table>
<thead>
<tr>
<th>Foods</th>
<th>Resveratrol cup serving in mg</th>
<th>mg/g/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Blueberry</td>
<td>32 ng/gm</td>
<td>32 ng/gm</td>
</tr>
<tr>
<td>2. Bilberries</td>
<td>16 ng/g</td>
<td>16 ng/g</td>
</tr>
<tr>
<td>3. Cranberry raw juice</td>
<td>0.2 mg/L</td>
<td>0.2 mg/L</td>
</tr>
<tr>
<td>4. Mulberry</td>
<td>0.0021–0.0053 mg/g</td>
<td>0.0021–0.0053 mg/g</td>
</tr>
<tr>
<td>5. Peanuts (raw)</td>
<td>0.01–0.26 (per serving of 146 g)</td>
<td>0.01–0.26 (per serving of 146 g)</td>
</tr>
<tr>
<td>6. Peanuts (boiled)</td>
<td>0.32–1.28 (per serving of 180 g)</td>
<td>0.32–1.28 (per serving of 180 g)</td>
</tr>
<tr>
<td>7. Peanut butter</td>
<td>0.04–0.13 (per serving of 258 g)</td>
<td>0.04–0.13 (per serving of 258 g)</td>
</tr>
<tr>
<td>8. Red grapes</td>
<td>0.24–1.25 (per serving of 160 g)</td>
<td>0.24–1.25 (per serving of 160 g)</td>
</tr>
<tr>
<td>9. Red grape juice (Spanish)</td>
<td>0.17–1.30 (per serving of 150 ml)</td>
<td>0.17–1.30 (per serving of 150 ml)</td>
</tr>
<tr>
<td>10. Black chocolate</td>
<td>4 mg/L</td>
<td>4 mg/L</td>
</tr>
<tr>
<td>11. Cocoa liquor</td>
<td>5 mg/L</td>
<td>5 mg/L</td>
</tr>
</tbody>
</table>
## Resveratrol content of wines

<table>
<thead>
<tr>
<th>Wines</th>
<th>Total resveratrol (mg/L)</th>
<th>Total resveratrol 150ml glass (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. White wine</td>
<td>0.05 –1.80</td>
<td>0.01–0.27</td>
</tr>
<tr>
<td>2. Rose wine</td>
<td>0.43 –3.52</td>
<td>0.06–0.53</td>
</tr>
<tr>
<td>3. Red wine (Spanish)</td>
<td>1.92–12.59</td>
<td>0.29–1.89</td>
</tr>
<tr>
<td>4. Red wine (Global)</td>
<td>1.98 –7.13</td>
<td>0.30–1.07</td>
</tr>
<tr>
<td>5. Pinot noir</td>
<td>0.0 –2.0</td>
<td>0.06–0.30</td>
</tr>
<tr>
<td>6. Red wine (Italian)</td>
<td>0.05</td>
<td>0.008</td>
</tr>
<tr>
<td>7. Merlots wine (Chilean)</td>
<td>2.25</td>
<td>0.35</td>
</tr>
</tbody>
</table>
Resveratrol Natural Sources

- Arachis hypogea
  - Peanut
- Morus rubra
  - Mulberry
- Vitis vinifera
  - Grapes
- Veratrum grandiflorum
  - White hellebore
- Vaccinium sp.
  - Blueberry
- Vaccinium sp.
  - Cranberry
- Cassia sp.
  - Legumes
- Polygonum cuspidatum
  - Ko-jo-Kon (Japanese)
- Eucalyptus
- Gnetum montanum
- Picea sp.
  - Spruce
- Bauhinea sp.
- Pinus sylvestris
  - Scots pine
- Veratrum sp.
  - Corn lily
- Artocarpus sp.
  - Jackfruit
- Rheum rhamonticum
  - Rheum
Resveratrol content of wines

• It is difficult to estimate the normal human consumption of Resveratrol as the intake of red wine (verified main source of Resveratrol) differs greatly in the population and the content of
  • Average of resveratrol in wines
    mean 1.9 ± 1.7 mg/L
  • consumption estimated dose may be up to
    4 mg/person/day
Average values in wines of the isomers of Resveratrol and Piceído

- t-piceído: 0,67 mg/L
- c-piceído: 0,48 mg/L
- t-resveratrol: 2,15 mg/L
- c-resveratrol: 7,55 mg/L
Resveratrol
Bioavailability and Metabolism - Fase I

