All You Need to Know About Advanced Resveratrol

Introduction

Resveratrol (RES) is a phytoalexin produced by several plants. Phytoalexin is a natural substance that is toxic to fungi and is synthesized by a plant as a response to fungal infection.

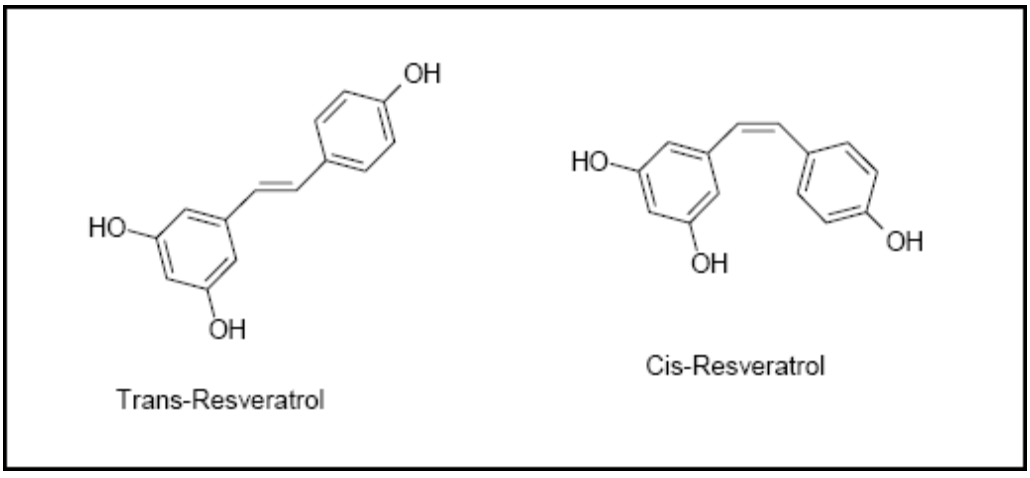
Resveratrol (3,4',5-trihydroxystilbene) is a stilbenol, a derivative of stilbene, and is

produced in plants with the help of the enzyme stilbene synthase. Stilbenes are polyphenolic compounds that act as cancer chemopreventitive agents[1].

It exists as two geometrical isomers: cis-(Z) and trans- (E). Trans-resveratrol is the

active form. Trans-resveratrol can undergo isomerization to the cis- form when heated or

exposed to UV irradiation. The two geometrical isomers of resveratrol are given below:



There had been no interest in RES and its applications in clinical science until 1992. In

that year, Siemann and Creasy announced the presence of trans-resveratrol in wine. This finding drew attention to the fact that RES was a component of traditional medicinal practice for those suffering from liver, skin, heart, and lipid disorders[2].

It is now realized that resveratrol offers significant health benefits and offers antiaging/ longevity properties to those who consume it. This is crucial, because we live in a world where we pass away from disease, not old age. In recent years, scientists have realized that there is a molecular basis to understand aging, and that certain things can be done to increase longevity and ward off diseases. One of the focal points of this research has been the sirtuin gene set that appears to be responsible for preserving the lives of cells. Scientists are therefore eager to develop a drug that mimics how sirtuins protect cells. Since this type of drug is not yet a reality, we need to look to other things for similar effects. Enter Resveratrol!

This powerful compound found in certain foods offers numerous health benefits for the promotion of longevity and works with the sirtuin enzymes as well. It has already been shown that RES extends the life of yeast, round worms, and mice[3]. These facts are important because all mammals share the sirtuin gene set.

Research shows that resveratrol (RES) exerts numerous health protective actions in *vitro*, *ex vivo* and in animal experiments. Some of these biological actions include protection against athersclerosis, antioxidant activity, modulation of hepatic apolipoprotein and lipid synthesis, inhibition of platelet aggregation, and the production of proatherogenic eicosanoids by human platelets and neutrophils[2].

There was an interesting study performed on short-lived seasonal fish (average lifespan of only thirteen weeks) to see what would occur if they were fed RES. RES was added to food in their early stages of life, and it wound up increasing their medium and maximum lifespan in a dose dependent manner[4]. RES also impedes the faltering of locomotor activity and mental performance associated with old age, and decreases the expression of neurofibrillary deterioration in the brain[4]. Taken together, all of this suggests that RES can potentially extend lifespan and halt the undesirable signs of old age.

