Review

Resveratrol - The New Rasayan (Anti aging) Drug

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Abstract

Resveratrol is the new Rasayan. The discovery point of resveratrol was red wine, conferring positive health in Europeans in general and the French in particular. This is similar to Ayurvedic product Drakshasav (alcoholic preparation prepared from grapes). The Rasayan products specifically extend life (anti aging, provide stamina and tone up health in general). The resveratrol has been found to extend life in several research projects. It is Anti oxidant, anti-inflammatory, Anti viral and protects against Cancer, Diabetes, Alzheimer and other brain disorders. There are some controversies also. This work enlists both the positive findings of the research as well as the negative ones. Overall the resveratrol may prove to be of great value therapeutically. The clinical trials, both underway and future ones will finally set the controversies at rest.

Key words: Resveratrol, Rasayan, Anti aging, Anti oxidant, Anti cancer

1. Introduction

Resveratrol (3,5,4'-trihydroxy-trans-stilbene) is a stilbenoid, a type of natural phenol, and a phytoalexin produced naturally by several plants when under attack by pathogens such as bacteria or fungi.

Other names
trans-3,5,4'-Trihydroxystilbene;
3,4',5-Stilbenetriol;
trans-Resveratrol;

(E)-5-(p-Hydroxystyrlyl)resorcinol  (E)-5-(4-hydroxystyrlyl)benzene-1,3-diol

Chemical and physical properties
Molecular formula: C_{14}H_{12}O_{3}
Molar mass: 228.24 g mol$^{-1}$
Exact mass: 228.078644
Appearance: white powder with slight yellow cast
Solubility in water: 0.03 g/L
Solubility in DMSO: 16 g/L
Solubility in ethanol: 50 g/L

It exists as two geometric isomers: cis- (Z) and trans- (E), with the trans-isomer shown in the top image. The trans- and cis-resveratrol can be either free or bound to glucose.[1] The trans- form can undergo isomerisation to the cis- form when exposed to ultraviolet irradiation.[2] Trans-resveratrol in the powder form was found to be stable under "accelerated stability" conditions of 75% humidity and 40°C in the presence of air.[3] Resveratrol content also was stable in the skins of grapes and pomace taken after fermentation and...
stored for a long period.[4] ¹H- and ¹³C-NMR data for the four most common forms of resveratrols are reported in literature.[1]

1.2 Origin

Resveratrol was initially mentioned in a Japanese article in 1939 by M. Takaoka, who isolated it from the poisonous but medicinal Veratrum album, variety grandiflorum. The name presumably comes from the fact that it is a resorcinol derivative coming from a Veratrum species.[5] In 1963, it was then isolated from the roots of Polygonum Cuspidatum, a traditional Chinese and Japanese medicinal plant. Resveratrol is one of a group of compounds (called phytoalexins) that are produced in plants during times of environmental stress such as adverse weather or insect, animal or pathogenic attack. Resveratrol is produced in plants with the help of the enzyme resveratrol synthase.

It attracted the wider attention only in 1992, when its presence in wine was used as the explanation for cardioprotective effects of wine.[6]

1.3 Source

In grapes, resveratrol is found primarily in the skin,[7] and in muscadine grapes also in the seeds.[8] The amount found in grape skins also varies with the grape cultivar, its geographic origin, and exposure to fungal infection. The amount of fermentation time a wine spends in contact with grape skins is an important determinant of its resveratrol content.[7]

The amount of resveratrol in food varies greatly. Red wine contains between 0.2 and 5.8 mg/L.[9] depending on the grape variety, while white wine has much less the reason being that red wine is fermented with the skins, allowing the wine to absorb the resveratrol, whereas white wine is fermented after the skin has been removed.[7] Wines produced from muscadine grapes, however, both red and white, may contain more than 40 mg/L.[10]

<table>
<thead>
<tr>
<th>Resveratrol Content in wines and grape juice</th>
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<tr>
<td>Beverage</td>
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<tr>
<td>Muscadine Wines</td>
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<td>Red Wines (Global)</td>
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<td>Pinot Noir</td>
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<td>White Wines (Spanish)</td>
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The trans-resveratrol concentration in 40 Tuscan wines ranged from 0.3 to 2.1 mg/L in the 32 red wines and had a maximum of 0.1 mg/L in the 8 white wines tested. Both the cis- and trans-isomers of resveratrol were detected in all tested samples. cis-Resveratrol levels were comparable to those of the trans-isomer. They ranged from 0.5 mg/L to 1.9 mg/L in red wines and had a maximum of 0.2 mg/L in white wines.[11]

Resveratrol was detected in grape, cranberry, and wine samples. Concentrations ranged from 1.56 to 1042 nmol/g in Concord grape products, and from 8.63 to 24.84 micromol/L in Italian red wine. The concentrations of resveratrol were similar in cranberry and grape juice at 1.07 and 1.56 nmol/g, respectively.[12]

Blueberries have about twice as much resveratrol as bilberries, but there is great regional variation. These fruits have less than ten percent of the resveratrol of grapes. Cooking or heat processing of these berries will contribute to the degradation of resveratrol, reducing it by up to half. [13]

2. Physiological effects:

This drug has been found to be useful in following diseases and disorders.

