Scientists are discovering significant additional benefits that resveratrol confers in fighting aging and degenerative disease. While much of this research was initiated by a prolific group at Harvard University and in the biotech industry, scientists around the globe are now making unprecedented discoveries that define resveratrol’s multiple preventive and therapeutic potentials.

Most exciting are findings showing how resveratrol may help protect against devastating age-related diseases including cancer, diabetes, atherosclerosis, and Alzheimer’s.

We’ll start with an in-depth look at just what they’re discovering and then review the most compelling findings about resveratrol’s current and future roles in sustaining human health and prolonging life span.
Sirtuins: Inducing the Benefits
of Caloric Restriction

At the forefront of the cutting-edge investigations into resveratrol and health and longevity are Drs. Christoph Westphal and David Sinclair.

Christoph Westphal, MD, PhD, has been referred to by Fortune Magazine as “dreamer-in-chief” of biotech startup company Sirtris Pharmaceuticals based near Harvard University in Cambridge, MA. The moniker is well-earned; Westphal’s dreams appear to include the application of some very exciting science toward the goal of life extension by utilizing resveratrol.

Westphal’s work builds on (and incorporates) that of Harvard scientist David Sinclair, PhD, whose research group is pursuing connections buried deep within the cells of every animal on the planet, that of caloric restriction and longevity. Thanks to the work of Westphal and Sinclair, it is becoming clear that resveratrol mimics the life-span-prolonging effects of caloric restriction, even in animals fed normal or high-fat diets.

It has been known for over 70 years that a drastic reduction in caloric intake slows the pace of aging and increases maximum life span in many so-called “lower organisms” such as yeast, simple worms, and fruit flies; more recently, this form of drastic dieting has been shown to have similar effects in mammals. For years, scientists had no notion of just how caloric restriction worked to prolong life. In 2005, however, Sinclair brought together what was then known about this phenomenon to suggest a new hypothesis, namely that this effect is “an active, highly conserved stress response that evolved early in history to increase an organism’s chance of surviving adversity” (scientists use the term “conserved” to describe a characteristic that remains present in organisms over tremendously long periods of time, indicating that it is fundamental to survival of life itself).

The specific molecules that were being conserved turn out to be members of a protein family called the sirtuins (for silent information regulators), which are activated by caloric restriction. Like a combination of cellular police, fire, and ambulance services, sirtuins exert myriad effects aimed at preserving intracellular civilization—they stabilize chromosomes and DNA molecules, preventing breaks and damage that can lead to cancer, they promote DNA repair, and they regulate genetic functions that in turn control every activity in the living cell. Most remarkably, decreased sirtuin activity seems to be intimately connected with the cell, tissue, and organ changes that typically occur with aging and that lead to many of the diseases we label “chronic age-related conditions” such as cancer, diabetes, cardiovascular diseases, and neurodegenerative disorders such as Alzheimer’s disease. In fact, Sinclair’s colleague Dohoon Kim recently wrote that sirtuins “constitute a unique molecular link between aging and human neurodegenerative disorders and provide a promising avenue for therapeutic intervention.”
Resveratrol has the remarkable ability to activate and promote sirtuin activity in virtually all cells, which has been shown to promote the repair and longevity functions that are observed in caloric restriction. In a stunning demonstration of this effect, a group of Sinclair's colleagues at the National Institute on Aging fed resveratrol to laboratory mice, producing the same changes in gene expression as those induced by caloric restriction. Astonishingly, elderly mice fed resveratrol along with a normal diet also showed a dramatic reduction in signs of aging. These reduced markers of aging included decreased protein loss in urine, decreased inflammation, increased elasticity in the aorta, beneficial changes in blood vessel lining cells, greater motor coordination, reduced cataract formation, and preserved bone mineral density! This study, begun when the mice were at mid-life, did not show any increases in longevity—but translated into human terms, these mice would have enjoyed dramatic improvements in the quality of their lives.

Pathologists collaborating with Dr. Sinclair at Harvard have demonstrated increased survival of mice on a high-calorie diet when supplemented with resveratrol, further elucidating the benefits of sirtuin activation. This group provided a group of middle-aged mice with a high-calorie diet plus resveratrol, and examined a host of physiological parameters that are affected by age, diet, and obesity. The supplemented mice underwent changes associated with increase in life span, including increased insulin sensitivity, increased numbers of mitochondria in cells, and improved motor function. In fact, the researchers discovered that resveratrol reversed the effects of the high-caloric diet in 144 out of 153 biochemical pathways! Their conclusion was that "these data show that improving general health in mammals using small molecules [such as resveratrol] is an attainable goal, and point to new approaches for treating obesity-related disorders and diseases of ageing."

