Growing Evidence Links Resveratrol to Extended Life Span

By Laurie Barclay, MD

The Life Extension Foundation has a 27-year history of introducing cutting-edge therapies for extending life and preventing disease. In 2003, we reported on findings that resveratrol (a substance found in red grapes and other plants) extended the life span of certain cells by as much as 70%.

Since our initial report, resveratrol has continued to demonstrate extraordinary potential in prolonging life. In numerous studies—including those at BioMarker Pharmaceuticals, a Life Extension-sponsored research institution—resveratrol has demonstrated effects that mimic those of caloric restriction, the best-documented anti-aging strategy to date. In all animals in which it has been tested, caloric restriction—the practice of restricting calorie intake while maintaining good nutritional status—improves multiple aspects of age-related decline. Caloric restriction does this, in part, by producing changes in gene expression that are associated with long life and a slowing of the aging process.

Resveratrol is also gaining growing recognition for its promise in fighting age-related diseases ranging from dementia to diabetes. For example, the National Institutes of Health is currently sponsoring a clinical trial investigating resveratrol’s ability to fight colon cancer.

In this article, we bring our readers up to date on the latest clinical research on resveratrol, and why leading researchers believe this remarkable nutrient may hold the key to living a longer, more vibrant, disease-free life. > > >
Resveratrol and Caloric Restriction

To date, the most reliable, best-researched way to extend life span is through the practice of caloric restriction, which involves reducing calorie intake while simultaneously maintaining good nutritional status.

In numerous studies, restricting calorie intake in laboratory animals has been shown to prolong their life span by as much as 60%. While scientists have not yet determined whether caloric restriction extends life span in humans, the preliminary evidence is very promising. In humans, consuming a low-calorie diet is associated with several possible markers of greater longevity, such as lower insulin levels and reduced body temperatures, along with less of the chromosomal damage that typically accompanies aging.

Furthermore, people who consume a low-calorie diet may be less prone to diseases associated with being overweight or obese, such as metabolic syndrome, diabetes, cancer, and atherosclerosis.

Although caloric restriction may be effective in promoting longevity, the problem is that most adults find this stringent lifestyle strategy to be impractical. As a result, scientists have sought to uncover the precise mechanisms by which caloric restriction promotes longevity, in order to help people capture its life-extending benefits through more practical means.

Resveratrol Offsets Perils of a High-Calorie Diet

Remarkable new research suggests that it may be possible to achieve the life-extending benefits of caloric restriction using the readily available, plant-derived compound known as resveratrol. Resveratrol and caloric restriction appear to work via similar mechanisms to promote health and longevity in numerous animal species.

In an interview, a leading resveratrol researcher, Dr. Xi Zhao-Wilson of BioMarker Pharmaceuticals, told Life Extension, "There has been a great deal of attention focused on resveratrol in the past few years, following a study showing that resveratrol activates molecular pathways involved in life-span extension, now demonstrated in yeast, worms, flies, fish, and mice, and which possibly bear a relationship to mechanisms underlying caloric restriction."

This heightened interest in resveratrol has produced several recent breakthroughs. In a landmark study, Harvard University scientists showed that resveratrol could prolong survival by regulating a gene associated with aging that is present in all life forms. They demonstrated that while middle-aged mice fed a high-calorie diet suffered the ravages of obesity—including metabolic changes resembling diabetes, liver and heart damage, and premature death—mice that were fed resveratrol in addition to the high-calorie diet actually exhibited beneficial changes in their physiology, resembling those of mice fed a standard diet.

Among the life-prolonging benefits of resveratrol supplementation demonstrated in the study were:

- increased insulin sensitivity
- lower blood sugar
- enhanced mitochondrial energy production
- improved motor function.

While mice on the non-supplemented high-calorie diet developed enlarged, fatty livers, resveratrol supplementation prevented these changes. Similarly, heart disease and evidence of atherosclerosis were seen in mice fed the high-calorie diet, but not in those that were also given resveratrol. Resveratrol significantly increased survival, reducing the risk of death from the high-calorie diet by 31%.

Together, these findings offer powerful evidence that resveratrol protected the animals from the harmful effects of a high-calorie diet.

Resveratrol's positive impacts on insulin sensitivity and survival were apparent after only six months of treatment. Resveratrol also improved the animals' quality of life, as reflected in their physical abilities. On a test of balance and coordination, the resveratrol-fed mice on the high-calorie diet steadily improved as they aged. The obese resveratrol-supplemented animals experienced all of these benefits without a significant reduction in body weight.