2.1 Life extension

2.1.1 The groups of Howitz and Sinclair reported in 2003 in the journal Nature that resveratrol significantly extends the lifespan of the yeast Saccharomyces cerevisiae.[14] Later studies conducted by Sinclair showed that resveratrol also prolongs the lifespan of the worm Caenorhabditis elegans and the fruit fly Drosophila melanogaster.[15] In 2007 a different group of researchers was able to reproduce the Sinclair’s results with C. elegans[16] but a third group could not achieve consistent increases in lifespan of Drosophila or C. elegans.[17]

2.1.2 In 2006, Italian scientists obtained the first positive result of resveratrol supplementation in a vertebrate. Using a short-lived fish, Notobranchius furzeri, with a median life span of nine weeks, they found that a maximal dose of resveratrol increased the median lifespan by 56%. Compared with the control fish at nine weeks, that is by the end of the latter life, the fish supplemented with resveratrol showed significantly higher general swimming activity and better learning to avoid an unpleasant stimulus. The authors noted a slight increase of mortality in young fish caused by resveratrol and hypothesized that it is its weak toxic action that stimulated the defense mechanisms and resulted in the life span extension.[18] Later the same year, Sinclair reported that resveratrol counteracted the detrimental effects of a high-
fat diet in mice. The high fat diet was compounded by adding hydrogenated coconut oil to the standard diet; it provided 60% of energy from fat, and the mice on it consumed about 30% more calories than the mice on standard diet. Both the mice fed the standard diet and the high-fat diet plus 22 mg/kg resveratrol had a 30% lower risk of death than the mice on the high-fat diet. Gene expression analysis indicated the addition of resveratrol opposed the alteration of 144 out of 155 gene pathways changed by the high-fat diet. Insulin and glucose levels in mice on the high-fat+resveratrol diet were closer to the mice on standard diet then to the mice on the high-fat diet. However, addition of resveratrol to the high-fat diet did not change the levels of free fatty acids and cholesterol, which were much higher than in the mice on standard diet. [19].

2.1.3 Resveratrol, increases longevity in the short-lived invertebrates Caenorhabditis elegans and Drosophila and exerts a variety of biological effects in vertebrates, including protection from ischemia and neurotoxicity. Its effects on vertebrate lifespan were not yet known. The relatively long lifespan of mice, which live at 2.5 years, is a hurdle for life-long pharmacological trials. Here, the authors used the short-lived seasonal fish Nothobranchius furzeri with a maximum recorded lifespan of 13 weeks in captivity. Short lifespan in this species is not the result of spontaneous or targeted genetic mutations, but a natural trait correlated with the necessity to breed in an ephemeral habitat and tied with accelerated development and expression of ageing biomarkers at a cellular level. Resveratrol was added to the food starting in early adulthood and caused a dose-dependent increase of median and maximum lifespan. In addition, resveratrol delays the age-dependent decay of locomotor activity and cognitive performances and reduces the expression of neurofibrillary degeneration in the brain. These results demonstrate that food supplementation with resveratrol prolongs lifespan and retards the expression of age-dependent traits in a short-lived vertebrate [20].

2.1.4 A small molecule that safely mimics the ability of dietary restriction (DR) to delay age-related diseases in laboratory animals is greatly sought after. These authors have shown that resveratrol mimics effects of DR in lower organisms. In mice, resveratrol induces gene expression patterns in multiple tissues that parallel those induced by DR and every-other-day feeding. Moreover, resveratrol-fed elderly mice show a marked reduction in signs of aging, including reduced albuminuria, decreased inflammation, and apoptosis in the vascular endothelium, increased aortic elasticity, greater motor coordination, reduced cataract formation, and preserved bone mineral density. However, mice fed a standard diet did not live longer when treated with resveratrol beginning at 12 months of age. The findings indicate that resveratrol treatment has a range of beneficial effects in mice but does not increase the longevity of ad libitum-fed animals when started midlife. [21].

2.1.5 Resveratrol also consistently extends the mean and maximum life span in model organisms including nematode worms. It has been suggested that resveratrol exerts its life-span-extending effect through calorie restriction or hormesis mimetic effects. This study characterizes the effect of resveratrol on stress resistance, developmental rate, growth, and fecundity in the nematode worm Caenorhabditis elegans in order to determine whether the beneficial effects of resveratrol on life span are associated with trade-offs in terms of early life fitness in nematodes. This study found that resveratrol treatment increases stress resistance, specifically to oxidative stress, and causes a small but significant decrease in fecundity early in life without affecting overall fecundity. Resveratrol increased mean and maximum life span by delaying the onset of the exponential increase in mortality characterizing the "dying phase" in C. elegans, but did not affect the dying phase itself, suggesting that it did not act by directly affecting metabolism. [22].

