RESVERATROL AND HEALTH

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SUMMARY

INTRO

RESVERATROL AND DEGENERATIVE DISEASES

Resveratrol, a polyphenol produced by plants and more particularly grapes, is mainly consumed in France in the form of red wine. For centuries, this substance has been known for its beneficial and protective effect on numerous diseases, notably cardiovascular.
This is the famous « French Paradox »: the French, and more particularly those living in the south west regions, have a higher calorie intake, blood cholesterol levels equivalent to those of other industrialized countries and diets not particularly low in animal fat. Likewise, they consume more vegetable fat, fruits and vegetables... and wine. Yet, fewer French people suffer from heart attacks compared to other countries. Hence the idea of a French paradox and multiple hypotheses that attempt to explain this phenomenon.

To date, no definite evidence has been put forward to explain this phenomenon. What if resveratrol were responsible for this paradox?

This question is currently arousing considerable interest around resveratrol. Numerous studies, in vitro or on animals, showing the ubiquitous protective effect of this small molecule have been carried out since the 90s. To such an extent that clinical trials are currently in progress on humans with various pathologies, notably cancer.

01

CHEMICAL STRUCTURE, FOOD SOURCES AND BIOAVAILABILITY

Resveratrol (3,4',5-trihydroxystilbene) is a phytoalexin (antibiotic substance produced by plants to defend themselves against fungi or bacteria) that belongs to the class of stilbenes and more widely the bigger family of polyphenols. Resveratrol is the leader of the family of polymers called « viniferins ». It is synthesized by plants, notably vines *(Vitis vinifera)*, in response to a cryptogamic disease, « grey rot », caused by a *Bottrytis cinerea*. Resveratrol acts as a natural antibiotic by blocking the proliferation of this parasite. Resveratrol can also be synthesized in response to various types of environmental stress, such as the climate, ozone, UV rays, etc. (1).

The presence of resveratrol has been confirmed in over 70 plant species from 32 types. In terms of food sources, the highest concentrations can be found in the skin of grapes, black berries (blackberries, blueberries), but also raspberries, bilberries, cranberries... and certain dry fruits such as peanuts. The skin of fresh grapes contains approximately 50 to 100 mg of resveratrol per gram of total weight, which explains its relatively high concentration in wine and grape juice (1). Wine contains 0.6 to 8 µg/ml of resveratrol, the highest concentrations being found in tannic red wines. According to a study Pinot noir, Merlot and Zweigeltrebe grapes are the richest in resveratrol (2). However, this component is synthesized by the plant in response to infestations more widespread in cool climates, thus higher concentrations are found in wines made in temperate regions (3). Moreover, it is likely that the concentrations vary highly from year to year.

In comparison, peanuts, renowned for being rich in resveratrol, contain only 0.03 to 0.14 µg/g of resveratrol. The only exception is the Spanish variety called « small white » which can contain up to 1.8 µg/g (4). On average, roasted peanuts contain 0.055 µg/g, boiled peanuts approximately 5 µg/g and peanut butter 0.32 µg/g (5). Pistachio nuts contain from 0.09 to 1.67 µg/g (5).

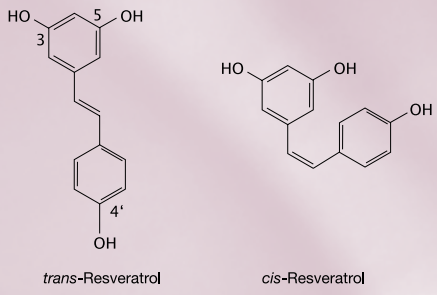
Ref. 1

Cell Cycle

Resveratrol, a multitargeted for age-associated chronic diseases

[Cell Cycle 7:8, 1020-1035 April 2008]

CHEMICAL STRUCTURE, FOOD SOURCES AND BIOAVAILABILITY



trans-Resveratrol *cis*-Resveratrol

"Resveratrol consists of two phenolic rings linked by a styrene double bond, generating cis and trans orientations."

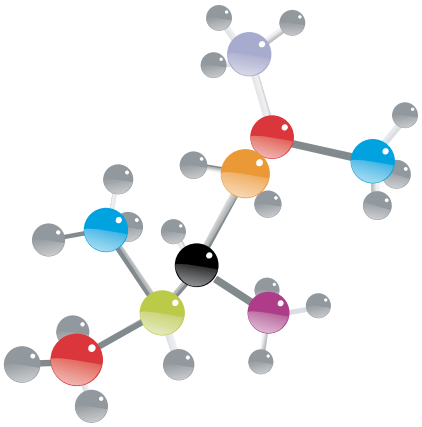
Resveratrol consists of two phenolic rings linked by a styrene double bond, generating *cis* and *trans* orientations. The *cis* isomer is predominant in the grape before fermentation whilst the proportion of *trans* isomer increases after fermentation.

The *cis-trans* ratio in wine therefore depends on the duration of fermentation. The trans isomer is the most stable and can remain stable for several months when protected from light. It undergoes isomerisation to the cis isomer by heating or exposure to UV. Resveratrol, particularly in its *cis* form, is rapidly degraded by exposure to light, heat or oxygen (3).
The two isomers can currently be produced by synthetic chemistry.

Experiments using carbon 14 labelled resveratrol have shown its high digestive absorption in humans, reaching at least 70% with a plasmatic peak after 30 to 60 minutes (491 ± 90 ng/ml) following the administration of an oral dose of 25 mg, and a half-life of 9.2 ± 0.6 h. After absorption, resveratrol is rapidly transformed into sulfo- or glycuroconjugates or even hydrogenated metabolites, in the liver and intestine. Native resveratrol is only found in very small doses in the plasma, suggesting that its metabolites are either active molecules or are reconverted into resveratrol in the target organs (7). Its elimination is mainly renal and secondarily digestive, and highly variable in faeces (1).

02

MOLECULAR TARGETS[1]



Resveratrol has been identified as a direct or indirect modulating agent of a large number of patho-physiological cell signalling pathways, notably cell proliferation, oxidation and inflammation.

Resveratrol interacts with numerous active proteins: kinase C protein, aromatase, integrin, MRP (Multidrug Resistance Protein), β-lactoglobulin, serum albumin, DNA-topoisomerase, plasmatic lipoprotein, nucleic acids, DNA-polymerases, tubulin, oestrogen receptors, myeloperoxidases... In most cases, this interaction leads to the inactivation of this molecule (1).

Resveratrol inhibits the growth of different types of cells by modulating the expression of cell cycle regulator genes.

It is also capable of inducing apoptosis through positive regulation of the p-53 gene or negative regulation of anti-apoptotic genes. Resveratrol activates the SIRT-1 protein that is also involved in apoptosis. The additional modulation of different kinase proteins (notably AMP-activated kinase) may also play a role in its growth regulatory effects. Resveratrol inhibits angiogenesis and the patho-physiological pathway of metastases mediated by the expression of MMP, VGEF, cathepsin D, ICAM-1 and E-selectin.