Occurrence

Resveratrol is found in widely varying amounts in grapes (primarily the skins), raspberries, mulberries, blue berries, bilberries, cranberries, peanuts, scots pine, eastern white pine, and the roots and stalks of giant knotweed and Japanese knotweed (*Polygonum cuspidatum*), called hu zhang in China. This is extracted from the dry root and stem of Polygonum cuspidatum in China.

The amount of resveratrol in food substances varies greatly. One ounce of peanut contains 79.4 micro gram. Fresh grape skins contain about 50 – 100 micro grams of resveratrol per gram. Wines produced from muscadine grapes, both red and white, may contain more than 40 mg/L. France is known for this wine, and the incidence of coronary heart disease is relatively low in southern France despite high dietary intake of saturated fats. This is known as the **"**French Paradox**"**, which is attributed to the resveratrol found in red

wine. Trans-resveratrol can be produced by synthetic process in more than 98 % assay.

Figure 1 below illustrates the resveratrol content in certain beverages, and figure 2 portrays the resveratrol content of certain foods.

Figure 1: Resveratrol Content of Selected Wines[5,6,7]

Beverage	Resveratrol Content (mg) In a 5 Ounce Glass
White wines	0.01-.27
Rose wines	0.06-.53
Red wines	0.30-1.07
Red grape juice	0.17-1.30

Figure 2: Resveratrol Content of Selected Foods[8,9]

Food	Serving	Total Resveratrol Content (mg)
Red Grapes	160 g	0.24-1.25
Peanuts (boiled)	180 g	0.32-1.28

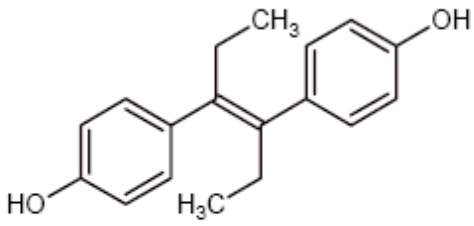
In humans resveratrol rapidly undergoes phase II conjugation, both glucuronidation and sulphation at multiple sites on the molecule. Little is known about the absorption and clearance of resveratrol, the identities of its metabolites, or its effect on the liver.

Resveratrol Is A Phytoestrogen

As we age, there is a natural decrease in estrogen and androgen levels that leads to poor functioning of tissues and organs. This decrease in hormones and hormonal stimulation usually favors cell proliferation instead of cell differentiation and senescence, which can therefore increase the chances of cancer. There is hope however, as hormone dependent tumors such as breast and prostate can be averted by daily consumption of selective estrogen receptor modulators (SERMs)[10]. SERMs are powerful compounds that exert estrogen agonism or antagonism, based on the cell type, expression of genes targeted by estrogen receptors (ERs) and other intracellular responses. Resveratrol is a polyphenol that acts as a

phytoestrogen with positive effects on estrogen receptor-expressing and nonexpressing

human tumors[10]. RES functions as a phytoestrogen because it has a similar structure to that of synthetic estrogen diethylstilbestrol.



synthetic estrogen diethylstilbestrol (4,4′-dihydroxy-*trans*-diethylstilbene)[10].