2.1.6 Resveratrol extends the lifespan of diverse species including Saccharomyces cerevisiae, Caenorhabditis elegans and Drosophila melanogaster. In these organisms, lifespan extension is dependent on Sir2, a conserved deacetylase proposed to underlie the beneficial effects of caloric restriction. This study shows that resveratrol shifts the physiology of middle-aged mice on a high-calorie diet towards that of mice on a standard diet and significantly increases their survival. Resveratrol produces changes associated with longer lifespan, including increased insulin sensitivity, reduced insulin-like growth factor-1 (IGF-1) levels, increased AMP-activated protein kinase (AMPK) and peroxisome proliferator-activated receptor-gamma coactivator 1alpha (PGC-1alpha) activity, increased mitochondrial number, and improved motor function. Parametric analysis of gene set enrichment revealed that resveratrol opposed the effects of the high-calorie diet in 144 out of 153 significantly altered pathways. These data show that improving general health in mammals using small molecules is an attainable goal, and point to new approaches for treating obesity-related disorders and diseases of ageing. [23].

2.1.7 In Drosophila, lifespan extension by dietary restriction (DR) is associated with a reduction in fecundity. However, a slight increase in fecundity was reported upon treatment with resveratrol, suggesting a mode of action at least partially distinct from that of DR. To probe this mechanism further, this work initiated a new study of the effects of resveratrol on Drosophila. We saw no significant effects on lifespan in seven independent trials. The resveratrol was analyzed and its structure was found to be normal, with no oxidative...
modifications. The effects of resveratrol were retested in C. elegans, in both wild-type and sir-2.1 mutant worms. The results were variable, with resveratrol treatment resulting in slight increases in lifespan in some trials but not others, in both wild type and sir-2.1 mutant animals. It is postulated that the effect of resveratrol upon lifespan in C. elegans could reflect induction of phase 2 drug detoxification or activation of AMP kinase.[24]

2.2 Alzheimer's disease:
2.2.1 Resveratrol is known to protect against cardiovascular diseases and cancers, as well as to promote antiaging effects in numerous organisms. It also modulates pathomechanisms of debilitating neurological disorders, such as strokes, ischemia, and Huntington's disease. The role of resveratrol in Alzheimer's disease is still unclear, although some recent studies on red wine bioactive compounds suggest that resveratrol modulates multiple mechanisms of Alzheimer's disease pathology. Emerging literature indicates that mechanisms of aging and Alzheimer's disease are intricately linked and that these mechanisms can be modulated by both calorie restriction regimens and calorie restriction mimetics, the prime mediator of which is the SIRT1 protein, a human homologue of yeast silent information regulator (Sir)-2, and a member of NAD+-dependent histone deacetylases. Calorie restriction regimens and calorie restriction-mimetics trigger sirtuins in a wide variety of organisms, ranging from bacteria to mouse. In a mouse model of Huntington's disease, resveratrol-induced SIRT1 was found to protect neurons against ployQ toxicity and in Wallerian degeneration slow mice, resveratrol was found to protect the degeneration of neurons from axotomy, suggesting that resveratrol may possess therapeutic value to neuronal degeneration. This paper mainly focuses on the role of resveratrol in modulating AD pathomechanisms.[25]

2.2.2 Resveratrol was reported effective against neuronal cell dysfunction and cell death, and in theory could help against diseases such as Huntington's disease and Alzheimer's disease.[26][27]

2.3 Cancer
2.3.1 In a study by Pezzuto and colleagues, it was demonstrated that resveratrol was effective during all three phases of the cancer process: initiation, promotion and progression. Resveratrol was found to have antioxidant and antimutagenic activity and also increased levels of the phase II drug-metabolizing enzyme quinone reductase, an enzyme capable of metabolically detoxifying carcinogens, thereby ridding them from the body.[28]

2.3.2 In 1997 Jang reported that topical resveratrol applications prevented the skin cancer development in mice treated with a carcinogen.[28] There have since been dozens of studies of the anti-cancer activity of resveratrol in animal models.[29] The effectiveness of resveratrol in animal cancer models is limited by its poor bioavailability. The strongest evidence of anti-cancer action of resveratrol exists for the tumors it can come into direct contact with, such as skin and gastrointestinal tract tumors. For other cancers, the evidence is equivocal, even if massive dose of resveratrol are used.[29]