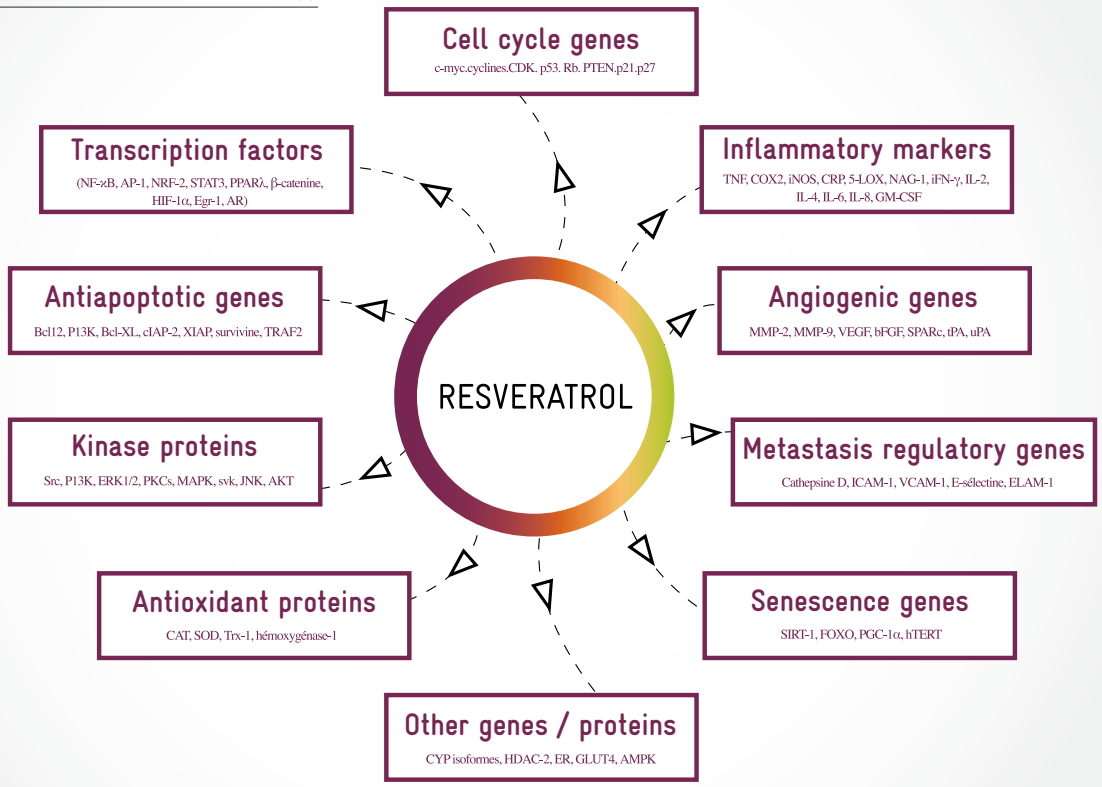
Oxidative stress, through excess production of free radicals or insufficiency of endogenous defences, is currently considered as an essential factor in ageing and degenerative diseases due to the deterioration of cell structures that it causes, and notably mutations induced by DNA damage. The antioxidant effects of resveratrol are probably linked to its capacity to induce the activity of certain enzymes such as the catalase, the superoxide dismutase and the glutathion peroxidase, rather than a direct free radical scavenger effect.

Its anti-inflammatory effects involve the negative regulation of multiple biomarkers such as TNF, COX-2, iNOS, CRP, interferon-γ and various interleukins. Resveratrol is a strong inhibitor of COX-2 and transcription factor NFκB inactivation, which play a crucial role in the inflammatory, immunological and oncogenic processes. It also interferes with the patho-physiological pathways leading to the metabolism of arachidonic

DNA double helix

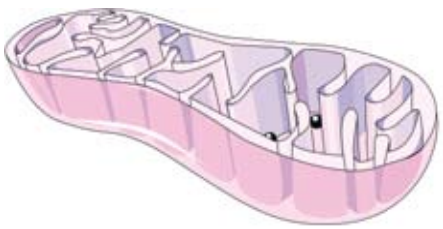
MOLECULAR TARGETS[1]

MOLECULAR TARGETS OF RESVERATROL (1)



acid and eicosanoids.

Mitochondria, central organelles for energy production, generation, detoxication of oxidative stress and regulation of apoptosis are probably the chosen target of the resveratrol action.



Mitochondria

03

RESVERATROL AND CANCER

Ref. 7

NATURE REVIEWS
DRUG DISCOVERY

Therapeutic potential of resveratrol: the in vivo evidence

[NATURE REVIEWS | DRUG DISCOVERY - VOLUME 5 | JUNE 2006]

Resveratrol has shown its ability to prevent carcinogenesis at different stages by modulating the cascade of transduction signals that leads to cell growth and division, apoptosis, inflammation, angiogenesis and the metastatic process (1).
The efficacy of relatively low doses (approximately 200 µg/kg) in a model of rat colon carcinogenesis suggests that the intake equivalent to that in red wine can have a therapeutic effect in certain cases (7). At higher, pharmacological doses more significant protective effects are frequently observed: for example, a daily dose of 40 mg/kg increases survival from 0 to 70% in mice suffering from sub-cutaneous neuroblastomas (7). Phase I and II clinical trials are in progress, notably at the Universities of Michigan (USA) and Leicester (UK), as well as in California (6, 8).
The protective effects regarding cancer have several explicative hypotheses: inhibition of cyclooxygenase 2 (COX-2), inhibition of angiogenesis, effects on the metabolism of carcinogens, alteration of the cell cycle and apoptosis, antioxidant effects (6).

Hormone associated cancers

Resveratrol is frequently considered as a phyto-oestrogen due to its structural similarity with synthetic oestrogen, diethylstilesterol, and as an SERM (Selective Oestrogen Modulator) (1). Although controversial, certain epidemiological studies suggest a correlation between the daily absorption of SERMs and the prevention of hormone associated tumours such as breast or prostate cancers.

Resveratrol exerts a variable agonism on the oestrogen receptors. Some publications highlight an oestrogenic effect and others an anti-estrogenic effect.
On cells of the MCF-7 line (line of human mammary cancer cells), a dose-dependent effect was brought to light: the lowest concentrations (1µM) produced no effect, whilst the medium concentrations had a growth promoter effect and the highest concentrations (> 50 µM) induced cytotoxic effects and apoptosis (1).

Ref. 6

IUBMB *Life*

Resveratrol: one molecule, many targets

[IUBMB *Life*, 60(5): 323-332, May 2008]

Several works on animals have shown that when compared with subjects not receiving resveratrol, resveratrol can prevent the appearance of anthracenic carcinogenic agent-induced mammary cancer by modulating the NFκB, COX-2 and MMP-9 factors (1). Moreover, resveratrol has been shown to be capable of inhibiting the growth of human mammary tumour cells implanted in mice. Resveratrol may inhibit the progression of prostate cancer in TRAMP mice (1).

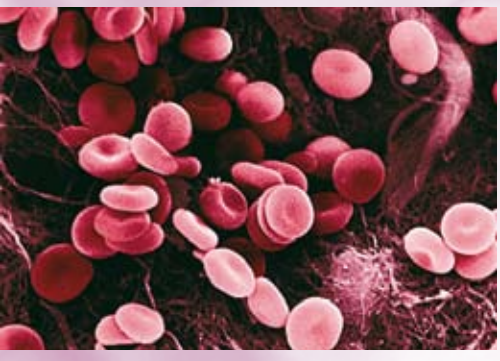
A team has shown an association between mutations of BRCA1 genes, which promote ovary and breast cancers, and the reduced expression of the SIRT-1 protein as well as the over-expression of survivin, reversed by the induction of BRCA1 gene expression. Thus, BRCA1 binds to the SIRT-1 promoter of which it reinforces the expression and thus leads to the inhibition of survivin. Resveratrol activates SIRT-1 and inhibits survivin expression, leading to an inhibitory effect on the growth of mammary cancer cells that is particularly significant with BRCA1 mutations (9).