Diethylstilbesterol

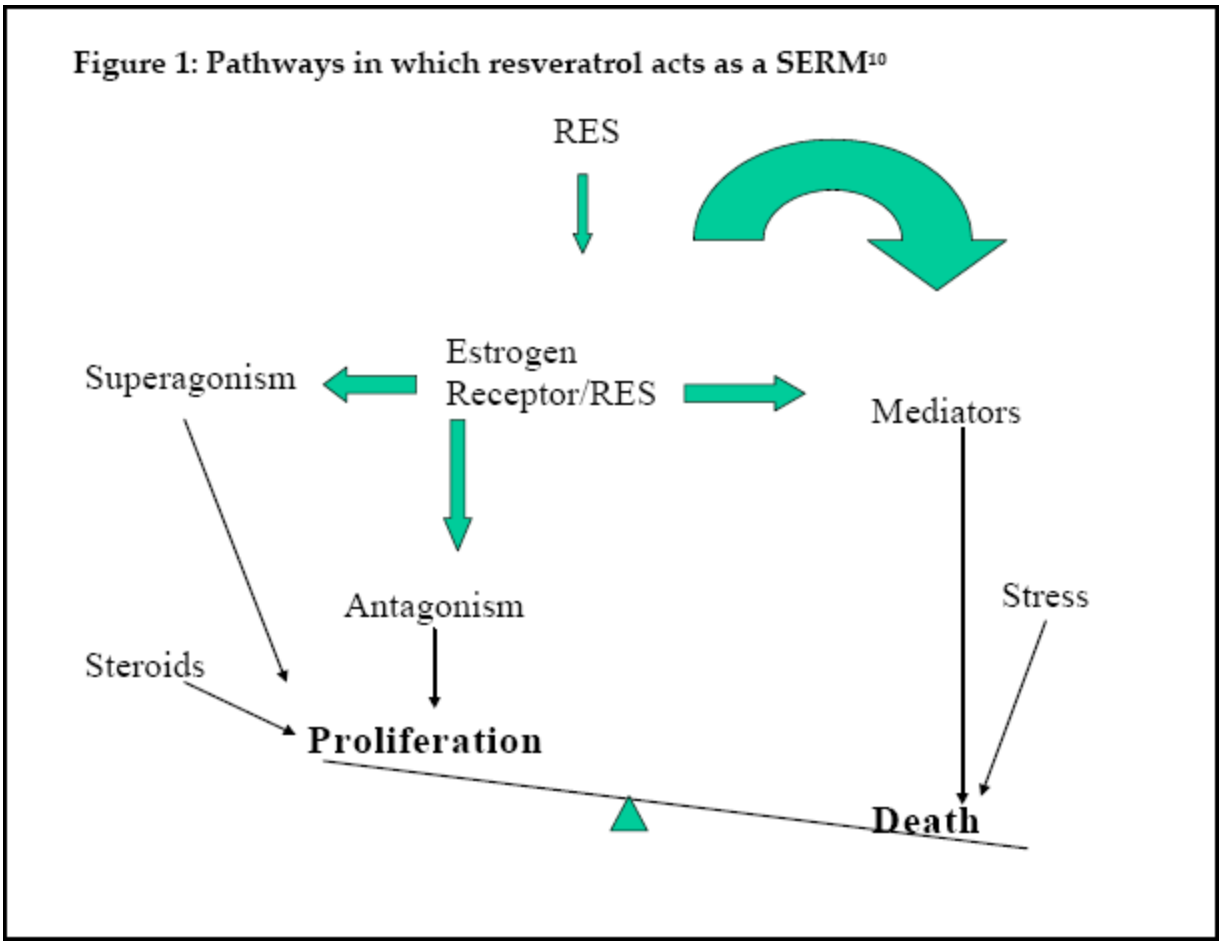
RES is a member of the estrogen type I class, meaning it binds to estrogen receptors with weaker affinity than estradiol, acting as a weak competitor. RES also has an

antiestrogen effect by generating parallel pathways that block estrogen-induced cellular

outcomes, such as proliferation, tumoral transformation and progression[10]. With estrogen

present, RES creates a mixed agonistic–antagonistic action in estrogen receptor-positive

breast cancer cells. It can therefore be said that RES functions as natural SERM[10]. The diagram below illustrates how RES can function as a natural SERM.



Cardiovascular Health Support

Resveratrol possesses interesting cardio protective characteristics. It turns out that the antioxidant and anti-platelet activities of RES allow it to function as a powerful heart protectant[11]. Researchers showed that RES prevented thromboxane B2 synthesis and thrombin-induced aggregation of human platelets *in vitro*[12]. One study reported that treating rat heart cells called fibroblasts with resveratrol prevented the actions of the hormone angiotensin II[13]. Angiotensin II is an important hormone that is produced in large quantities during hypertension and heart failure. The body does this because it is attempting to repair damage to the heart and to increase blood pressure. Unfortunately, the hormone usually causes cardiac fibroblast production to soar, and as a result these cells make extreme amounts

of collagen- a fibrous substance found in bone, tendons, ligaments and other connective tissues. In turn, the over secretion of collagen produces stiffening of the heart muscle and the heart has to exert much more effort to pump blood, all of which leads to even more damage of the myocardium (muscular tissue of the heart).