2.3.3 Thus, topical application of resveratrol in mice, both before and after the UVB exposure, inhibited the skin damage and decreased skin cancer incidence. However, oral resveratrol was ineffective in treating mice inoculated with melanoma cells.[29] Resveratrol (1 mg/kg orally) reduced the number and size of the esophageal tumors in rats treated with a carcinogen.[30] In several studies, small doses (0.02-8 mg/kg) of resveratrol, given prophylactically, reduced or prevented the development of intestinal and colon tumors in rats given different carcinogens.[29]

2.3.4 Resveratrol interferes with all three stages of carcinogenesis - initiation, promotion and progression. Experiments in cell cultures of varied types and isolated subcellular systems in vitro imply many mechanisms in the pharmacological activity of resveratrol. These mechanisms include modulation of the transcription factor NF-κB,[31] inhibition of the cytochrome P450 isoenzyme CYP1A1[32] (although this may not be relevant to the CYP1A1-mediated bioactivation of the procarcinogen benzo(a)pyrene[33]), alterations in androgenic[34] actions and expression and activity of cyclooxygenase (COX) enzymes. In some lineages of cancer cell culture, resveratrol has been shown to induce apoptosis, which means it kills cells and may kill cancer cells.[34][35][36][37][38][39] Resveratrol has been shown to induce Ras/Raf ligand mediated apoptosis, p53 and cyclins A, B1 and cyclin-dependent kinases cdk 1 and 2. Resveratrol also possesses antioxidant and anti-angiogenic properties.[40][41]

2.3.5 This study found that resveratrol, at doses of 2.5 and 10 mg/kg, significantly reduced the tumor volume (42%), tumor weight (44%) and metastasis to the lung (56%) in mice bearing highly metastatic Lewis lung carcinoma (LLC) tumors. Resveratrol did not affect the number of CD4+, CD8+ and natural killer (NK)1.1+ T cells in the spleen. Therefore, the inhibitory effects of resveratrol on tumor growth and lung metastasis could not be explained by natural killer or cytotoxic T-lymphocyte activation. In addition, resveratrol inhibited DNA synthesis most strongly in LLC cells. Resveratrol inhibited tumor-induced neovascularization at doses of 2.5 and 10 mg/kg in an in vivo model. Moreover, resveratrol significantly inhibited the formation of capillary-like tube formation from human umbilical vein endothelial cells (HUVEC). Resveratrol inhibited the binding of vascular endothelial growth factor (VEGF) to HUVEC. The study
suggests that the antitumor and antimetastatic activities of resveratrol might be due to the inhibition of DNA synthesis in LLC cells and the inhibition of LLC-induced neovascularization and tube formation (angiogenesis) of HUVEC by resveratrol [42].

2.3.6 Resveratrol (3,5,4′-trihydroxy-trans-stilbene) is a natural product occurring in grapes and various other plants with medicinal properties associated with reduced cardiovascular disease and reduced cancer risk. To evaluate the possibility and potential mechanism(s) of which resveratrol inhibits N-nitrosomethylbenzylamine (NMBA)-induced rat esophageal tumorigenesis, 96 F344 male rats were divided into 10 groups and resveratrol (1 and 2 mg/kg) was administered orally or intraperitoneally (i.p.). In the groups in which resveratrol was administered at 2 mg/kg (orally, for 16 weeks), 1 and 2 mg/kg (i.p., for 16 weeks) and 1 mg/kg (i.p., for 20 weeks), the number of NMBA-induced esophageal tumors per rat was significantly reduced to 78, 62, 54 and 48, respectively (P < 0.05), and the size of maximum tumors in each group with resveratrol treatment was also significantly smaller than that in NMBA alone group (P < 0.05). Although the pathological examination did not indicate significantly decreased incidence of carcinomas by administering resveratrol, the tendency of carcinogenesis suppression was observed (P = 0.177). Semi-quantitative RT-PCR and ELISA analysis demonstrated that following NMBA treatment, the expression of COX-1 mRNA was strongly present in tumor tissues, while weakly present in non-tissues; the expression of COX-2 mRNA was induced in both tumor and non-tumor tissues. The production of prostaglandin E2 (PGE2) increased approximately 6-fold, compared with the normal esophageal mucosa. The higher expression of COX-1, the up-regulated COX-2 expression and the increased levels of PGE2(2) synthesis were all significantly decreased by administering resveratrol. Our study suggests that resveratrol suppressed NMBA-induced rat esophageal tumorigenesis by targeting COXs and PGE(2), and therefore may be a promising natural anti-carcinogenesis agent for the prevention and treatment of human esophageal cancer.[43]

2.3.7 Cavalieri and Rogan turned to resveratrol in their quest to stop this first step of cancer growth. They found that a combination of resveratrol, n-acetyl-l-cysteine (an amino acid), Lipoic Acid and Melatonin greatly enhanced the body's natural protective mechanisms. When triggered by the resveratrol compound, the triggering mechanism involved in the formation of breast and cancer cells was greatly diminished. [44]