Leukaemia, lymphomas and myelomas

Resveratrol induces apoptosis of acute lymphoblastic leukaemia human T cells (MOLT-4 line). It dose- and time-dependently inhibits the growth of the HL-60 line and, in this cell line, induces the expression of the CD95L (=FasL) protein, apoptosis mediator. On the other hand, in acute lymphoblastic leukaemia cells resistant to the CD95L signal, resveratrol activates apoptosis by activation of the caspase 9 mitochondrial pathway, without modifying CD95 expression.

In acute myeloid leukaemia, resveratrol inhibits proliferation linked to IL-1β as well as the main negative regulation mechanism of NFκB. It also induces significant apoptosis in KG-1 leukaemic myeloid line cells, with negative regulation of bcl2 expression and positive regulation of bax (10).

Resveratrol negatively regulates the secretion of VEGF, induces apoptosis and stops the S phase cell cycle and abolishes dose and time-dependently the proliferation of U937 cells (human lymphoma monocytic line).



Blood cells - Microscope

Resveratrol also possesses a potential with regard to human multiple myeloma cells, of which it inhibits the proliferation, induces apoptosis and reduces chemoresistance by negative regulation of STAT3 (transcription activator associated with different types of cancer) and the expression of cell survival and anti-apoptotic genes regulated by the NFKB transcription factor (10).

Hepatic cancer

In vitro, resveratrol induces a dose and time-dependent stoppage of the HepG2 cell line cell cycle. It increases iNOS activity (gene responsible for intracellular release of free radical NO) and activates apoptosis mediated by the p53 gene.
In culture, resveratrol also inhibits the invasive potential of a hepatocarcinoma rat cell line and the growth of the H22 line.

In vivo, resveratrol exerts an antitumour activity and improves the therapeutic effect of chemotherapy in a model of murine liver cancer. It prolongs the survival of the allograft after hepatic transplantation in the rat (1).

Pancreatic cancer

In culture, resveratrol inhibits the growth and proliferation of pancreatic cancer cells. It positively regulates the macrophage inhibitory cytokine (MIC-1), member of the bigger family of TGFbeta (Transforming Growth Factor Beta) and possessing anti-tumour activity. It sensitizes certain cell lines to apoptosis through the induction of protein p21 independently of p53, leading to depletion in survivin (1).

A synthetic analogue of resveratrol tested on pancreatic cancer cell lines was shown to be capable of dose-dependently and totally stopping cell proliferation by inducing apoptosis. The authors conclude to the considerable antitumour potential of this derivative (11).

APOPTOSIS FOR NEOPHYTES IN MOLECULAR BIOLOGY

Apoptosis is the programmed death of cells and represents a major phenomenon in the physiological prevention of tumours. Unlike necrosis, it generally affects isolated cells and is a survival mechanism that enables cells with deteriorated DNA to be eliminated. This mechanism relies on numerous cell signalling pathways. The main factors determining this programmed cell death are the deprivation of growth factors (VEGF, TGF-β...) and/or the emission of death signals (FasL or CD95L, TNF-α ...). The protein p53 also plays a vital role in the regulation of the cell cycle: in the case of cell proliferation, the protein p53 controls cell division by verifying the integrity of the DNA. If the DNA is defective, stimulation of the apoptosis pathway is observed. Conversely, If the DNA is repairable, the cell cycle continues.

Whichever signals spark off apoptosis, they all lead to a mutual pathway via the mitochondria, the Bcl-2/Bax proteins and the activation of enzymes called caspases, also nicknamed the cell's « protein executors ». Bcl-2 is the leader of the family of proteins of which certain have an antiapoptotic effect (Bcl-2, Bcl-XL) and others a pro-apoptotic effect (Bax, Bak, Bad, PUMA, Noxa, Bim ...).

During the cancerization process, defects in the starting up of apoptosis probably exist when DNA anomalies occur. So, the tumours are capable of expressing antiapoptotic factors such as survivin that bind to the caspases to inhibit their action. The transcription factor NFκB is also a survival signal that counters the death signals sent to the cancerous cell.

A molecule such as resveratrol that promotes apoptosis and reduces cell proliferation acts as an anti-tumour agent. The regulation of proteins in the Bcl-2 family seems to be a major axis of this pro-apoptotic effect of resveratrol (12).

Ref. 12

Frontiers in Bioscience

Chemoprevention by reserveratrol : molecular mechanisms and therapeutic potential

[Frontiers in Bioscience 12, 4839-4857, September 1, 2007]

Digestive cancers

In gastric adenocarcinomas, resveratrol induces apoptosis without requiring the rupture of the mitochondrial membrane. Depending on the cell lines, it induces positive regulation of the p53 gene (knowing that at least half of human cancers are accompanied by inactivating mutation of the protein p53) (12) or negative regulation of survivin and positive regulation of Fas and FasL, or caspase-3 over-expression. In other lines, apoptosis is mediated by endoplasmic reticulum stress.

Resveratrol also inhibits the growth of primitive gastric cancer cells injected in Nude mice. An induction of apoptosis was observed, possibly via negative regulation of Bcl-2 and positive regulation of Bax. Resveratrol also inhibits an oesophageal cancer model induced by a carcinogen, NMBA. The over-expression of COX-1 and COX-2 and the high levels of prostaglandins were significantly reduced by resveratrol (1).

In vitro it prevents the appearance of colon cancer induced by carcinogenic agents, azoxymethane and DMH, with a decrease in the number of abnormal focus and modulation of the expression profile of p21 and Bax (1).

The administration of resveratrol for 7 weeks to Min mice (an animal model of familial polyposis) reduced intestinal tumorogenesis by 70%. Furthermore, resveratrol decreased the expression of genes directly implicated in the cell cycle such as D1, D2 and DP1, as well as TGFβ levels (1).

Phase I and II trials are currently in progress in the United States to evaluate resveratrol in human colon cancer (8).

04

RESVERATROL AND AGING

The effects of resveratrol on longevity and ageing have been studied since the beginning of 2000. Firstly, it was observed that resveratrol increases life expectancy by 30 to 50% and delays the signs of ageing in various immature organisms (yeasts, insects, fish) (13, 14, 15, 16).

Such an effect can also be obtained in mammals, through moderate calorie restriction and apparently through a molecular mechanism identical to that of resveratrol: the activation of the SIRT-1 gene and AMP-kinase.

Calorie restriction notably enables the inhibition of processes such as inflammation, atherosclerosis or insulin resistance and increases longevity.

Resveratrol is the leading SIRT-1 protein activator: it exerts effects similar to calorie restriction on the increase in life expectancy and at metabolic level.

Ref. 16

Cell Cycle

Resveratrol and The Pharmacology of Aging
A New Vertebrate Model to Validate an Old Molecule

[Cell Cycle 5:10, 1027-1032, 15 May 2006]

05

SIRTUINS, IMMORTALITY PROTEINS?