"These data demonstrate that resveratrol can alleviate the negative impact of a high-calorie diet on overall health and life span," the Harvard scientists concluded. "The ability of resveratrol to prevent the deleterious effects of excess caloric intake and modulate known longevity pathways suggests that resveratrol and molecules with similar properties might be valuable tools in the search for key regulators of energy balance, health, and longevity."
Mechanisms by Which Resveratrol May Extend Life

Today, scientists around the world are studying resveratrol to determine how it helps fight aging and prolong life span. Current evidence suggests that resveratrol exerts antioxidant effects, boosts energy production, and favorably alters patterns of gene expression. Oxidative stress is implicated in numerous disease processes and in aging itself. Resveratrol demonstrates powerful antioxidant capabilities, with profound implications for human health. Scientists report that resveratrol inhibits the oxidation of dangerous low-density lipoprotein (LDL) and scavenges harmful hydroxyl radicals. Resveratrol also helps preserve levels of glutathione, one of the body's most essential antioxidants. According to prominent resveratrol investigator Dr. Milos Sovak, “There is no question that resveratrol is one of the best free-radical scavengers and that it has many effects whose ramifications might affect not only longevity but also general health.”

Resveratrol stimulates energy production in the cellular powerhouse known as the mitochondria. Diminished mitochondrial energy production is associated with reduced longevity. By enhancing the production of life-sustaining energy, resveratrol may help protect against metabolic disease and obesity, thereby improving health and prolonging survival in animals.

Growing evidence indicates that resveratrol influences many genetic pathways, which may underlie its ability to lengthen life. In the recent Harvard study, investigators noted that a high-calorie diet produced numerous changes in gene expression. However, supplemental resveratrol opposed the effects of this high-calorie diet in 144 of 153 significantly altered genetic pathways. Moreover, resveratrol’s effects were dose dependent, with larger amounts yielding greater effects, leading the investigators to suggest that resveratrol may offer “new approaches for treating obesity-related disorders and diseases of aging.”

Some of the genetic pathways influenced by resveratrol are similarly affected by caloric restriction. For example, caloric restriction is associated with long-term activation of AMP-activated kinase (AMPK), a metabolic enzyme promoting insulin sensitivity and fatty-acid oxidation. Resveratrol likewise increases AMPK activity, which is associated with life-span extension.

Scientists believe that caloric restriction increases life span in part through its effects on the sirtuin genes. Present in all life forms, sirtuin genes are associated with aging and longevity. Resveratrol may confer benefits similar to those of caloric restriction by influencing the sirtuin gene known as SIRT2. In the Harvard study, resveratrol helped counteract changes in SIRT2 expression induced by a high-calorie diet.

“The genes and pathways affected by resveratrol or by caloric restriction are related to activation of sirtuins, a class of histone deacetylase enzymes (HDACs) involved in cell death and life-span regulation,” Dr. Zhao-Wilson told Life Extension. “Based on the large body of evidence, the resveratrol/sirtuin activators have become the focus of pharmaceutical drug discovery efforts now targeting HDACs.”

Researchers believe that compounds like resveratrol that either activate or inhibit sirtuin activity may have therapeutic potential for a broad array of human diseases, including cancer, diabetes, heart failure, and neurodegenerative conditions such as Alzheimer’s and Huntington’s disease.

Resveratrol, a health-promoting compound found in grapes, has been shown to increase life span in several animal species. In a recent Harvard study, mice that consumed a high-calorie diet known to shorten life lived longer when they also consumed resveratrol. These mice also had better coordination, less heart and liver damage, and better insulin sensitivity than overweight mice that were not fed resveratrol.

Scientists have proposed that resveratrol in red wine may help explain the “French paradox”—the fact that cardiovascular disease rates in France are relatively low, despite a diet traditionally high in fat. Because widespread use of pesticides has diminished the amount of resveratrol contained in grapes and red wine, supplemental resveratrol may be the best way to ensure optimal intake.

Laboratory and animal studies suggest that resveratrol may have therapeutic potential for cardiovascular disease, cancer, inflammatory arthritis, Alzheimer’s disease, and other neurodegenerative conditions. Clinical trials studying resveratrol’s effects on cancer and diabetes are also underway.