2.3.8 Resveratrol has cancer chemopreventive properties in preclinical models. It has been shown to down regulate levels of insulin-like growth factor-1 (IGF-1) in rodents. The purpose of the study was to assess its safety, pharmacokinetics and effects on circulating levels of IGF-1 and insulin-like growth factor binding protein-3 (IGFBP-3) after repeated dosing. Forty healthy volunteers ingested resveratrol at 0.5, 1.0, 2.5 or 5.0g daily for 29 days. Levels of resveratrol and its metabolites were measured by HPLC-UV in plasma obtained before and up to 24h after a dose between days 21 and 28. IGF-1 and IGFBP-3 were measured by enzyme-linked immunosor bent assay in plasma taken pre-dosing and on day 29. Resveratrol was safe, but the 2.5 and 5g doses caused mild to moderate gastrointestinal symptoms. Resveratrol-3-O-sulfate, resveratrol-4′-O-gluconuride and resveratrol-3-O-gluconuride were major plasma metabolites. Maximal plasma levels and areas under the concentration versus time curve (AUC) for the metabolites dramatically exceeded those for resveratrol, in the case of the AUC by up to 20.3-fold. Ingestion of resveratrol caused a decrease in circulating IGF-1 and IGFBP-3 (P<0.04 for both), respectively, compared to pre-dosing values, in all volunteers. At the 2.5g dose level the decrease was most marked. The results suggest that repeated administration of high doses of resveratrol generates micromolar concentrations of parent and much higher levels of glucuronidate and sulfate conjugates in the plasma. The observed decrease in circulating IGF-1 and IGFBP-3 may contribute to cancer chemopreventive activity.[45]

2.3.9 Resveratrol was purified and shown to have cancer chemopreventive activity in assays representing three major stages of carcinogenesis. Resveratrol was found to act as an antioxidant and antimutagen and to induce phase II drug-metabolizing enzymes (anti-initiation activity); it mediated anti-inflammatory effects and inhibited cyclooxygenase and hydroperoxidase functions (antipromotion activity); and it induced human promyelocytic leukemia cell differentiation (antiproliferation activity). In addition, it inhibited the development of preneoplastic lesions in carcinogen-treated mouse mammary glands in culture and inhibited tumorigenesis in a mouse skin cancer model. These data suggest that resveratrol, a common constituent of the human diet, merits investigation as a potential cancer chemopreventive agent in humans.[46]

Not effective against cancer?
Resveratrol has been shown to have anticarcinogenic activity. The authors previously found that resveratrol inhibited growth and induced apoptosis in 2 human melanoma cell lines. In this study it was determined whether resveratrol would inhibit human melanoma xenograft growth. Athymic mice received control diets or diets containing 110 micromol/L or 263 micromol/L resveratrol, 2 wk prior to subcutaneous injection of the tumor cells. Tumor growth was measured during a 3-wk period. Metabolism of resveratrol was assayed by bolus gavage of 75 mg/kg resveratrol in tumor-bearing and nontumor-bearing mice. Pellets containing 10-100 mg resveratrol were implanted into the mice, next to newly palpated tumors, and tumor growth determined. We also determined the effect of a major resveratrol metabolite,
piceatannol, on experimental lung metastasis. Resveratrol, at any concentration tested, did not have a statistically significant effect on tumor growth. The higher levels of resveratrol tested (0.006% in food or 100 mg in slow-release pellets) tended to stimulate tumor growth (P = 0.08-0.09). Resveratrol and its major metabolites, resveratrol glucuronide and piceatannol, were found in serum, liver, skin, and tumor tissue. Piceatannol did not affect the in vitro growth of a murine melanoma cell line, but significantly stimulated the number of lung metastases when these melanoma cells were directly injected into the tail vein of the mouse. These results suggest that resveratrol is not likely to be useful in the treatment of melanoma and that the effects of phytochemicals on cell cultures may not translate to the whole animal system.[47]

Possible carcinogenicity:
Resveratrol in common with other polyphenols, was found to be a strong topoisomerase inhibitor, sharing similarities to chemotherapeutic anticancer drugs, such as etoposide and doxorubicin.[48][49] This may simultaneously contribute to both the potential antitumor and carcinogenic properties of the substance in given circumstances. Harmful properties of resveratrol may be pronounced in the human fetus, as it has diminished detoxification systems. Therefore, resveratrol as commonly sold combined with other "bioflavonoids", should be not used by pregnant women.[50]  