Sirtuins are deacetylase NAD-dependent proteins capable of modulating the transcriptional activity of numerous genes. Seven in all, they regulate a large number of cell functions in mammals. In SIRT-1 deficient mice, development anomalies and an abnormally short lifetime are observed: the main function of sirtuins is the promotion of survival and stress resistance. SIRT-1, the most studied, is involved in protection against oxidative stress and deterioration of DNA, and seems to play an important role in the metabolism of the pancreas, adipose tissue and liver. The experimental studies have shown the protective effects of these components against obesity, diabetes, cardiovascular diseases, cancer and certain neurodegenerative processes (17).

Calorie restriction stimulates SIRT-1 expression leading to multiple effects: increase in the release of vascular NO by stimulation of endothelial NO synthase, decrease in adipogenesis and rise in fat cell lipolysis, with stimulation of the PPARγ 1-α co-activator (PGC-1α) and decrease in fatty tissue. SIRT-1 induces an increase in neoglucogenesis in the liver and positive regulation of the secretion of insulin stimulated by glucose in the pancreatic β-cell (18).

In mammals, SIRT-1 is equivalent to SIR 2 in less advanced species (SIR = Silencing Information Regulator).

Currently, many studies focused the research on sirtuin activators in the prevention or treatment of metabolic dysfunctions or pathologies associated with ageing.

SIRTUINS, IMMORTALITY PROTEINS?

A study on mice published at the end of 2006 evaluated, in an obesogenic context, whether the activation of SIRT-1 by resveratrol was likely to influence the regulation of the energetic balance and so to exert a protective effect against the appearance of obesity and associated metabolic changes.
Mice were put on a high fat diet, with or without administration of resveratrol at a dose of 400 mg/kg/d. During the 9 weeks of monitoring, the weight gain and the increase in fat tissue were significantly reduced by resveratrol without the food consumption or the digestive absorption of the fat being affected in the treated group.

The resistance mechanism of weight gain induced by resveratrol seems to be the energy release by thermogenesis, as shown by the higher body temperature in the treated mice. Resistance to muscular tiredness was doubled in the treated mice compared with the control mice, with no spontaneous increase in physical activity. This suggests a conversion of muscular fibres in favour of type 1 oxidative slow fibres under the action of resveratrol. In comparison with the control mice, the mice receiving resveratrol presented increased muscular strength, as well as better motor coordination.
An increase in mitochondrial activity in brown fat tissue as well as in muscle tissue seems to underlie the effects of resveratrol.
The genetic analysis has shown an increase in the expression of genes associated with muscle contraction and oxidative metabolism, notably with the cell of respiratory apparatus, oxidative enzymes and ATPases. So, the sustained production of ATP by the mitochondria could explain the increase in muscle endurance observed with resveratrol.

Finally, the sensitivity to insulin, normally decreased with induced obesity, was significantly improved in the treated group. No toxic side effects were observed in animals receiving resveratrol (19).

Ref. 19

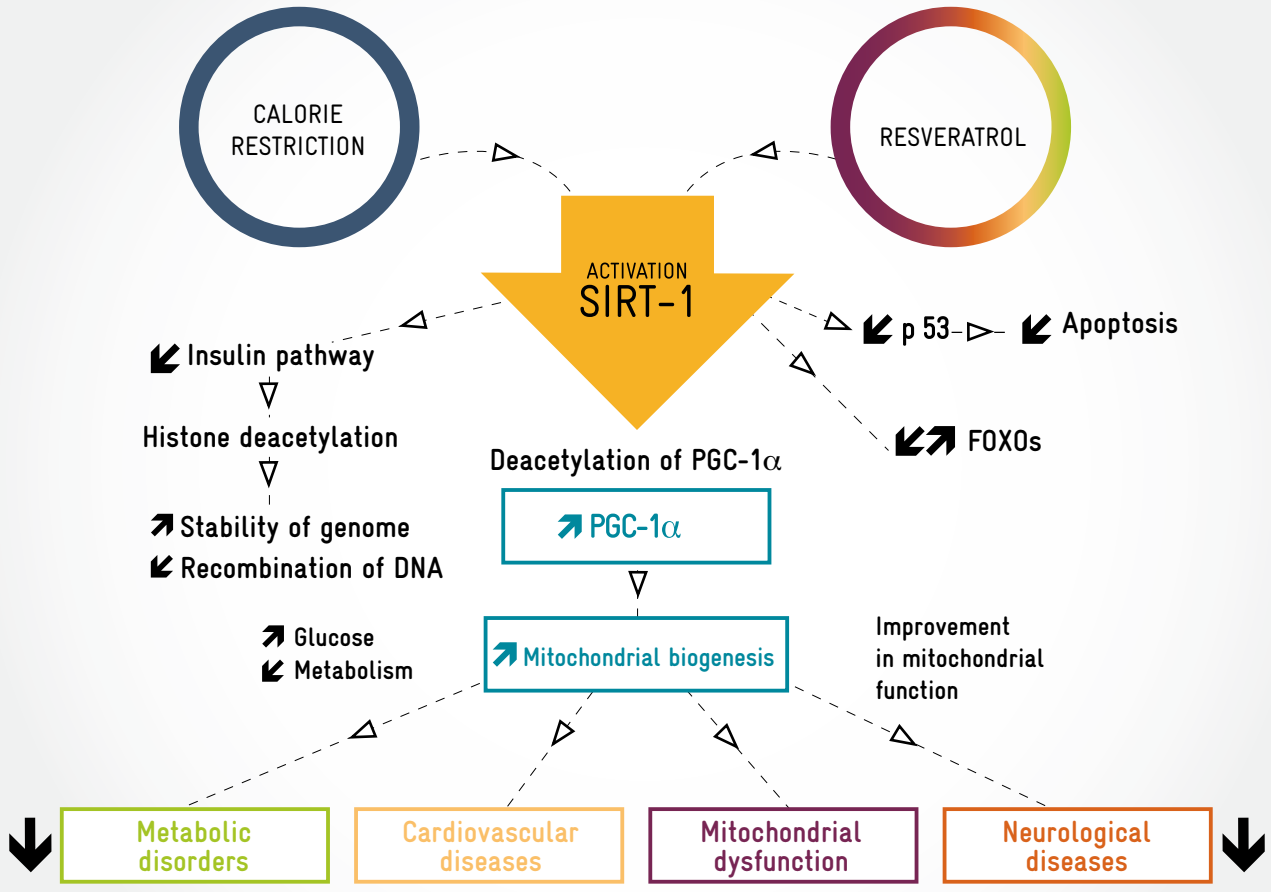
Cell, Volume 127

Resveratrol Improves Mitochondrial Function and Protects against Metabolic Disease by Activating SIRT-1 and PGC-1

[Cell, Volume 127 - Supplemental Data]

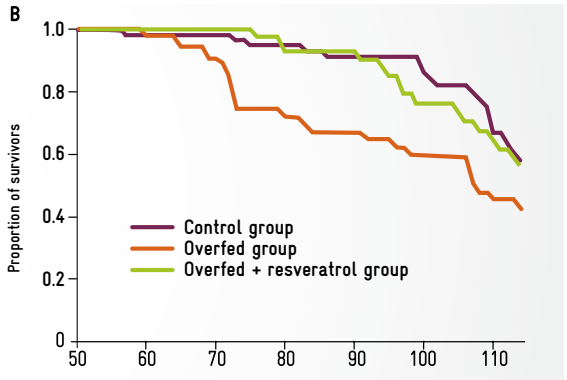
SIRTUINS, IMMORTALITY PROTEINS?