The cardioprotective action of RES is due large in part to its antioxidant activity. RES has been to shown to exert powerful inhibitory activity against superoxide anion and hydrogen peroxide production[14]. Furthermore, RES has hydroxyl-radical scavenging properties and it has been found to have glutathione-sparing activity[15]. One study that was performed on mice showed that RES treatment decreased the occurrence of ventricular dysrhythmias, including ventricular tachycardia and ventricular fibrillation[16]. RES was also shown to increase nitric oxide and decrease levels of lactate dehydrogenase in the blood. In this study, the cardioprotective properties of RES is due to its antioxidant activities, upregulation of nitric oxide synthesis, and protection against endothelial dysfunction[16].

RES also offers anti-inflammatory properties. A study found that RES inhibited anti-inflammatory mediator release from human airway epithelial cells[17]. It was reported that RES was more effective, though less powerful than glucocorticoids[17]. RES also inhibits IL-8 (interleukin-8) and GM-CSF (granulocyte-macrophage colony-stimulating factor)[17]. IL-8 is a huge player in the recruitment of inflammatory leukocytes, most notably neutrophils; and

GM-CSF is a cell survivor factor that prolongs the resident time of inflammatory cells. Some

of the applications of this study are that RES should be valuable in inflammatory diseases

where glucocorticosteroids have proved to be unsuccessful, such as COPD, steroid-resistant

asthma, and arthritis.

It is also interesting to consider whether the estrogenic properties of RES contribute to its beneficial cardiovascular effects. Orally adminstered estrogens produce similar results in regards to cardio protective effects.

Immune Support

Resveratrol interferes with all three stages of carcinogenesis – initiation, promotion and progression. Experiments in cell cultures of varied type in vitro imply many mechanisms in pharmacological activity of resveratrol. These mechanisms include

modulation of the transcription factor NF-kB, inhibition of the cytochrome P450 isoenzyme

CYP1A1, alterations in androgenic actions and expression and activity of COX enzymes. 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. In some lineages of cancer cell culture, resveratrol has been shown to induce apoptosis, which means it can kill cancer cells. Resveratrol is under extensive investigation as a cancer chemopreventive agent. Indeed, the Chemoprevention database reports six studies showing that small doses of dietary resveratrol can reduce colon carcinogenesis in rats and mice[11].

After entering the cell via either a receptor-mediated pathway or direct infusion

through the plasma membrane, by affecting the normal dynamics of DNA, Resveratrol triggers the p53 protective pathway. As a result, the GADD45 (implicated in DNA repair)

and p21 WAF1 will be induced, both of which will affect cdc2 (cycline-dependent kinase-2).

Cdc2 is essential for cell cycle progression through the G2/M phase and its diminished activity results in cell cycle arrest. Alternatively, Resveratrol, via the p53/p21 pathway can affect specific cyclins and cyclin-dependent kinases of the G1 and S phases (CDK2, 4, 6 and cyclins D, E) of the cell cycle. This will result in increased phosphorylation of the Rb protein, which causes its association with and inhibition of E2F transcriptional activity. The cells will subsequently become arrested at the G1S transition phase[11].

It was shown that resveratrol can protect rodents from mammary cancer (breast cancer)[18]. Research shows that resveratrol exerts this protective effect by creating changes in cell creation and death in terminal ductal structures of the mammary gland[18]. Resveratrol exerts antioxidant and anti-inflammatory effects, and can potentially modulate cell death as well as cell cycle and estrogen receptor function in breast cancer cell lines[19].