2.4 Brain protection

2.4.1 A previous study from our lab has shown that the polyphenol rich pomegranate juice (PJ) can protect the neonatal mouse brain against hypoxic-ischemic (H-I) injury when given to mothers in their drinking water. To test the hypothesis that this protection is due to the polyphenols in the juice we studied the effects of the pomegranate polyphenol extract in the same neonatal H-I model. To further explore the role of a specific polyphenol in neonatal H-I we investigated the effects of resveratrol. The neuroprotective effects of resveratrol have been demonstrated in adult models of stroke, but had not previously been examined in neonates. We show that pomegranate polyphenols and resveratrol reduce caspase-3 activation following neonatal H-I. Resveratrol reduced caspase-3 activation when given before the injury but not when given 3 hours after the injury. In addition to preventing caspase-3 activation, resveratrol also reduced calpain activation. Finally, we show that resveratrol can protect against tissue loss measured at 7 days after the injury. These and other recent findings suggest that polyphenols should be further investigated as a potential treatment to decrease brain injury due to neonatal H-I.[51]

2.4.2 Neuroprotective effect: Neuroprotective effects: In November 2008, researchers at the Weill Medical College of Cornell University reported dietary supplementation with resveratrol significantly reduced plaque formation in animal brains, a component of Alzheimer's disease and other neurodegenerative diseases.[52] In mice, oral resveratrol produced large reductions in brain plaque in the hypothalamus (-90%), striatum (-89%), and medial cortex (-48%) sections of the brain. In humans, oral doses of resveratrol theoretically may reduce beta amyloid plaque associated with aging changes in the brain. Researchers theorize that one mechanism for plaque eradication is the ability of resveratrol to chelate (bind) copper. The neuroprotective effects have been confirmed in several animal model studies.[53][54][55][56][57]  

2.5 CARDIAC DISEASES

2.5.1 Research at the Northeastern Ohio Universities College of Medicine and Ohio State University indicates that resveratrol has direct inhibitory action on cardiac fibroblasts and may inhibit the progression of cardiac fibrosis.[58]

2.5. Based on its structural similarity to diethylstilbestrol, a synthetic estrogen, this study examined whether resveratrol might be a phytoestrogen. At concentrations (approximately 3-10 microM) comparable to those required for its other biological effects, resveratrol inhibited the binding of labeled estradiol to the estrogen receptor and it activated transcription of estrogen-responsive reporter genes transfected into human breast cancer cells. This transcriptional activation was estrogen receptor-dependent, required an estrogen response element in the reporter gene, and was inhibited by specific estrogen antagonists. In some cell types (e.g., MCF-7 cells), resveratrol functioned as a superagonist (i.e., produced a greater maximal transcriptional response than estradiol) whereas in others it produced activation equal to or less than that of estradiol. Resveratrol also increased the expression of native estrogen-regulated genes, and it stimulated the proliferation of estrogen-dependent T47D breast cancer cells. We conclude that resveratrol is a phytoestrogen and that it exhibits variable degrees of estrogen receptor agonism in different test systems. The estrogenic actions of resveratrol broaden the spectrum of its biological actions and may be relevant to the reported cardiovascular benefits of drinking wine.[59]

2.5.3 Cardioprotective effects: Moderate drinking of red wine has long been known to reduce the risk of heart disease.[60] This is best known as "the French paradox".[61][62][63] Studies suggest resveratrol in red wine may play an important role in this phenomenon.[64] It achieves the effects by the following functions:

(1) Inhibition of vascular cell adhesion molecule expression;
(2) Inhibition of vascular smooth muscle cell proliferation;
(3) Stimulation of endothelial nitric oxide synthase (eNOS) Activity;[70][71][72]
(4) Inhibition of platelet aggregation:[73][74][75]
(5) Inhibition of LDL peroxidation;[76][77]

The cardioprotective effects of resveratrol are also theorized to be a form of preconditioning—the best method of cardioprotection, rather than direct therapy.[78] A 2011 study [79] concludes, “Our data demonstrate that both melatonin and resveratrol, as found in red wine, protect the heart in an experimental model of myocardial infarction via the SAFE pathway.”

2.6 Diabetes Resveratrol, a ubiquitous stress-induced phytoalexin, has demonstrated a wide variety of biological activities which make it a good candidate for the treatment of diabetes mellitus. The present study was aimed to evaluate its therapeutic potential by assaying the activities of key enzymes of carbohydrate metabolism in streptozotocin-nicotinamide-induced diabetic rats. The daily oral treatment of resveratrol (5 mg/kg body weight) to diabetic rats for 30 days demonstrated a significant (p<0.05) decline in blood glucose and glycosylated hemoglobin levels and a significant (p<0.05) increase in plasma insulin level. The altered activities of the key enzymes of carbohydrate metabolism such as hexokinase, pyruvate kinase, lactate dehydrogenase, glucose-6-phosphatase, fructose-1,6-bisphosphatase, glucose-6-phosphate dehydrogenase, glycogen synthase and glycogen phosphorylase in liver and kidney tissues of diabetic rats were significantly (p<0.05) reverted to near normal levels by the administration of resveratrol. Further, resveratrol administration to diabetic rats improved hepatic glycogen content suggesting the antihyperglycemic potential of resveratrol in diabetic rats. The obtained results were compared with glyclazide, a standard oral hypoglycemic drug. Thus, the modulatory effects of resveratrol on attenuating these enzymes activities afford a promise for widespread use for treatment of diabetes in the future.[80]