- **Resveratrol has a high absorption**
- Reaches various organs
- Is metabolized mainly to glucuronide and sulfate derivatives.
- Has a significant role in intestinal microflora metabolite production dihidroresveratrol
- Resveratrol reaches peak plasma concentration peaks about 30 minutes after intake, with the glucuronide and sulfate, whose concentration varies depending on the dose
- **Mainly, elimination is by urine**
  
  (Sulfate derivatives 37%. Glucuronide derivatives 19% Traces of resveratrol aglycone). Total 56%.
- A high 44% Resveratrol whose fate is unknown?
- Also, some metabolites remain unidentified?
Mean total (free and conjugated) \textit{trans}-resveratrol in serum of four subjects given 25 mg of \textit{trans}-resveratrol in various matrices.
Mean plasma concentrations of resveratrol (A), resveratrol-4′-O-glucuronide (B), resveratrol-3-O-glucuronide (C), and resveratrol-3-O-sulfate (D) versus time in healthy volunteers after the last of between 21 and 28 daily doses of resveratrol at either 0.5 ...
Clinical trials of resveratrol
Resveratrol pharmacokinetics in healthy volunteers following multiple dosing.

Annals of the New York Academy of Sciences
Resveratrol
Bioavailability and Metabolism

• Half-life in blood of resveratrol’s metabolites approximates the 9 hours, indicating that exposure to these derivatives is much higher than that due to resveratrol aglycone.

• Excretion in man with time depends on the concentration of resveratrol in plasma.

• Therefore, when ingested small amounts of resveratrol, it is rapidly metabolized and eliminated whereas if the amount ingested is large, then can be detected in tissues and can potentially enter the cells to display their action.
Resveratrol mg/day

Intestinal space

Intravascular space

Intracellular space

Meng et al., 2004).
Resveratrol
Bioavailability and Metabolism

• In vivo activity is sometimes greater than that described in vitro, suggests that some form conjugate generated in vivo, is more potent than the precursor (aglycone) ingested.
Resveratrol
Bioavailability and Metabolism

- It was shown that resveratrol accumulates in LDL particles, may help reduce their susceptibility to oxidation and thus stressing a key step in atherogenesis.
Diverse health benefits of Resveratrol including cardioprotection

- Induces vasorelaxation through NO and adenosine
- Stimulates angiogenesis
- Anti-hypertensive
- Anti-thrombin activity
- Inhibits Endothelin
- Anti-aging?
- Reduces cardiovascular risk due to diabetes & obesity
- Inhibits LDL and stimulates HDL
- Inhibits ROS and lipid peroxidation
- Inhibits Ischemia reperfusion injury
- Reduces ventricular arrhythmias
- Inhibits Ischemia Reperfusion Injury
- RESVERATROL → Kills cancer cells
- Neuroprotection
Resveratrol in the health and disease

• Cancer
Resveratrol has shown much promise in treating cancer in laboratory animals and in vitro human cell studies, yet there is still a large void in human research. This may soon change, as six of the clinical trials currently listed for resveratrol on www.clinicaltrials.gov include cancer patients as a target population.

Acts by inhibiting the 3 stages of carcinogenesis
1) initiation 2) promotion 3) progression

Resveratrol in the health and disease

• Cardiovascular effects
One of the key cardioprotective mechanisms of resveratrol stems from its ability to upregulate endothelial nitric oxide synthase (eNOS) which ultimately increases nitric oxide (NO) mediated vasodilation and increases blood flow.

Resveratrol in the health and disease

• Oxidative stress and inflammation
  Atherosclerosis, diabetes mellitus, chronic obstructive pulmonary disease, and cancer are examples of diseases associated with ROS-induced chronic inflammation.

Resveratrol in the health and disease

• Obesity and diabetes
  Multiple mechanisms have been proposed to account for the insulin-sensitizing effects of resveratrol, including anti-inflammatory effects.

Mol. Nutr. Food Res. 55, 1129-1141
Anti-diabetic effects of Resveratrol
Resveratrol in the health and disease

• Neuroprotective activity

  250 mg trans-resveratrol to increase cerebral blood flow compared to placebo by FMD

Mol. Nutr. Food Res. 55, 1129-1141
Resveratrol in the health and disease

• Longevity

Resveratrol’s ability to combat aging at the cellular level may ultimately lead to breakthroughs in geriatric and anti-aging medicine, but the data supporting this in humans are scant.

