RESVERATROL
A REAL BENEFIT OR JUST A CONUNDRUM?

Dr Zulya Maizetova
Blossom Clinic
London, UK
blossomclinic@gmail.com

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HISTORY

Ayurvedic medicine - "darakchasava", a well-known Indian herbal preparation of *Vitis vinifera L. Used as cardiotonic*

1939 **from White Hellebore**

1959 **from Eucalyptus wandoo, Eucalypt tree native to Western Australia**

1963 **from Japanese Knotweed (syn. Polygonum cuspidatum)**

Takaoka, M., 1939. [Resveratrol, a new phenolic compound, from *Veratrum grandiflorum*] Nippon Kagaku Kaishi (Journal of the Chemical Society of Japan) 60, 1090-1100.
Hathway, D. E., Seakins, J. W. T., 1959. Hydroxystilbenes of Eucalyptus wandoo. Biochemical Journal 72, 369-374.
Nonomura, S., Kanagawa, H., Makimoto, A., 1963. [Chemical constituents of polygonaceous plants. I. Studies on the components of Ko-Jo-Kon. (Polygonum cuspidatum Sieb. et Zucc.)] (Translation of Japanese Title). Yakugaku Zasshi (= Journal of the Pharmaceutical Society of Japan) 83, 988-990.

RES-VERATR-OL

RES :
might be an abbreviation of the class of molecules: resveratrol belongs to the **res**orcinols

VERATR:
abbreviation of the plant name, **Veratr**um

OL:
is generally used for indicating hydroxyl groups: resveratrol has three of them.

Resveratrol

WHY PLANTS SYNTHESISE RESVERATROL?

Plants, when stressed by mold, various infections, ultraviolet radiation, or injury, synthesize specialized polyphenol compounds phytoalexins.

Resveratrol -a potent phytoalexinIt, acts as the plant"s antibiotic or fungicide to ward off attacks, particularly from various fungi.

Found in Japanese Knotweed, peanut skins, grapes, and blueberries, Scots pine.

SIRTUIN ACTIVATOR

- Mimicking the positive effect of calorie restriction
- interacts with multiple molecular targets
- promising field of the medicinal chemistry
- improves the response to insulin
- increase the number and activity of mitochondria in obese mice
- Resveratrol has low bioavailability
- Human trials with a formulation of resveratrol with improved bioavailability and with a synthetic SIRT1 activator are in progress
- New SIRT1 activators that are up to 1000 times more effective than resveratrol have recently been identified

SIRTUIN1 (SIRT1)

- Deacetylases - member of the sirtuin family
- Dependent on NAD^+ for their activity.
- Down-regulates p53 activity - increasing lifespan, cell survival, and neuroprotection;
- Deacetylates peroxisome proliferator-activated receptor-gamma and its coactivator 1α, promoting fat mobilization, increasing mitochondrial size & number,positively regulating insulin secretion.
- Link nutrient availability & energy metabolism.
- Activated by calorie restriction

SIRT1 ACTIVITY

- Down-regulates fat storage by increased lipolysis via the inactivation of PPARγ (peroxisome proliferator-activated receptor gamma
- In pancreatic β-cells enhances glucose-stimulated insulin secretion via down regulation of UCP2 (uncoupling protein 2)
- In the liver, under low-nutrient conditions, induces gluconeogenesis and inhibits glycolysis by deacetylating PGC-1α
- In skeletal muscle of obese mice, mediates the insulin sensitizing effect of resveratrol. Resveratrol induces increased exercise endurance and higher basal energy expenditure in mice, thereby promoting resistance against diet-induced obesity and mortality

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CALORIE RESTRICTION AND LIFE SPAN

- In the budding yeast *Saccharomyces cerevisiae*, calorie restriction extends lifespan by increasing the activity of Sir2
- Resveratrol mimics calorie restriction by stimulating Sir2, increasing DNA stability and extending lifespan by 70%.
- Resveratrol lowers the Michaelis constant of SIRT1 for both the acetylated substrate and NAD(+), and increases cell survival by stimulating SIRT1-dependent deacetylation of p53.
- SIRT1- human deacetylase that promotes cell survival by negatively regulating the p53 tumour suppressor.

K. T., Bitterman, K. J., Cohen, H. Y., Lamming, D. W., Lavu, S., Wood, J. G., Zipkin, R. E., Chung, P., Kisielewski, A., Zhang, L. L., Scherer, B., Sinclair, D. A., 2003. Small molecule activators of sirtuins extend *Saccharomyces cerevisiae* lifespan. Nature 425, 191-196.

CALORIC RESTRICTION

A major cause of aging is thought to result from the cumulative effects of cell loss over time.

In yeast, caloric restriction (CR) delays aging by activating the Sir2 deacetylase. Expression of mammalian Sir2 (SIRT1) is induced in CR rats as well as in human cells that are treated with serum from these animals.

Insulin and IGF-1) attenuated this response. SIRT1 deacetylates the DNA repair factor Ku70, inhibiting stress-induced apoptotic cell death.