Resveratrol activation SIRT-1 (20)



SIRTUINS, IMMORTALITY PROTEINS?

Another study published in 2006 compared the survival and the state of health in mice fed normally or overfed, half of the latter also received a dose of approximately 22 mg/kg/d of resveratrol.
The lifetime of the overfed mice was significantly increased with resveratrol in comparison with the untreated group, even though the excess weight was the same in both groups.
The death rate at 114 weeks was 42% in the overfed + resveratrol group, identical to the control group and significantly higher than the overfed group alone (58%). That is to say a decrease in 31% in the risk of death linked to a high calorie diet.
The motor performances of the overfed mice were degraded, but improved throughout the study with resveratrol, to be finally comparable with those of the controls and much higher than those of the untreated overfed mice.
In parallel, resveratrol significantly improved sensitivity to insulin, and reduced the level of insulin, glucose and IGF-1. After 18 months, the hepatic and lipidic deterioration induced by the excess calories of the overfed group was absent in the overfed group treated with resveratrol. The number of hepatic mitochondria in the treated mice was higher than in the overfed group without treatment, as observed with the effects of physical exercise or calorie restriction. Overall, all the parameters deteriorated by the high calorie diet were normalised in overfed mice treated with resveratrol and were comparable to the control mice (21).



INCREASE IN LIFETIME OF OVERFED MICE TREATED WITH RESVERATROL (21)

SIRTUINS, IMMORTALITY PROTEINS?

Very recently, the gene expression profile, correlated to the biological age and not with the chronological age, was used to compare the effects of calorie restriction (CR) and resveratrol on ageing. Mice were given either a low calorie diet, or resveratrol (4.9 mg/kg/d) from the age of 14 months up to 30-31 months, age at which they were sacrificed and their tissues collected.

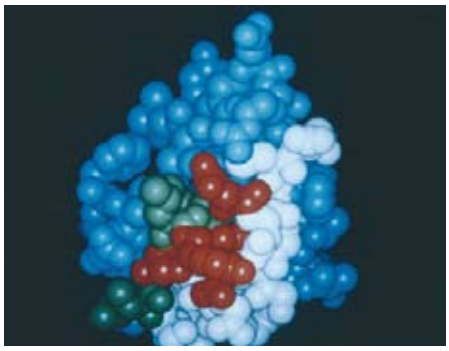
1029 genes were identified in the myocardial tissue as having deteriorated expression with ageing. The deteriorations were reduced by CR in 90% of the genes concerned and by resveratrol in 92%. More moderate but comparable effects between the 2 strategies were observed in the skeletal muscle and in the cortex.

From a functional point of view when compared with the control mice, resveratrol, like calorie restriction, preserved the cardiac function from the effects of ageing.

In the same way as calorie restriction, resveratrol modified the expression of genes only affected by the dietary measures not by ageing, with a cross reference of over 99% between calorie restriction and resveratrol. This underlines the mimicry of resveratrol on a large part of the transcriptional profile 1 of calorie restriction (22).

06

RESVERATROL AND DIABETES



Several epidemiological studies point to an association between moderate consumption of alcohol and insulin sensitivity (3).
The cross-sectional analysis of the IRAS study (Insulin Resistance and Atherosclerosis Study, 1196 patients) showed an inverted U-curve between the consumption of alcohol and insulin sensitivity, as well as with fasting insulinaemia, plasmatic lipids and blood pressure (23). This study also suggests that the improved insulin sensitivity associated with the moderate consumption of alcohol is the consequence of a lower BMI (Body Mass Index) and a lower abdominal adiposity.
In a cohort of 486 individuals suffering from severe obesity, an inverted U-curve is also observed between the frequency of alcohol consumption and triglycerides, fasting blood sugar, glycated haemoglobin and insulin resistance index (24).
A prospective study over 10 years carried out in Denmark on 2916 men and 3970 women showed that the moderate consumption of beer and liqueurs is associated with a subsequent increase in waist size, whilst the moderate consumption of wine has the opposite effect (25).

Moreover, the moderate consumption of alcohol is inversely correlated to glucose intolerance and C-reactive protein (CRP) (26).
Vitis vinifera extract has hypoglycaemic and antioxidant effects comparable to that of a hypoglycaemic agent, tolbutamide. On cell cultures, the toxicity of high levels of glucose and oxidative stress are inhibited by grape polyphenols, with an inhibition of the over-expression of NFκB, COX-2, iNOS and Bax (27).

The activation of sirtuin SIRT-1 by resveratrol in diabetic rats improves glucose homoeostasis and insulin sensitivity of adipose tissue, muscle tissue and the liver (28).

In comparison with untreated diabetic rats, pre-treatment with resveratrol before induction of diabetes in the rat leads to an increase in catalase activity, the level of NO and zinc concentrations and a decrease in lipid peroxidation products and copper concentrations, showing the strong activity of resveratrol against oxidative stress (29).

Ref. 31

Life Sciences

Effects of resveratrol on nerve functions, oxidative stress and DNA fragmentation in experimental diabetic neuropathy

[*Life Sciences* 80 (2007) 1236-1244]

In diabetic neuropathy in rats, resveratrol improves the conduction speed in motor nerves, nervous blood flow and reduces hyperalgesia. In parallel, in comparison with untreated diabetic rats, resveratrol attenuates the increase in MDA levels (malonedialdehyde, product of lipid peroxidation) and peroxinitrite and increases catalase activity. It markedly decreases DNA fragmentation. These results suggest that the beneficial effect of resveratrol in diabetic neuropathy may be mediated by a reduction in oxidative stress and DNA fragmentation (30, 31).

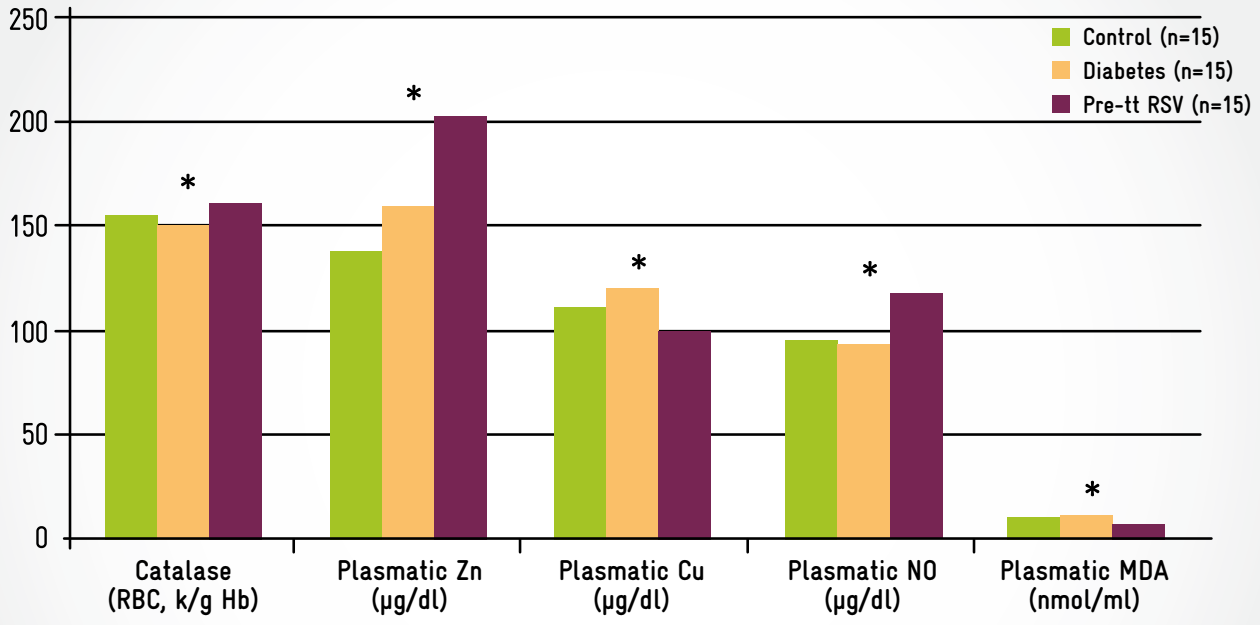
Resveratrol prevents diabetic nephropathy and improves renal dysfunction and oxidative stress in diabetic rats. Treatment with resveratrol reduces also insulin secretion and the period of emergence of insulin resistance. In diabetic rats, resveratrol stimulates the physiological processes such as glucose uptake by hepatic cells, fat cells and muscle cells, as well as hepatic glycogenesis.