Number of healthy volunteers who experienced adverse events deemed intervention-related after daily ingestion of resveratrol for 29 d

<table>
<thead>
<tr>
<th>Symptom</th>
<th>No. of volunteers</th>
<th>Dose (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0.5</td>
</tr>
<tr>
<td>Increased blood bilirubin</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>Conjugated</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Unconjugated</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Skin discoloration</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Cystitis</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Acne</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Cramp</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td></td>
<td>2 [17] / 2 [17]</td>
</tr>
<tr>
<td>Diarrhea</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Discomfort on passing stool</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Fatigue</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Flatulence</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Nausea</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Pruritis</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Chest pain</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Dizziness</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Dry mouth</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Red/orch eyes</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Urine color change</td>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>

NOTE: Overall number of volunteers per dose was 10 to 12.

Severity grading (NCI CTCAE v.4.0): no asterisk = 1; * = 2; ** = 3.
Recommendations for the use of Resveratrol

Which relevant (overall) mechanisms of action of Resveratrol have been documented?

- Modulation of cell proliferation and apoptosis
- Modulation of angiogenesis
- Inhibition of metastasis
- Modulation of redox status
- Suppression of adipogenesis and stimulation of adipocyte lipolysis
- Stimulation of osteogenesis
- Modulation of mitochondria activity
- Suppression of inflammation
- Modulation of DNA damage
- Modulation of xenobiotic metabolism
- Modulation of glutamate metabolism
- Estrogenic activity/anti-estrogenic activity
<table>
<thead>
<tr>
<th>Rank</th>
<th>Status</th>
<th>Study</th>
<th>Condition</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Active, not recruiting</td>
<td><strong>Resveratrol With or Without Piperine to Enhance Plasma Levels of Resveratrol</strong></td>
<td>Pharmacokinetics</td>
<td>Dietary Supplement: Resveratrol; Dietary Supplement: Resveratrol 2.5grams with 5mg piperine; Dietary Supplement: Resveratrol 2.5g with 25mg piperine</td>
</tr>
<tr>
<td>2</td>
<td>Active, not recruiting</td>
<td><strong>Resveratrol and Midazolam Metabolism</strong></td>
<td>Healthy</td>
<td>Drug: Midazolam; Dietary Supplement: resveratrol (single dose); Dietary Supplement: resveratrol (multiple dose)</td>
</tr>
<tr>
<td>3</td>
<td>Recruiting</td>
<td><strong>Long-term Investigation of Resveratrol in Obesity</strong></td>
<td>Obesity; Inflammation; Insulin Sensitivity; Osteoporosis</td>
<td>Dietary Supplement: Resveratrol</td>
</tr>
<tr>
<td>4</td>
<td>Completed Has Results</td>
<td><strong>The Cognitive and Cerebral Blood Flow Effects of Resveratrol</strong></td>
<td>Cognitive and Cerebral Blood Flow Effects of Resveratrol</td>
<td>Dietary Supplement: Trans- resveratrol; Other: Placebo (silica)</td>
</tr>
</tbody>
</table>
Resveratrol

45 Intervention Studies in Humans
Resveratrol and Wine

• Is important to note that the resveratrol concentrations in wine vary widely, even within a given variety of grape or growing region.

• It is unclear if small doses of resveratrol on a regular basis (i.e. years of wine consumption) would have the same physiological effect as the high Cmax observed from supplementation.
Conclusion

• We believe the evidence is sufficiently strong to conclude that a single dose of resveratrol is able to Induce beneficial physiologic responses, and that either weeks or months of resveratrol supplementation produces physiologic changes that are predictive of improved health, especially in clinical populations with compromised health.

Resveratrol and health – A comprehensive review of human clinical trials.

James M. Smoliga, Joseph A. Baur and Heather A. Hausenblas.
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Another great aid is our DVD collection of previous CR Conferences sponsored by the CR...
Bibliografía

- Informe del Comité Científico de la Agencia Española de Seguridad Alimentaria y Nutrición (AESAN) en relación con la aplicación de luz UVC para la inducción de compuestos bioactivos en uvas. Documento aprobado por el Comité Científico en sesión plenaria de 14 de noviembre de 2007. Revista del comité científico nº 7
- www.clinicaltrials.gov
Thanks for your attention