We can now review some of the impressive evidence of resveratrol's health benefits in the context of Sinclair and Westphal's foundational work on longevity. What is not clear yet is just how many of these benefits relate directly to resveratrol's effect on sirtuins and how many are tied to its antioxidant and inflammation-fighting activities. Regardless, the following studies offer stunning affirmation of the importance of resveratrol in the quest for longer and healthier lives.

Cardiovascular Benefits

In laboratories around the world, innovative studies identified the impact of resveratrol on reducing the risks of heart disease and the damage from strokes. Some of these discoveries include the reduction of

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**What You Need to Know**

**Resveratrol**

- The plant-derived polyphenol resveratrol probably accounts for many of the beneficial effects of the "French Paradox" in which high-fat diets fail to produce devastating effects when red wine is also consumed.
- Most of resveratrol's benefits have traditionally been ascribed to its powerful antioxidant and anti-inflammatory effects.
- Emerging research now shows that resveratrol also stimulates cells to behave as if they had been exposed to caloric restriction, the most powerful life-extending approach known.
- Through its action on potent cellular-regulating proteins called sirtuins, resveratrol mimics caloric restriction, stimulating healthy cells to survive and diseased cells to die in an organized fashion.
- Resveratrol-mediated sirtuin activation is now understood to be responsible for many of the health benefits associated with resveratrol supplementation, including protection from aging-associated disorders like cardiovascular disease, the metabolic syndrome, neurodegenerative disorders, and cancer.
- Drug companies are rushing to exploit the new findings about resveratrol by turning it into a drug—but highly active supplements are already available, and existing data are all based on use of the natural product.
atherosclerosis, including control of blood vessel diameter and muscle tone, inhibition of oxidative stress, anti-inflammatory effects, inhibition of LDL (low-density lipoprotein) oxidation, and a reduced "stickiness" of platelets leading to a reduction in deadly clot formation.\textsuperscript{14}

The multiple health benefits have led even the conservative US Department of Health and Human Services to recommend moderate wine consumption because of its resveratrol content in its Healthy People 2010 initiative.\textsuperscript{21}

In a unique study seeking more knowledge about the complex interaction of resveratrol and heart disease, Korean scientists demonstrated the relationship between resveratrol, inflammation, and blood lipids, immune cells, and the cells lining arterial walls.\textsuperscript{22} In this remarkable study, the researchers supplemented atherosclerosis-prone mice with either resveratrol, a prescription lipid-lowering drug called clofibrate, or a control diet. The scientists found that resveratrol-supplemented mice had consistently lower total cholesterol and LDL levels than did control animals. Both the resveratrol and the clofibrate-supplemented animals experienced consistently higher levels of beneficial HDL (high-density lipoprotein) than controls. Importantly, the resveratrol-supplemented group also saw significantly higher levels of a vital enzyme called paraoxonase, which is an HDL-associated protein capable of preventing the LDL oxidation that triggers the inflammatory cascade of atherosclerosis.\textsuperscript{23} And in a remarkable finding, the activity of the cholesterol-producing enzyme HMG-CoA-reductase (HMGR) was significantly lower in both the resveratrol and the clofibrate group—a noteworthy finding, since reducing HMGR activity is the target of the widely prescribed lipid-lowering medications called statins.

Resveratrol also diminished levels of adhesion molecules in vessels walls that are responsible for promoting plaque and clot formation. Of course, the most exciting finding from this comprehensive study was that resveratrol actually reduced the number of atherosclerotic changes and the amount of fat deposition in and around the arteries in the supplemented animals. These researchers concluded that "these results provide new insight into the anti-atherogenic and cholesterol-lowering properties of resveratrol in mice that were fed a normal diet."

Animal studies also demonstrate resveratrol's impressive power to prevent or reverse damage even when a cardiovascular event does occur. For example, chronic hypertension and obesity can contribute to an overgrowth of heart muscle known as cardiac hypertrophy, which in turn is a major contributor to congestive heart failure.\textsuperscript{24,25} Canadian researchers showed that resveratrol could reduce rat cardiac cell hypertrophy by blocking inflammatory signals.\textsuperscript{26} Further, Korean scientists used resveratrol to protect heart cells from free radical-induced cell death.\textsuperscript{27} And Chinese cardiologists were able to use resveratrol to prevent death of rat cardiac cells through the activation of sirtuins, preventing the subsequent remodeling of heart muscle that contributes to congestive heart failure following a heart attack.\textsuperscript{28} Similar results are now being obtained in laboratories around the world.\textsuperscript{29,30}