Inflammation mediators (TNFα, IL-1, IL-5, COX-2, ...) generated by adipose tissue contribute to a chronic inflammatory state in obese individuals, which may be linked to the appearance of cardiovascular diseases and insulin resistance associated with type 2 diabetes. In cultured fat cells, the activation of the NFκB factor by TNFα leads to an increase in mRNA corresponding to IL-6 and COX-2. Resveratrol has been shown to be capable of inhibiting the action of the NFκB factor as well as the expression of inflammatory mediator genes (32).

Resveratrol prevents insulin resistance induced by a considerable intake of 10, 12 CLA (conjugated linoleic acid) by attenuating inflammation and cell stress and by stimulating PPAR activity (33).

The interest of resveratrol in diabetes is such that synthetic analogues are currently being developed in type 2 diabetes (34).

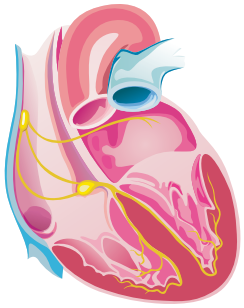
PROTECTIVE EFFECT OF PRE-TREATMENT WITH RESVERATROL AGAINST OXIDATIVE STRESS IN DIABETIC RATS (29)



* = significant difference between the 3 groups

07

RESVERATROL AND CARDIO-PROTECTION



The potential cardioprotection of resveratrol was initially suggested by 2 observations: on the one hand, the low prevalence of coronary disease in France despite eating habits encouraging saturated fats and relatively high levels of cholesterol: it's the famous « French paradox ». On the other hand, epidemiological studies show a lower incidence of cardiovascular mortality with the moderate consumption of alcohol.

This cardioprotector effect may be due to the anti-inflammatory and antioxidant action of resveratrol.

Antioxydant action

Resveratrol blocks oxidation of LDL-cholesterol by chelating copper (pro-oxidant) and by directly antagonising free radicals (1).

Indeed, resveratrol can be identified in LDL particles in humans after consumption of red wine. It prevents the oxidation of these particles induced by a tumour or UV rays (6).

In hypertensive rats, it significantly reduces the signs of oxidative stress such as glycated serum albumin or 8-hydroxyguanosine in urine. In guinea pigs, resveratrol induces DT-diaphorase and catalase activity (2 antiradical enzymes) in the myocardial tissue and reduces the concentration of free radicals generated by menadione (1, 35).

Following induction of oxidative stress in cardiac muscle tissue, resveratrol improves survival of these cells by activating AMP-activated kinase, thus inhibiting the cardiac lesion process (36).

Moreover, resveratrol seems to be capable of reducing the formation of atherosclerotic plaques and restoring vasodilatation in hypercholesterolemic rats (6).

Ref. 36

Genes Nutr

Resveratrol protects ROS-included cell death by activating AMPK in H9c2 cardiac muscle cells

[Gens Nutr (2008) 2:23-326]

Effects on ischemia-reperfusion lesions

The production of free radicals plays a major role in ischemia-reperfusion lesions.

On isolated rat hearts, the protective effect of resveratrol on the ischemia-reperfusion lesions is highlighted by the improvement in the post-ischemic ventricular function of treated hearts and by the reduction in the size of the heart attack. The formation of malone-dialdehyde (MDA) measured in the effluent coronary vessels is significantly lower in treated hearts than in control hearts, indicating a lower oxidative stress in hearts pre-treated with resveratrol (37).

In comparison with untreated diabetic rats, treatment of diabetic rats with resveratrol improves myocardial resistance to ischemia-reperfusion process by reducing the size of the necrosis and apoptosis of the cardiac muscle. This effect of resveratrol comes not only from the reduction in glycaemia, but also the induction of certain proteins (notably thioredoxin, heme oxygenase and VEGF) as well as the activation of Mn Superoxide-Dismutase. These effects are cancelled out by the administration of a nitric oxide synthesis inhibitor, suggesting that the cardioprotective action of resveratrol is linked to the production of NO (38). Indeed, several works have shown that the enzyme iNOS (inducible NO Synthase) is necessary for the cardioprotective effect of resveratrol to be operational (1).

In hypercholesterolemic rats the association of statin and resveratrol induces better cardio-protection against heart attacks than statin alone (39).

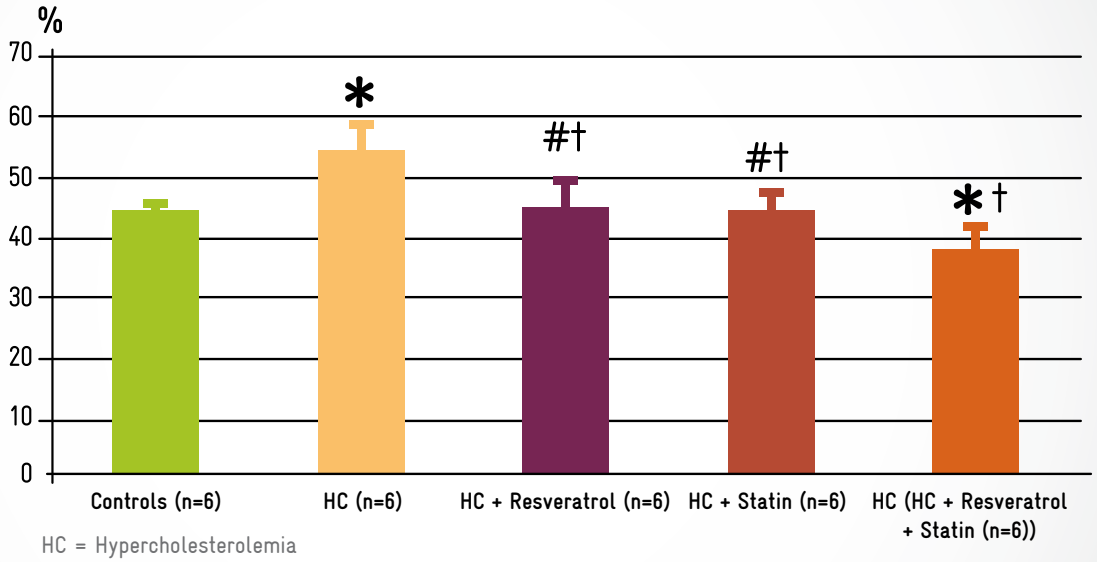
Ref. 39

J Mol cell Cardiol

Statin and Resveratrol in Combination induces Cardioprotection against Myocardial Infarction in Hypercholesterolemic Rat