It turns out that resveratrol can block the steps of carcinogenesis including tumor initiation, promotion and progression[14]. Its mechanisms of actions include its ability to profoundly inhibit nitric oxide generation in activated macrophages and to reduce the amount of iNOS(Induced Nitric Oxide Synthase)[14]. Furthermore, studies show that RES inhibits the initiation of NF kappa B induced by lipopolysaccharide[14]. The ability of RES to act as a reactive oxygen species scavenger (free radical scavenger) leads to a quelling of tumor formation[14]. Another possible mechanism is a blockade of cancer via mitotic signal transduction blockage[14].

RES exhibits many interesting biological properties. It has been shown that RES is a non-competitive inhibitor of cyclooxygenase activity of COX-1in a concentration dependent manner[20]. Moreover, an inhibition of COX-1 hydroperoxidase and COX-2 hydroperoxidase was shown[21]. Decreased prostaglandin synthesis was exhibited via direct inhibition of COX-

1, and it was shown that the oedema-suppressing activity of resveratrol is better than indomethacin or phenylbutazone[21]. There is also evidence that RES inhibits the activation of cytochrome P-45022.

Other research shows that RES can prevent the growth of leukemia cells in culture23. Mechanisms for this attribute include induction of leukemia cell differentiation, apoptosis, and cell cycle arrest at S-phase; and inhibition of DNA synthesis by blocking ribonucleotide reductase or DNA polymerase.

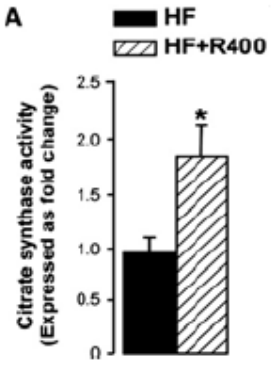
Some studies show that resveratrol induces cell death via a p53 independent mechanism involving the mitochondrial apoptotic pathway[24]. It was shown that resveratrol has the ability to abrogate EGF- and tissue-type plasminogen activator (TPA)-induced ERK 1/2 activation by blocking PKC _activation, which induced apoptosis in androgenindependent prostate cancer cells[125]. Resveratrol has also been shown to inhibit TNF induced activation of mitogen-activated protein kinase and c-Jun N-terminal kinase[26]. The inhibition of MAPK pathways allows RES to potentially induce cell death and sensitize tumor cells to drug mediated apoptosis.

These findings demonstrate that Resveratrol (RSV) is capable of sensitizing drugresistant tumor cells to the apoptotic effects of chemotheraputic drugs. Resveratrol, either via a receptor-mediated pathway or by direct infusion through the plasma membrane, interferes with type I and type II apoptosis signaling pathways[11].

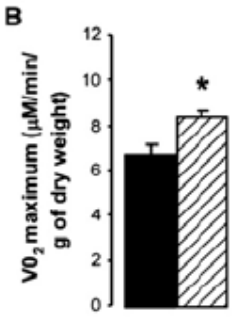
Sports Nutrition

Mitochondria are the chief energy sources of the cell that change nutrients into energy through cellular respiration. Mice fed RES had bigger and denser mitochondria amassed between adjacent myofibrils in their nonoxidative fibers[27]. Growth of mitochondria was confirmed by increased mitochondrial size and mtDNA (mitochondrial DNA) content[27]. The max VO2 rate (the maximum capacity to transport and utilize oxygen during incremental exercise) was much higher in the nonoxidative muscle fibers of mice given RES, which means there was an increased oxidative capacity. All of the aforementioned factors greatly imply that RES increases the ratio of oxidative to nonoxidative muscle fibers[27]. Since RES has the possibility to change muscle fibers to a dominance of oxidative type 1 fibers, it should make sense that this would improve endurance due to the fact that these type of fibers have a higher resistance to muscle fatigue[27]. Mice given RES were shown to outrun the control group by almost twice the distance[27]. Therefore it can be said that RES greatly increases the animal's resistance to muscular fatigue due to increased mitochondrial activation and a conversion of muscle to slow twitch fibers[27]. These results are exemplified below.