Stroke is another devastating outcome of atherosclerosis, and one that is also ripe for prevention by resveratrol's multiple modes of action.\textsuperscript{31} Through its activation of sirtuin molecules, resveratrol can prevent injury to brain cells subjected to stroke-like conditions in the laboratory.\textsuperscript{32,33} Chinese neuroscientists found that when resveratrol was given to live animals for seven days before an experimentally induced stroke, it reduced the amount of brain tissue injured, while limiting the actual neurological deficits the stroke produced.\textsuperscript{34} These changes were accompanied by a substantial reduction in the inflammatory markers that are among the hallmarks of brain injury in stroke. Similar results, with the additional benefit of reduction in markers of brain cell oxidation, have been reported by others.\textsuperscript{35,36}

Studies with humans and human tissues have also been promising. A dramatic finding comes from the work of Turkish cardiac surgeons who applied resveratrol to cross-sectional pieces of blood vessels obtained from 38 men undergoing cardiac bypass operations.\textsuperscript{37} The
in-vitro treatment produced relaxations of the vessels of 35%—a dramatic increase in their capacity to carry blood efficiently. They went on to show that these results were directly related to the effects of resveratrol on the vital endothelial layer lining the vessels—the layer that is the most immediate site of atherosclerotic change.

In a 2005 study of 30 men with coronary heart disease, Greek cardiologists examined the effects of a resveratrol-containing red grape extract on flow-mediated dilation (FMD), a sensitive measure of endothelial function in a large artery of the arm. Fifteen of the men received the supplement, and 15 a placebo. An ultrasound machine determined FMD after fasting and then at 30-, 60-, and 120-minute intervals following the supplement. Men who took the supplement experienced an increase in FMD significantly above baseline values, peaking at one hour after intake of the supplement, while no change was found in the placebo recipients. Since FMD is a direct measure of arteries' ability to respond to changes in blood flow, this study provided powerful evidence for a benefit of resveratrol-containing red grape extract on arterial performance.

Another manifestation of resveratrol's cardiovascular benefit comes from the work of internists in Italy, who were interested in platelet aggregation (clumping), an important part of both atherosclerosis and acute clot formation in heart attacks and stroke. This study examined blood parameters from healthy volunteers before and after 15 days of controlled red or white wine intake. The researchers found that wine intake increased the production of the biochemical signaling molecule nitric oxide, blunting a pathological response that ultimately increases platelet aggregation. The scientists pursued the effect further, treating platelets directly with resveratrol at the concentrations they had measured in subjects' blood. In addition to a number of beneficial effects on nitric oxide production, the researchers also identified reductions in the activity of inflammatory pathways and systems that produce destructive reactive oxygen species.

**Diabetes and the Metabolic Syndrome**

Type 2 diabetes is associated with development of the metabolic syndrome, which dramatically elevates risk of cardiovascular disease, the number one cause of death in the aging population. Epidemiologic studies have established beyond doubt that red wine consumption is associated with a lower incidence of metabolic syndrome and heart disease, and scientists believe the resveratrol component may explain why red wine is more effective than alcohol in general. According to Dr. Ling Liu of the University of Hong Kong, "[resveratrol] can act as a potent activator of... sirtuins to expand the life span and to prevent the deleterious effects of excess intake on insulin resistance and metabolic derangement." In fact, resveratrol's activation of sirtuins is so effective that many researchers are now interested in its use as a potential drug for the treatment of diabetes. Let's examine in more detail a few of the landmark studies of resveratrol's metabolic effects.

Since cellular uptake of glucose is impaired in diabetes, Canadian researchers decided to examine the effects of resveratrol on enhancing muscle cells' ability to absorb sugar—an insulin-like function. In a laboratory culture of skeletal muscle, the researchers found that addition of resveratrol stimulated glucose uptake to more than 200% of baseline, similar to the action of insulin itself. They were able to trace this effect to the stimulation of sirtuins in the muscle cells. Such activity in humans has the potential to help regulate glucose levels in the blood of diabetic patients, while enhancing delivery of much-needed glucose to hungry skeletal muscles. Of interest is that a similar improvement in insulin-glucose function occurs in response to calorie restriction.