CR could extend life-span by inducing SIRT1 expression and promoting the long-term survival of irreplaceable cells.

Cohen, H. Y., Miller, C., Bitterman, K. J., Wall, N. R., Hekking, B., Kessler, B., Howitz, K. T., Gorospe, M., De Cabo, R., Sinclair, D. A., 2004. Calorie restriction promotes mammalian cell survival by inducing the SIRT1 deacetylase. Science 305, 390-392.

RESVERATROL CLINICAL BENEFITS

Calorie restriction mimetic
Anti-atherogenic
Anti-cancer
Anti-viral
Anti- inflammatory
Neuroptotective
Cell Sensitivity to insulin

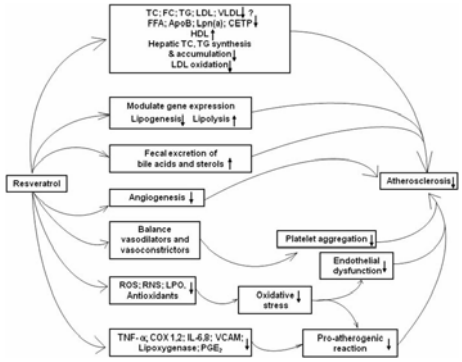
(Das and Maulik, 2006; Sun et al.,2008; Udenigwe et al., 2008).

ANTI-ATHEROGENIC EFFECTS OF RESVERATROL

- LDL level decrease
- preventing oxidation of LDL cholesterol
- Free radical scavenging
- Regenerates a-tocopherol
- Prevent platelet aggregation
- Increase the expression of nitric oxide
- Inhibit cyclooxygenase-1

Wang et al., 2002a.; European Journal of Clinical Nutrition (2010) 64, 660-668; doi:10.1038/ejcn.2010.77; published online 19 May 2010; Ref : Resveratrol: preventing properties against vascular alterations and ageing.Delmas D, Jannin B, Latruffe N.University of Burgundy, Laboratory of Molecular and Cell Biology, Dijon, France.

ANTI-ATHEROGENIC MECHANISMS OF RESVERATROL



VASCULAR HEALTH

- *Resveratrol restored endothelial function in type 2 diabetes by inhibiting TNF-induced activation of NAD(P)H oxidase*
- *Thus preserving eNOS phosphorylation*
- *potential for new treatment approaches to promote vascular health in metabolic diseases.*

(*Arterioscler Thromb Vasc Biol.2009;29:00-00)*

THE ANTICANCER EFFECT

Interfere with all 3 stages of cancer:

- Initiation – neutralises free radicals
- Promotion – suppress inflammation
- Progression – inhibits angiogenesis

The growth-inhibitory effects of resveratrol are mediated through cell-cycle arrest; upregulation of p21Cip1/WAF1, p53, and Bax; down-regulation of survivin, cyclin D1, cyclin E, Bcl-2, Bcl-xL, and cIAPs

M.Jang, J.M. Pezzuto, "Cancer chemopreventice activity of resveratrol", *Drugs under Experimental and Clinical Research* 25 (2-3) (1999): 65-67

ANTI-CANCER PROPERTIES OF RESVERATROL

- *inhibits experimental tumorigenesis in a wide range of animal models*
- *targets many components of intracellular signaling pathways:*

including pro-inflammatory mediators, regulators of cell survival and apoptosis, tumor angiogenic and metastatic switches by modulating a distinct set of upstream kinases, transcription factors and their regulators

Kundu JK, Surh YJ.
National Research Laboratory of Molecular Carcinogenesis and Chemoprevention, College of Pharmacy, Seoul National University, Shillim-dong, Kwanak-gu, Seoul 151-742, Republic of Korea.

INHIBITION OF GASTRIC CANCER CELL PROLIFERATION BY RESVERATROL: ROLE OF NITRIC OXIDE

RESULTS

- *Resveratrol inhibits DNA synthesis in gastric adenocarcinoma SNU-1 cells*
- *Resveratrol stimulates NOS activity in SNU-1 cells*
- *Resveratrol and ionomycin deplete cellular NADPH*
- *High-resveratrol concentration induces apoptosis in SNU-1 cells.*

OKSANA HOLIAN, SHAHID WAHID, MARY JO ATTEN, AND BASHAR M. ATTAR
Department of Medicine, Division of Gastroenterology, Cook County Hospital and Hektoen Institute for Medical Research, Chicago, Illinois 60612
Am J Physiol Gastrointest Liver Physiol 282: G809–G816, 2002

DIFFERENTIAL EFFECTS OF RESVERATROL ON ANDROGEN-RESPONSIVE LNCAP HUMAN PROSTATE CANCER CELLS

In vitro :

Growth inhibitory effects on cultured LNCaP cells at concentration as low as 5 μM through multiple pathways, including steroid hormone-dependent pathways

In vivo:

- delayed the initial development of xenograft LNCaP cell tumors, consistent with an effect on steroid hormone-mediated events.

NB!