Figure 2: Increased Oxidative Capacity and Endurance in Mice Given RES[27]

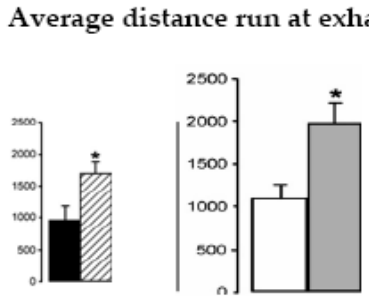


A) Activity of the citrate synthase, as measured in homogenates of gastrocnemius fibers isolated from RSV-treated (HF + R400) and nontreated HF-fed mice. N = 3 animals/group, and values are expressed relative to control.



B) Maximum VO_2 consumption in isolated gastrocnemius fibers measured ex vivo. N = 5 animals/group

C)



(C) The effect of RSV on endurance, as measured by an exercise test. Individual animal performances as well as the average distance run until exhaustion are presented for animals treated with HF or HF + R400 (top) or chow

diet (C) or chow diet and RSV at 400 mpk (C + R400) (bottom). N = 8 animals/group. * = $P < 0.05$. Values represent means ± SEM.

Antiviral effects

Resveratrol seems to increase the potency of some antiretroviral drugs against HIV *in vitro*. Infection by herpes simplex virus ordinarily activates the cell protein Nuclear Factor

(NF-kB). Studies in Vero cells from Northeastern Ohio Universities College of Medicine

indicate 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.

RES has some interesting anti-influenza properties28. An in vitro study found that

RES profoundly inhibited influenza virus replication in cell cultures[28]. The best effects were witnessed when RES was given three hours after the virus. In the mice group it was shown that RES given after influenza infection increased survival by 40% compared to placebo. After six days with the virus, the mice treated with RES had 98% lower pulmonary viral titers

in their lung as compared to the placebo. The proposed mechanism of action is that RES inhibits a cellular function instead of a viral function.

RES has also been shown to exhibit activity against herpes simplex virus types I and II[29]. The RES disturbs a crucial early event in the viral reproduction cycle.

Brain Health

As we age, our mental acuities and faculties usually decline. More often than not, this process begins with short-term memory loss and difficulty learning new material. What starts as simple forgetfulness can gradually become much worse. Luckily, all hope is not lost because there are certain things one can do to delay or even prevent these occurrences. One of such things we have on our side in the fight against age related diseases is RES.
RES has the special ability to modulate the mechanisms of neurological disease such as strokes, ischemia, Alzheimer's, and Huntington□s diseases[30]. It seems that this occurs through the SIRT1 protein. 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, showing that resveratrol may possess therapeutic value to neuronal deterioration[30]. SIRT1induction by a sirtuin activator such as RES is neuroprotective in numerous ways. It can promote the nonamyloidogenic cleavage of the amyloid precursor protein, enhance clearance of amyloid betapeptides, and reduce neuronal injury through possible inhibition of neuroinflammatory signaling pathways[31]. Moreover, increased SIRT1 action can modify neuronal transcription profiles to augment anti-stress and anti-apoptotic gene activities[31].

A study found that mice with ischemia in the brain had improved blood flow from one dose of resveratrol[32]. Results of the study acknowledged that RES administration led to increase blood flow in the brain and protected the mice from neuron loss due to ischemia. This neuroprotective effect offered by RES comes from its stimulation of nitric oxide formation or release, which henceforth increases cerebral blood flow[32]. When blood clots or an artery ruptures in the brain a stroke occurs there is a disruption of blood flow to a part of the brain. As a result, the person is usually left with disabilities. Stroke is the leading cause of disability and the third leading cause of death in Europe and the US[33].