Antidiabetic effects: Studies have shown resveratrol possesses hypoglycemic and hypolipidemic effects in both streptozotocin (STZ)-induced diabetes rats and STZ-nicotinamide-induced diabetes rats. Resveratrol ameliorates common diabetes symptoms, such as polyphagia, polydipsia, and body weight loss.[81] Other diabetic animal model studies by different researchers have also demonstrated the antidiabetic effects of resveratrol.[82][83] In human clinical trials, resveratrol has lowered blood sugar levels in both Phase Ia and Phase Ila, conducted by Sirtris Pharmaceuticals, Inc.[83][84]

2.7 OXIDATIVE STRESS
In December, 2007, work from Irfan Rahman's laboratory at the University of Rochester demonstrated that resveratrol increased intracellular glutathione levels via Nrf2-dependent upregulation of gamma-glutamylcysteine ligase in lung epithelial cells, which protected them against cigarette smoke extract induced oxidative stress. [85]

2.8 Effect on individuals with SIRT1 gene variations. 2.8.1 In a study of 123 Finnish adults, those born with certain increased variations of the SIRT1 gene had faster metabolisms, helping them to burn energy more efficiently indicating that the same pathway shown in the lab mice works in humans too.[86]

2.8.2 Sirtuins represent a novel family of enzymes that are collectively well situated to help regulate nutrient sensing and utilization, metabolic rate and ultimately metabolic disease. Activation of one of these enzymes, SIRT1, leads to enhanced activity of multiple proteins, including peroxisome-proliferator activated receptor coactivator-1alpha (PGC-1alpha), which helps to mediate some of the in vitro and in vivo effects of sirtuins. As such, enhanced SIRT1 activity decreases glucose levels, improves insulin sensitivity, increases mitochondrial number and function, decreases adiposity, improves exercise tolerance and potentially lowers body weight. SRT-501 is a proprietary formulation of resveratrol with improved bioavailability. As such, SRT-501 represents the first in a novel class of SIRT1 activators that has proven to be safe and well-tolerated in humans. Clinical trials in type 2 diabetic patients are currently underway.[87]

2.8.3 Diminished mitochondrial oxidative phosphorylation and aerobic capacity are associated with reduced longevity. We tested whether resveratrol (RSV), which is known to extend lifespan, impacts mitochondrial function and metabolic homeostasis. Treatment of mice with RSV significantly increased their aerobic capacity, as evidenced by their increased running time and consumption of oxygen in muscle fibers. RSV’s effects were associated with an induction of genes for oxidative phosphorylation and mitochondrial biogenesis and were largely explained by an RSV-mediated decrease in PGC-1alpha acetylation and an increase in PGC-1alpha activity. This mechanism is consistent with RSV being a known activator of the protein deacetylase, SIRT1, and by the lack of effect of RSV in SIRT1(-/-) MEFs. Importantly, RSV treatment protected mice against diet-induced-obesity and insulin resistance. These pharmacological effects of RSV combined with the association of three Sirt1 SNPs and energy homeostasis in Finnish subjects implicates SIRT1 as a key regulator of energy and metabolic homeostasis.[88]

2.9 Antiviral effects
2.9.1 Resveratrol seems to increase the potency of some antiretroviral drugs against HIV in vitro.[89]
2.9.2 Infection by herpes simplex virus ordinarily activates the cell protein Nuclear Factor Î”B (NF-Î”B). A Northeastern Ohio Universities College of Medicine study undertaken in Vivo found that resveratrol suppresses the activation of this transcription- and apoptosis-related protein. The study further found that multiple viral protein products were reduced or completely blocked, as well as a reduction in viral DNA production.[90]

2.9.3 A cell culture study found that resveratrol blocks the influenza virus from transporting viral proteins to the viral assembly site, hence restricting its ability to replicate. The effect was 90% when resveratrol was added six hours after infection and continued for 24 hours thereafter.[91]

Antiviral effects: Studies show resveratrol inhibits herpes simplex virus (HSV) types 1 and 2 replication by inhibition of an early step in the virus replication cycle. In vivo studies in mice found resveratrol inhibits or reduces HSV replication in the vagina and limits extravaginal disease. The skin of resveratrol-treated animals showed no apparent dermal toxicity, such as erythema, scaling, crusting, lichenification, or excoriation.[92][93] Studies also show resveratrol inhibits varicella-zoster virus, certain influenza viruses, respiratory viruses, and human cytomegalovirus. Furthermore, resveratrol synergistically enhances the anti-HIV-1 activity of several anti-HIV drugs.[94][95]