[J Mol Cell Cardiol. 2007 March ; 42(3): 508-516]

PREVENTION OF ISCHEMIA-REPERFUSION LESIONS BY RESVERATROL: SIZE OF THE MYOCARDIAL NECROSIS IN PERCENTAGE OF ZONE AT RISK (HYPERCHOLESTEROLEMIC RATS) (39)



HC = Hypercholesterolemia
* = p < 0.05 in comparison with controls
† = p < 0.05 in comparison with HC group
# = p < 0.05 in comparison with HC + R + S group

Action on platelet aggregation

Resveratrol dose-dependently inhibits platelet aggregation. By systemic administration in rabbits, platelet aggregation induced by a hypercholesterolemic diet, is blocked. In genetically hypercholesterolemic mice, after experimental lesion of the vascular endothelium with a laser, resveratrol reduces the atherosclerotic surface and the size of generated thrombus.

One of the mechanisms evoked to explain this antiaggregating effect is the inhibition of COX-1 and COX-2. The synthesis of eicosanoids and leucotriens from arachidonic acid is linked to platelet aggregation and the family of cyclo-oxygenases (COX) plays a major role in the metabolism of arachidonic acid.

Several studies point to the inhibitory action of resveratrol on COX, prostaglandins and thromboxanes (1).
Free intracellular calcium is also an essential element in platelet aggregation. Resveratrol is a strong inhibitor of calcium channels and calcium influx in thrombin activated platelets.

Resveratrol blocks the early stages of platelet aggregation by inhibiting platelet adhesion to type 1 collagen and by reducing the aggregation of collagen induced by the platelets. Moreover, it prevents the adhesion of thrombin and activated platelets to fibrinogen and promotes fibrinolysis (1).

Effects on vascular relaxation

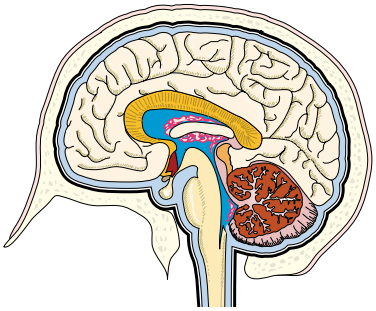
Resveratrol is capable of inducing vasodilatation in isolated arterial and arteriolar segments through an endothelium-dependent mechanism mediated by the release of NO, probably by the activation of NO synthase, and by an endothelium independent mechanism implementing, amongst others, the activation of BKCa potassium channels in smooth muscle (1).

Resveratrol also inhibits the production of vasoconstrictor substances. It inhibits the production of endothelin-1 induced by oxidative stress, angiotensin-II, TNF-α or thrombin. This effect may come from the anti-radical effect of resveratrol. Indeed, it increases vascular resistance to oxidative stress by trapping H2O2 and positively regulating antioxidant enzymes such as glutathion-peroxidase, catalase and heme-oxygenase-1 in the endothelial cells of coronary arteries in the rat (1).

Normal vascular responses can be restored by the chronic administration of resveratrol in diabetic rats: resveratrol inhibits the hyperreactivity of the vascular contractile response to noradrenalin and improves relaxation in response to acetylcholine (40).
Moreover, resveratrol may exert a vasodilator effect by inhibition of thromboxane A2 synthesis (6).

08

RESVERATROL AND NEURODEGENERATIVE DISEASES



The patho-physiological processes underlying neurodegenerative diseases are similar and are linked to the phenomena involved in ageing, so it is not surprising that resveratrol plays a role in neuroprotection.

In an Alzheimer's disease model it has been shown that by activating SIRT-1 resveratrol indirectly inhibits the nuclear factor κB (NF-κB) and consequently protects against the toxicity of microglial β-amyloid (20).

This neurodegenerative disease is characterised by the presence of microfibrils and extracellular β-amyloid plaques in the cortex and the hippocampus. A recent study in two animal models, one Alzheimer's and the other Amyotrophic Lateral Sclerosis (ALS), has shown that resveratrol significantly reduces the extent of neuronal death and neurotoxicity of the mutant proteins expressed in the 2 models. The administration of resveratrol decreases hypocampal degeneration and improves the capacities of associative learning in p25 mice (20).

These effects are mediated by SIRT-1, via increased deacetylation of p53 and/or PGC-1α, confirming the role of PGC-1α in neuronal metabolism.

By suppressing p53, resveratrol may protect the neurons against oxidative lesions and prevent apoptosis. Another hypothesis is the possible activation of FOXO proteins.

Other studies in mice have shown that the cerebral lesions caused by ischemia, CVA or epilepsy were significantly reduced by resveratrol (20).

Furthermore, in a mouse model of multiple sclerosis, the intra-vitreal injection of an SIRT-1 activator significantly attenuates optic neuritis, with a lower loss of ganglion retinal cells. This neuroprotective effect is cancelled out by sirtinol, an SIRT-1 inhibitor (41).

Ref. 20

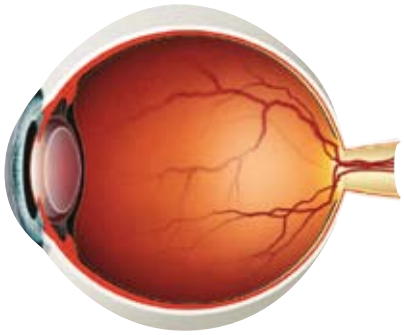
Clinical Interventions in Aging

Resveratrol in prevention and treatment of common clinical condition of aging

[Clinical Interventions in Aging 2008:3(2) 331-339]

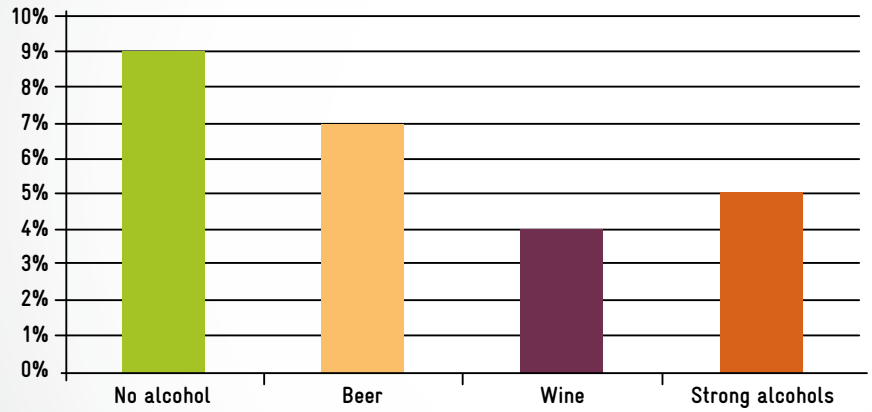
09

RESVERATROL AND RETINA



In 1998, an ancillary study of the epidemiological NHANES-1 study revealed that the moderate consumption of wine reduced the risk of ARMD by 19% (42). This finding created a new area of research around resveratrol: Age-Related Macular Degeneration.