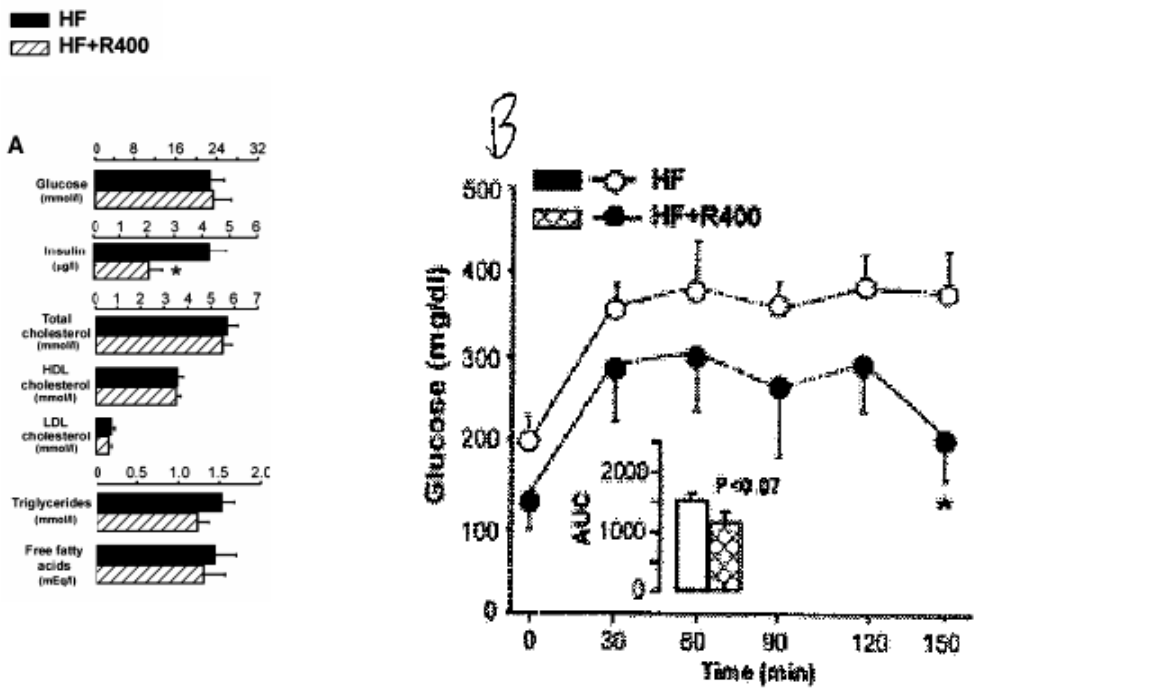
The use of RES after brain injury has potential to reduce oxidative stress and lesion volume[34]. After mice were induced with traumatic brain injury, there was a significant

increase in malondialdehyde (MDA), nitric oxide (NO), and xanthine oxidase (XO) and a decrease in glutathione (GSH)[34]. Upon treatment with RES, the mice had large decreases in MDA, NO, and XO and an increase in GSH compared to controls[34]. Furthermore, there was a decrease in tissue lesion area upon treatment with RES[34].

Metabolic Health

RES can also play a role in metabolic disease prevention. Metabolic diseases include epidemics such as obesity and diabetes. A study showed that when RES was given orally to mice it activated a protein in the Sirtuin family, which henceforth activated another protein for mitochondrial function[35]. This same study demonstrated that fasting insulin levels were significantly decreased after RES, suggesting an insulin sensitization. Increased insulin sensitivity is important because obesity is directly correlated with poor insulin sensitivity. Furthermore, the study proved that RES increases the association of the Sirt1 enzyme with energy expenditure, which therefore led to a reduction in weight gain. The following set of graphs illustrates the results from this study.

Figure 3: RES Increases Insulin Sensitivity and the Association of the Sirt1 gene with Energy Expenditure[35]



(A) Average glucose, insulin, and lipid levels in HF-fed C57Bl/6J mice treated with or without RES (HF + R400) for 16 weeks. N = 8–10 animals/group.

(B) Eight week-old male KKAy mice were treated with HF diet or HF diet plus RSV at a dose of 400 mpk (HF+R400) for 8 weeks. N = 5 animals/group. OGTT was performed, and the AUCs are shown in the inset bar graph (B). Values represent means ± SEM. * = P < 0.05.