Resveratrol may enhance health and support longevity via several mechanisms. These include its potent antioxidant effects, ability to enhance cellular energy production, and ability to influence patterns of gene expression in a manner similar to caloric restriction (the best-documented method of extending life span in animals).

Because resveratrol exerts protective effects through a variety of mechanisms, it may be a useful supplement for healthy adults wishing to reduce their risk of chronic disease and live a long and healthy life. Studies to date suggest that resveratrol is safe and nontoxic.
DOES RESVERATROL EXPLAIN THE "FRENCH PARADOX"?

Although French cuisine is world renowned for its rich sauces, gourmet cheeses, and fine wines, the French enjoy a relatively low incidence of coronary heart disease. This apparent anomaly has led scientists to wonder what dietary or lifestyle factors might account for the so-called "French paradox." Studies suggest that resveratrol, a constituent of red wine, may help protect the French from the adverse health effects of their traditionally rich diet, while also protecting the liver against the toxic effects of alcohol.

Technically, resveratrol is a chemical known as trans-3,5,4'-trihydroxystilbene. Produced by grapes, berries, peanuts, and certain other plants in response to stressful conditions, resveratrol and related biochemicals known as phytoalexins function as natural antibiotics, protecting plants against attack by pathogens.

Life Extension recently discussed the French paradox with Milos Sovak, MD, founder of Biophysica, Inc., a California-based biomedical and pharmaceutical research company. According to Dr. Sovak, the hearty wines of southern France, produced from the Vitis vinifera vine, used to produce up to 30 mg of resveratrol per liter. This is no longer the case. "The French who consumed up to 1 liter/day of wines originating in the South have had convincingly fewer cardiovascular afflictions than their brethren to the North," says Dr. Sovak. "That situation is rapidly changing. With the advent of pesticides, plants are now producing almost no phytoalexins and it is rare today to find more than 2-3 mg of resveratrol per liter. That alone should be sufficient reason for supplementation with this compound regardless of the many studies—some reliable, some not—that show various advantages to red wine."

Dr. Sovak notes that while grapes may no longer be a reliable source of resveratrol, this compound can be extracted from a shrub-like plant known as Polygonum cuspidatum, which originated in Japan and China but has since migrated to the United States and Europe. This plant contains high concentrations of resveratrol, up to 3-4%.

Specific Health Applications of Resveratrol

While resveratrol's impact on cardiovascular disease has undergone the most scrutiny to date, researchers are also exploring its effects on a broad array of diseases, including cancer, arthritis, diabetes, and Alzheimer's.

CARDIOVASCULAR HEALTH

One of resveratrol's most studied applications involves the prevention of cardiovascular disease. "The cardioprotective effects of resveratrol have been studied for years, based largely on the association of wine consumption with reduced risk of coronary heart disease," notes Dr. Zhao-Wilson.

This plant-derived compound appears to act through several mechanisms to protect the cardiovascular system. Resveratrol may inhibit platelets from clumping together, thus reducing the risk of deadly blood clots that can lead to heart attack and stroke. Furthermore, resveratrol helps improve blood flow by exerting beneficial effects on the linings of small blood vessels, known as the endothelium. This is a critical finding, since endothelial dysfunction is believed to underlie the progression of atherosclerosis.

In addition to its cardioprotective effects, resveratrol exhibits a range of anti-cancer properties. In laboratory cell studies, resveratrol has been found to inhibit the growth of numerous types of cancer, including leukemias, multiple myeloma, melanoma, and cancers of the breast, ovaries, prostate, stomach, colon, liver, pancreas, thyroid, uterine cervix, and head and neck.

Resveratrol suppresses tumor growth by increasing or decreasing the production of various enzymes and molecules that regulate cellular reproduction and blood supply to the tumor. Through these mechanisms, resveratrol may enhance the anti-cancer effects of chemotherapeutic drugs and radiation. With its potent antioxidant capabilities, resveratrol may even protect healthy tissues from damage induced by chemotherapy. Since chemotherapy harms both healthy and cancerous tissues, this finding may have important applications in helping cancer patients tolerate its effects.

Clinical trials in humans have shown that resveratrol has an excellent safety profile, and structural modifications of resveratrol with improved bioavailability are being studied as potential anti-cancer treatments.
Resveratrol shows promise in protecting the brain and nervous system against disorders associated with aging and genetic factors. In laboratory studies, resveratrol’s antioxidant effect has been shown to protect against nerve cell damage caused by beta-amyloid peptide, which accumulates in the brains of Alzheimer’s sufferers. This has led several research teams to propose that resveratrol may be a useful treatment for Alzheimer’s disease.