2.10 Anti-inflammatory effects: The anti-inflammatory effects of resveratrol have been demonstrated in several animal model studies. In a rat model of carrageenan-induced paw edema, resveratrol inhibited both acute and chronic phases of the inflammatory process.[96] Similarly, preincubation with resveratrol decreased arachidonic acid release and COX-2 induction in mouse peritoneal macrophages stimulated with tumor promoter PMA, ROI, or lipopolysaccharides (LPS).[97] In an experimental rabbit inflammatory arthritis model, resveratrol showed promise as a potential therapy for arthritis. When administered to rabbits with induced inflammatory arthritis, resveratrol protected cartilage against the progression of inflammatory arthritis.[98]

3. The controversies

3.1 Nicholas Wade’s interview-article with Dr. Auwerx [99] states that the dose was 400 mg/kg of body weight (much higher than the 22 mg/kg of the Sinclair study). For an 80 kg (176 lb) person, the 400 mg/kg of body weight amount used in Dr. Auwerx’s mouse study would com to 32,000 mg/day. Compensating for the fact that humans have slower metabolic rates than mice would change the equivalent human dose to roughly 4571 mg/day. Again, there is no published evidence anywhere in the scientific literature of any clinical trial for efficacy in humans. There is limited human safety data (see above). It is premature to take resveratrol and expect any particular results. Long-term safety has not been evaluated in humans.

3.2 While the health benefits of resveratrol seem promising, one study has theorized that it may stimulate the growth of human breast cancer cells, possibly because of resveratrol’s chemical structure, which is similar to a phytoestrogen.[100][101] However, other studies have found that resveratrol actually fights breast cancer.[102] Citing the evidence that resveratrol is estrogenic, some retailers of resveratrol advise that the compound may interfere with oral contraceptives and that women who are pregnant or intending to become pregnant should not use the product, while others advise that resveratrol should not be taken by children or young adults under 18, as no studies have shown how it affects their natural development.[103] A small study found that a single dose of up to 5 g of trans-resveratrol caused no serious adverse effects in healthy volunteers.

3.3 Rapamycin, But Not Resveratrol or Simvastatin, Extends Life Span of Genetically Heterogeneous Mice. Rapamycin was administered in food to genetically heterogeneous mice from the age of 9 months and produced significant increases in life span, including maximum life span, at each of three test sites. Median survival was extended by an average of 10% in males and 18% in females. Rapamycin attenuated age-associated decline in spontaneous activity in males but not in females. Causes of death were similar in control and rapamycin-treated mice. Resveratrol (at 300 and 1200 ppm food) and simvastatin (12 and 120 ppm) did not have significant effects on survival in male or female mice. Further evaluation of rapamycin’s effects on mice is likely to help delineate the role of the mammalian target of rapamycin complexes in the regulation of aging rate and age-dependent diseases and may help to guide a search for drugs that retard some or all of the diseases of aging.[104]

“Current status and future prospects

Research on Human needed for long term health safety;”

ScienceDaily (June 21, 2011) — A University of Florida review of research finds the polyphenol compound known as resveratrol found in red wine, grapes and other fruits may not prevent old age, but it might make it more tolerable. News stories have long touted resveratrol as a cure for various diseases and a preventative against aging.[105]

"We're all looking for an anti-aging cure in a pill, but it doesn't exist. But what does exist shows promise of lessening many of the scourges and infirmities of old age," said UF exercise psychologist Heather Hausenblas, one of the researchers involved in the study.
A comprehensive review of human clinical research on resveratrol has found it has "anti-aging, anti-carcinogenic, anti-inflammatory and antioxidant properties," but more research of its benefits is needed, she said.

The study, which appeared online this week in Molecular Nutrition and Food Research, examined results gleaned from thousands of laboratory studies with enzymes, cultured cells and laboratory animals. It was conducted by Hausenblas and fellow researchers James Smoliga of Marywood University and Joseph Baur of the University of Pennsylvania School of Medicine. Their review aimed to examine the current state of knowledge of the effects of resveratrol on humans and to use this information to guide much needed future human clinical trials.

Despite numerous clinical studies on resveratrol's tonic effects on animals, there is little evidence that it benefits human health. That's because "there haven't been many studies on humans," Hausenblas said.

However, she points out, for years many scientists have thought that a link between resveratrol and human health exists. The French people, for example, enjoy low levels of cardiovascular disease, even though their diets are rich in saturated fats and oils. Some researchers think the reason for this paradox lies in France's national drink -- red wine, which is the most important dietary source of resveratrol. The UF review, said Hausenblas, shows that the resveratrol has considerable potential to improve health and prevent chronic disease in humans. However, further research examining the long-term health effects of resveratrol is much needed.

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