Another study similar to the above had three groups of mice, one group fed a high calorie diet, a second group with a normal diet, and the third group was given RES along with a high calorie diet. The results showed that when the high calorie fed mice reached old age (114 weeks), greater than 50% had died compared to less than 33% of the high calorie mice receiving resveratrol[36]. Results also showed that mice receiving RES had lower plasma levels of insulin, glucose and insulin-like growth factor (IGF) 1– all of which are markers for the onset of diabetes in humans if elevated. After the mice died, researchers examined their hearts and found that inflammation and deterioration were incredibly less for the RES supplemented group and normal diet group as compared to the high calorie only mice. It

turns out that the mechanism of these biological effects is connected to the activation of the enzyme known as SIRT1[36]. This mechanism was proven by the fact that levels of PGC-1alpha were three-fold lower in the resveratrol group than in the high calorie group, which is what is expected to happen when SIRT1 is being activated by RES. Research has shown that calorie restrictions (CR) of at least 30-40% lengthens productive lifespan in numerous animals. This incredible effect is due to the activation of the SIRT1 enzyme. However, living a life with calorie restrictions is very arduous and in some cases burdensome. Therefore, researchers have looked upon other ways to activate the SIRT1enzyme. RES is one such compound that can activate the SIRT1 and mimic the effects of calorie restriction[36]. Basically, when RES enters cells, the enzyme SIRT1 is activated. This activation of SIRT1 creates new mitochondria in muscle and other tissues. As a result, the new mitochondria increase basal metabolic rate, which therefore mimics the effects of a CR diet. Mitochondria burn sugar to release energy. However, they are similar to coal fired power plants in that they pollute. The mitochondria belch chemicals known as free radicals which damage DNA, among other things. Eventually, the radicals destroy the mitochondria, thereby creating less efficient mitochondria that spew even more free radicals. This cascade is one of the major causes of aging. Fortunately, RES has the ability to create new mitochondria. This is important because new mitochondria are more efficient and produce less free radicals.

There is a very severe microvascular ailment known as diabetic nephropathy, which is one of the primary causes of the final stage of renal disease. Research has shown that oxidative stress is a major cause of this ailment. A study performed on diabetic mice treated with RES showed that the RES greatly eased renal distress and oxidative stress. This protective effect of RES is most likely due to its antioxidant properties[2,11,16,19].

Skin Health

Research has shown that RES applied topically can inhibit the expression of a cancer causing protein that is caused by UVB exposure (sun)[37]. This is of great significance because skin cancer is the most commonly diagnosed ailment in the United States. One study examined the effect that topically applied RES would have on UVB treated mice. The results showed that RES treatment profoundly decreased UVB exposure -mediated up-regulation in the mRNA levels and protein expression of Survivin[37]. Survivin is involved in the regulation

of cell division, and it has a unique structure that is part of the apoptosis inhibitors protein family. During most cases of human cancer Survivin becomes overexpressed, and it is therefore a good therapeutic target for innovative anticancer therapies. It was also shown that RES greatly prevented UVB related increases in skin thickness and edema, epidermal

cyclooxygenase (COX-2); ornithine decarboxylase (ODC) enzyme and protein levels; and

protein levels of proliferating cell nuclear antigen (PCNA), all of which are known warning signs of tumor production[37]. Moreover, RES created a UVB related increase in p53 protein levels and prevented UVB related increases in cell cycle promoting signs such as the initiation of cell division (cancer, simply defined, is uncontrolled cell division). Resveratrol also has the ability to inhibit *Propionibacterium acnes* growth[38]. This property could be useful to people who would like to get rid of their acne without resorting to harsh drugs or chemicals.

Many skin disease conditions have a twofold cause: microbes and the inflammatory response[39]. For instance, *Staphylococcus aureus* infection of hair causes folliculitis, which induces white blemishes bordered by small red areas. Other problems include *tinea pedis* ('athlete's foot'), *tinea cruris* ('jock itch') and *tinea corporsis* (ringworm), all of which cause redness and itching. In order to treat such ailments, the use of antimicrobial and antiinflammatory
agents needs to be used. When applied topically in sufficient quantities, RES has the ability to prevent the growth of fungal infections known as dermatophytosis[39]. RES has many possible applications in the cosmeceutical industry. Because it possesses certain antifungal properties, RES may have use in antifungal creams and ointments. Since it was also shown that RES provides protection against certain types of bacteria causing acne, it may have use in preparations used to rid one's body of acne. As mentioned, the fact that RES can offer protection from UVB related skin problems gives the applications for use in sunscreens, sunburn creams with aloe vera, and other natural emollients.

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