According to a recent report, resveratrol demonstrated a protective effect against Huntington’s disease in animal models. Huntington’s is a genetic disease associated with impaired motor skills and reduced mental abilities.

Additionally, grape seed extract appears to protect rat brain cells and maintain the overall viability of the nervous system. Grape seed exerts these effects by modulating proteins implicated in cognitive disorders.

**DIABETES**

Resveratrol may offer benefits in preventing or managing conditions associated with high blood sugar, such as metabolic syndrome or diabetes. Sirtris Pharmaceuticals, a company founded by Dr. David Sinclair, leader of the Harvard resveratrol study, is conducting a clinical trial to evaluate resveratrol’s effects in controlling blood sugar in patients with diabetes.

**EXTENDING HUMAN LIFE SPAN**

Based on his study of experimental life-span extension in mice, Dr. Richard A. Miller of the University of Michigan suggests that resveratrol may extend the human life span.

BioMarker Pharmaceuticals was recently recognized by the *Wall Street Journal* as a pioneer in the field of resveratrol research. Based in San Jose, California, BioMarker is an innovative research institute dedicated to the study of lengthening and enhancing the quality of human life.

With support from the Life Extension Foundation, BioMarker is currently studying how resveratrol affects specific genes and cellular pathways to increase longevity. Leading these research efforts is Dr. Xi Zhao-Wilson, BioMarker’s chief scientist.

"BioMarker as a company is committed to conducting high-quality scientific research to support products that will help people live longer, healthier lives," Dr. Zhao-Wilson told *Life Extension*. "The science in this area is young, but we are witnessing an explosion of information about how genes, proteins, specific molecular pathways, and normal and disease states are influenced by natural compounds like resveratrol. We believe this is just the tip of the iceberg, and that there will be tremendous advances in understanding the mechanisms underlying aging, and how these relate to diseases or maintenance of a disease-preventive state."

Under Dr. Zhao-Wilson’s direction, BioMarker was one of the first companies to conduct a high-quality, controlled, single-dose study of resveratrol and grape extract in a large group of mice. BioMarker scientists compared mice given resveratrol and grape extract with a group of calorie-restricted mice. Using techniques of genetic analysis developed in collaboration with other research groups, the scientists then determined similarities and differences in gene expression in the groups of mice. Preliminary data analysis suggests that resveratrol’s benefits overlap with those of caloric restriction. Much like caloric restriction, resveratrol appears to offer tremendous promise in extending life span and improving quality of life.

According to Dr. Zhao-Wilson, "Our focus as a company is to pursue known and novel compounds . . . to understand the mechanisms underlying the disease-preventive and life-span-extending effects of interventions that mimic the beneficial effects of caloric restriction. Resveratrol . . . has been very helpful in elucidating some aspects of the total caloric-restriction picture."

**INFLAMMATION AND ARTHRITIS**

A common culprit in heart disease, cancer, and arthritis is chronic inflammation, mediated by naturally produced compounds in the body known as prostaglandins and cytokines. By blocking the activity of such inflammatory compounds, resveratrol may have therapeutic applications for all of these conditions.

In a recently published study, scientists reported that resveratrol shows promise as a potential therapy for arthritis. When administered to animals with experimentally induced inflammatory arthritis, resveratrol protected cartilage against inflammatory changes related to the disease.

"Resveratrol is currently the subject of National Institutes of Health-sponsored clinical studies to evaluate its chemoprevention (cancer-preventive) effects," according to Dr. Zhao-Wilson. An ongoing clinical trial at the University of California is studying resveratrol in patients with colon cancer.

BioMarker Pharmaceuticals: Pioneering Life Extension Research

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Dr. Miller speculates that with effects similar to those of caloric restriction, resveratrol could extend human longevity to about 112 or even 140 years of healthy life.

Practical Considerations for Optimal Supplementation

While plentiful data attest to resveratrol's potential benefits for health and longevity, certain practical concerns must be addressed to obtain its optimal effects as a dietary supplement. These include resveratrol's stability, shelf life, dosage, and the variability of different available preparations. Even today, much remains to be learned about the pharmacokinetics of resveratrol—that is, how it is absorbed, utilized, broken down, and excreted in humans.