- However, exposure to resveratrol appeared to lead to promotion of angiogenesis and inhibition of apoptosis in LNCaP cell-derived tumors, as assessed by immunohistochemical markers.

Carcinogenesis vol.29 no.10 pp.2001–2010, 2008
doi:10.1093/carcin/bgn131 Advance Access publication June 26, 2008

SUPPRESSION OF ANGIOGENESIS, INVASION, AND METASTASIS BY RESVERATROL

Szende *et al. examined the* effect of resveratrol on endothelial cells and showed that low doses (0.1-1 Ig/ml) of resveratrol enhanced HUVEC proliferation while higher doses (10-100 Ig/ml) induced apoptosis and decreased mitotic activity, which is reflected in changes of cell number

Szende, B, Tyihak, E, and Kiraly-Veghely, Z Dose-dependent effect of resveratrol on proliferation and apoptosis in endothelial and tumor cell cultures. Exp Mol Med, 32: 88-92, 2000.

RESVERATROL PREVENTS CHEMO RESISTANCE

- ✓ Increases Chemo/Radiation Effectiveness
- ✓ Enhances the effectiveness of Taxol in lung cancer by altering
- ✓ multiple pathways including p21waf1, p27kip1, PTEN, Ecadherin,
- ✓ EGFR and Bcl-2

(*Anticancer Res. 2003 Sep-Oct;23(5A): 4039-46.*)

- ✓ Selectively down-regulates the expression of antiapoptotic proteins Bcl-xL and myeloid cell differentiation factor-1 (Mcl-1) and up-regulates the expression of proapoptotic proteins Bax and apoptosis protease activating factor-1 (Apaf-1).

(*Mol Cancer Ther. 2004 Jan;3(1):71-84.)*

- ✓ Reverses drug resistance of Taxol in prostate cancer by downregulating tyrosine kinases and STAT1

(*Mol Cancer Ther. 2007 Nov;6 (11):2938-47)*

ROLE OF RESVERATROL IN PREVENTION OF CANCER

- ✓ Inhibits the phase I CYP enzymes

In human hepatic microsomes, resveratrol inhibits CYP isoenzymes, such as CYP1A1, CYP1B1, and CYP2B6, which are involved in bioactivation of numerous carcinogens

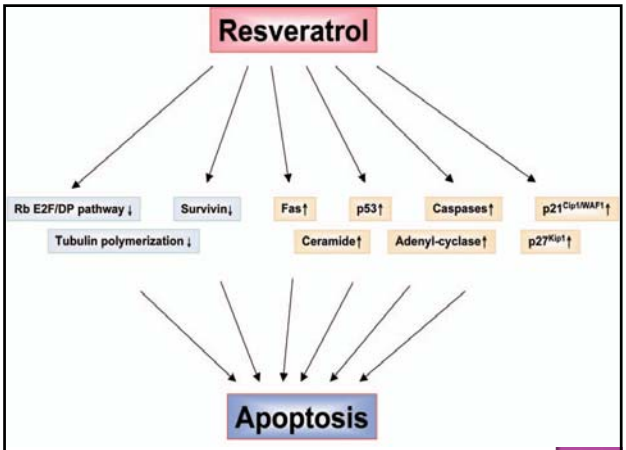
- ✓ Increases the activity/level of phase II Biotransformation detoxifying enzymes.
- ✓ decrease of toxic intermediate compounds
- ✓ Reduced risk of cancerogenesis

ROLE OF RESVERATROL IN THERAPY OF CANCER: PRECLINICAL & CLINICAL STUDIES

- ➢ Suppress proliferation
- ➢ induces apoptosis through
- ✓ the caspase-8-dependent pathway (receptormediated;type I)
- ✓ the caspase-9-dependent pathway (mitochondrial; type II)
- ➢ *p53 activation pathway: p53 is a tumor suppressor gene*

Huang *et al. found that resveratrol-induced apoptosis* occurred only in cells expressing wild-type p53 (*p53+/+), but* not in *p53-deficient (p53-/-) cells*

- ➢ suppressing NF-κB, a nuclear transcription factor that regulates the expression of various genes involved in inflammation, cytoprotection, and carcinogenesis



Effect of resveratrol on signalling proteins involved in apoptosis

COLON CANCER

Several reports suggest that resveratrol suppresses proliferation of colon cancer cells :

In human wild-type p53-expressing HCT116 colon carcinoma cell line and HCT116 cells with both *p53 alleles inactivated* by homologous recombination.

Mahyar-Roemer et al. Study:

Resveratrol induced apoptosis independently of p53 the apoptosis was mediated primarily by mitochondria and not by a receptor pathway

Mahyar-Roemer, M, Katsen, A, Mestres, P, and Roemer, K Resveratrol induces colon tumor cell apoptosis independently of p53 and precede by epithelial differentiation, mitochondrial proliferation and membrane potential collapse. Int J Cancer,94: 615-622, 2001

I believe that how we eat is an important determinant of how we feel and how we age. I also believe that food can function as medicine to influence a variety of common ailments.

Dr Andrew Weil