PREVALENCE OF ARMD DEPENDING ON TYPE OF ALCOHOL CONSUMED (42)



Ref. 42

JAGS

Moderate Wine Consumption Is Associated with Decreased Odds of Developing Age-Related Macular Degeneration in NHANES-1

[JAGS 46:1-7,1998]

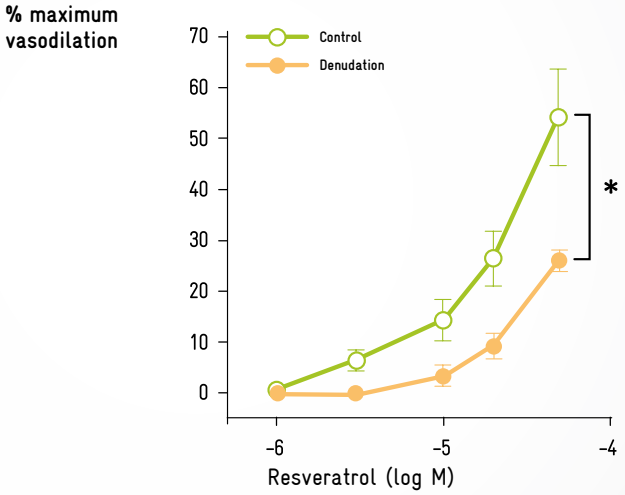
VASODILATOR EFFECT

Resveratrol exerts an arteriolar vasodilator effect on the retina (43), which is potentially interesting in degenerative pathologies involving circulatory insufficiency.

This vasodilation of retinal arterioles is dose-dependent and occurs above a threshold of 3µM, knowing that the dietary intake enables concentrations of 10 to 30µM to be reached in organs such as the liver, heart or kidney. Even though such measurements could not be carried out on the retina, the lipophilic nature of the component suggests largely sufficient tissue concentrations to lead to such a vasodilator effect.

The vasodilation caused by resveratrol is both endothelium-dependent – probably through the intermediary of nitric oxide (NO) – but also endothelium-independent, bringing into play the activation of BKCa potassium channels (dependent on intracellular calcium) of smooth muscle.

VASODILATION OF RETINAL ARTERIOLS BY RESVERATROL ON WHOLE VESSELS (CONTROL) AND ON VESSELS STRIPPED OF THEIR ENDOTHELIUM (DENUDATION) (43)



Antioxidant, protection of pigment epithelium and anti-senescence effect

Likewise, the mitochondrial lesions caused by endogenous oxygenated free radicals are heavily involved in the patho-physiology of ARMD and the effects of resveratrol provide with interesting therapeutic perspectives for this disease.

Pre-treatment with resveratrol of pigment epithelium cells isolated from retina of healthy donors or patients with ARMD before exposure to H2O2, a highly oxidizing component, confers significant protection of the mitochondrial oxidoreduction function and the activity of the IV complex in comparison with control retina. It also significantly reduces the lesions of mitochondrial DNA caused by hydrogen peroxide. These results indicate that the mitochondrial function can be preserved or restored in the retinal pigment epithelium thanks to resveratrol. This brings hope for an improvement in retinal pigment epithelium dysfunctions linked to ageing (44).

In another study trabecular cells of pig were submitted to oxidative stress by incubation in hyperoxic conditions (40% oxygen) for 15 days with resveratrol (25µg) or an excipient, and compared to cells incubated with 5% oxygen.

Following chronic oxidative stress, the treatment with resveratrol effectively prevents the production of free radicals, as well as the expression of inflammatory markers IL1α, IL6, IL8 and ELAM-1. Treatment with resveratrol also reduces the expression of senescence markers such as sa-β-gal (senescence associated β-galactosidase activity), lipofuscin and protein carbonilation. Furthermore, resveratrol exerts an anti-apoptotic effect in the acute oxidative stress model. The inhibition of the production of free radicals by resveratrol could thus prevent the induction of the expression of inflammation and senescence markers following oxidative stress (45).

Compared to untreated control retinas, retinas of rats treated with resveratrol reveal a greater expression of the anti-ageing protein SIRT-1 in the external and internal segments of the photoreceptors as well as the horizontal cells, the bipolar cells and the ganglion cells. The fluorescence corresponding to the anti-apoptotic protein Ku70 is comparable to that of SIRT-1 in treated rats, with similar localizations, particularly the external and internal segments of the photoreceptors (46). Treatment with resveratrol also provides a protective effect against apoptosis induced by intra-vitreal injection of antirecoverin antibodies. The authors suggest that this protective action exerted by resveratrol on the retina could thus be linked to the induction of SIRT-1 and Ku70 expression (46).

Protective effect on phagocytosis

The UVA irradiation of a culture of human pigment epithelium cells inhibits the phagocytic function of the human pigment epithelium cells, as does paxillin, an inhibitor of calcium dependent potassium channels BKCa. Meclofenamic acid, a BKCa channel activator, counters the lesions caused by UVA when administered as a pre-treatment, but not as a post-treatment after irradiation.

Pre-treatment with resveratrol has a protective effect on the phagocytic function comparable to that of meclofenamic acid regarding the lesions caused by UV radiation. This effect probably involves the BKCa potassium channels. Knowing that phagocytosis insufficiency seems to be one of the initial patho-physiological phenomena in ARMD, the beneficial effect of resveratrol in this disease could thus be explained in part by its capacity to protect the pigment epithelium and its phagocytic function against photo-induced lesions (48).

Retinal anti-inflammatory effect

In addition, the administration *per os* of resveratrol counters manifestations of retinal inflammation.

Escherichia coli lipopolysaccharides (LPS) injected in the peritoneum of mice increases the production of inflammation effectors (in particular intercellular adhesion molecule (ICAM 1) and Monocyte Chemotactic Protein (MCP-1)). The adhesion of leukocytes in the retinal vessels and the expression of inflammatory molecules in the retina were measured 24 hours after inoculation in control mice and in mice pre-treated with resveratrol (50 mg/kg/d) *per os* for 5 days before.

Leukocyte adhesion in the animals treated with resveratrol was reduced by 60% in comparison with the controls ($p < 0.05$). Moreover, the levels of ICAM-1 and MCP-1 increased by the injection of LPS, were significantly lower in the retina of treated animals, as were TNF-α and IL-6 (47).

10

CONCLUSION

Medical progress in the XXth century has enabled the western world to tame causes of premature death. However, drawbacks of population ageing are the emergence of age-linked degenerative pathologies: ARMD, cancers, neurodegenerative diseases, cardiovascular diseases...

Today's health challenge therefore lies in the prevention and delay of cell degeneration. By doing so, the term « life expectancy » takes on a meaning of increased longevity yet one that excludes as many ageing-related side effects as possible.

Resveratrol is the spearhead of this new epic of humanity and opens up vast perspectives in all aspects of ageing. Hundreds of publications each year in leading international journals such as Nature, Cell, Life... shed light on the understanding of cell ageing and the mechanisms of action of resveratrol, to the extent that the American pharmaceutical industry giants are developing new therapeutic agents derived from resveratrol...

This little molecule that is 100% natural is already available to everyone, today and now. The choice is yours according to your taste: red wine or food supplements.

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