BIOAVAILABILITY

Laboratory and animal studies clearly show that resveratrol and its derivatives are biologically active. However, Dr. Zhao-Wilson notes that there are "significant issues related to what is currently known about resveratrol's bioavailability—it appears to be rapidly metabolized in humans." Dr. Sovak agrees, commenting, "One problem with resveratrol is that we do not know that much about its resorption and bioavailability in humans, but as expected, the compound is rapidly metabolized and excreted."

Scientists are exploring ways to optimize resveratrol's pharmacokinetics. For example, in the Czech Republic, where resveratrol has been approved as a nutritional supplement, Dr. Sovak and his colleagues conducted a pilot study in humans comparing high-purity, pharmaceutical-grade resveratrol to resveratrol glycon, the natural form of resveratrol extracted from the Polygonum plant. Of the two preparations, resveratrol glycon was found to be more easily absorbed in the body and to have better pharmacokinetics.

Another method under investigation to improve resveratrol's bioavailability is administering it concomitantly with plant-derived flavonoids. Numerous studies suggest that the bioflavonoid quercetin slows the inactivation of resveratrol, thus improving its bioavailability. A novel type of quercetin, quercetin chalcone, demonstrates superior absorption and solubility, and may thus be the optimal form of this bioflavonoid.

STABILITY

Previously, scientists were concerned that the clinical usefulness of certain resveratrol-encapsulated preparations could be limited by poor stability, limited shelf life, or exposure to light and air. However, recent stability studies by Dr. Sovak and his colleagues at the Czechoslovak company Interpharma Praha have demonstrated these concerns to be unjustified. Resveratrol is generally stable for at least two years and does not require special packaging or storage.

PURITY

Not all resveratrol preparations are of equal quality. "As for the variability of different available preparations, this is always an issue with respect to manufacturing and quality control associated with dietary supplements in general," says Dr. Zhao-Wilson. "It is 'buyer beware,' and one must find a high-quality source with a vested interest in providing consumers with the best available products and scientific evidence to back them up."

Dr. Sovak agrees, and recommends only pure forms of resveratrol for study and consumption. Interpharma Praha has developed technology to produce high-purity resveratrol and resveratrol glycon according to GMP (good manufacturing practice) standards.

DOSAGE

In addition to exploring resveratrol's many potential health applications, researchers are also trying to determine the optimal dose needed to capture its benefits. "There have been insufficient studies to date in humans to address issues related to optimal dose," notes Dr. Zhao-Wilson. "Extrapolation of optimal dose from animal studies to humans is always more of an art than a science, and the appropriate studies still need to be done. Nevertheless, reasonable assumptions can be made, and there is even evidence that low doses may be effective for certain conditions."
Many commercially available supplements provide 20 mg of resveratrol daily. The rationale behind this dosage is that prior to the widespread use of pesticides, French red wine contained approximately 20 mg of resveratrol per liter, and those drinking about a liter daily appeared to derive the cardio-protective benefit associated with the French paradox. Now that the resveratrol content in red wine has decreased to 90 micrograms per fluid ounce,

a 20-mg (20,000-mcg) resveratrol supplement contains approximately 220 times the amount of resveratrol in one fluid ounce of red wine, or about 41 times the amount in one glass of red wine.

Studies by BioMarker have shown that resveratrol offers benefits for gene expression and longevity in a variety of species using a dosage comparable to 20 mg daily in humans. However, given the extraordinary findings of recent studies using high-dose resveratrol supplements—and their profound implications for human health—some resveratrol researchers and other health-conscious people are now consuming even larger daily dosages.

As for who should supplement with resveratrol, leading researchers maintain that in addition to benefiting patients with specific disease conditions, resveratrol may confer broad-spectrum protection to anyone seeking to live a long life in optimal health.

According to Dr. Zhao-Wilson, "the properties associated with resveratrol appear to be largely protective—cardioprotective, neuroprotective, anticarcinogenic, anti-inflammatory—and the current data suggest that most people could benefit from dietary supplementation with resveratrol obtained from a high-quality source." Dr. Zhao-Wilson adds that resveratrol is generally safe when taken in conventional dosages.

Dr. Sovak similarly recommends resveratrol as a health-protective agent, noting that resveratrol may be helpful both alone and in combination with other antioxidants, such as epigallocatechins derived from green tea. Turn to the next article for more precise information about optimal resveratrol dosing.
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