Taking resveratrol treatment a logical step further, Spanish researchers in the Basque country explored the effects of resveratrol on prevention of non-alcoholic fatty liver disease in laboratory rats. This is a crucial area of research because non-alcoholic fatty liver disease is linked to obesity, diabetes, and elevated triglyceride levels in blood—all independent risk factors for cardiovascular disease. The researchers fed
rats either a control diet or a high-carbohydrate diet for four weeks, including resveratrol in one group of the high-carbohydrate subjects. As expected, the high-carbohydrate group developed fatty liver and associated inflammatory biochemical changes seen in humans. The resveratrol group had decreased fat deposition in their livers compared with the untreated high-carbohydrate group, and also had significant reductions in levels of inflammatory and oxidative stress markers in their blood. The supplemented animals also had higher levels of natural antioxidant enzymes that help combat the effects of oxidized fat molecules. Finally, glucose levels were decreased in the resveratrol-supplemented group.

In a remarkable set of studies, biochemists in Madras reported on a direct comparison of resveratrol with an oral glucose-lowering drug, glyclazide, in control of blood sugar levels in diabetic rats. The animals were treated with resveratrol orally for 30 days, and experienced a significant decrease in blood sugar, the target outcome. Of clinical importance, the animals also had significant reductions in levels of hemoglobin A1C, a sensitive marker of long-term sugar levels and of protein damage caused by exposure to elevated sugars. The animals were also found to have lower levels of biomarkers of inflammation and liver injury. The researchers noted that these effects are comparable with those of glyclazide, and concluded that "resveratrol may be considered as an effective therapeutic agent for the treatment of diabetes mellitus."

Another group of Spanish investigators studied obese rats in a model of the metabolic syndrome. These animals, like their human counterparts, have high plasma lipid (fat) levels, insulin resistance, and increased levels of inflammatory molecules produced in their abdominal fat—all destructive changes we know to be associated with cardiovascular disease and other metabolic syndrome consequences. Amazingly, all of these metabolic disruptions were significantly reduced when the animals received resveratrol supplementation. Interestingly, and significantly for overweight and obese humans, the supplemented animals also had reductions in their blood pressure. Encouragingly, resveratrol mimics many of the metabolic benefits of caloric restriction through its activation of sirtuins, without the deprivation associated with a reduced calorie diet.

Neurodegenerative Diseases

According to the noted Spanish neuropharmacologist Merce Pallas, "healthy aging remains one of the ideals of modern society." Nowhere are the ravages of unhealthy aging more visible than in the terribly destructive neurodegenerative disorders such as Alzheimer's and Parkinson's diseases—and because these diseases are linked inexorably to oxidative damage and inflammation, resveratrol researchers hold high hopes for the molecule's potential impact in these areas. It has been suggested that, like caloric restriction, resveratrol helps to preserve and regulate energy levels in brain and nerve cells, prolonging their active lives.
Resveratrol May Reverse Arterial Aging

“Atherosclerosis is reversible” is not a phrase we expected to hear from mainstream medical researchers until very recently—since these are the precise opening words of a remarkable editorial about resveratrol that appeared in a recent issue of the prestigious New England Journal of Medicine. Just as astonishingly, the editorial was written by a renowned immunologist, Linda K. Curtiss, PhD, of the Scripps Research Institute in La Jolla, California. The fact that an immunologist is writing about cardiovascular disease in a trend-setting medical journal speaks volumes about how far we have come in our understanding of chronic diseases and their relationships with inflammation, which is an immune system phenomenon. What truly sets Dr. Curtiss’s article apart, though, is her description of a dramatic new phenomenon mediated by the grape polyphenol resveratrol.

Curtiss’s excitement comes from work done by Cleveland Clinic cell biologist Young-Mi Park, MD, who was exploring the role of oxidant stress and inflammation on the pathogenesis, or disease-causing mechanisms, of atherosclerosis. Knowing that fat-laden inflammatory cells called foam-cell macrophages trigger inflammation when they become trapped beneath the lining of blood vessels, Park’s team sought to understand why the cells become trapped, and how they could be freed from their “endothelial bondage,” thereby reversing the inflammatory process.

The most natural approach to take, Park’s group decided, was simply to test known antioxidants’ ability to prevent the foam cells from migrating into the endothelial lining in the first place, and their ability to release any cells that were already present. Specifically, they studied how oxidized low-density lipoprotein (LDL) promotes foam-cell formation and impairs migration. To do this they blocked LDL oxidation with several potent antioxidants. They found that oxidized LDL actually triggered production of a sort of cellular “glue” in the form of filaments of actin, one of the proteins also found in muscle tissue. The actin filaments were entangling the foam cells, preventing their natural migration out of the endothelial lining, leading to progressive inflammatory changes.

Park’s group chose resveratrol as one of the two antioxidants to test—another testimony to the respect that mainstream researchers are according this remarkable molecule (the other was N-acetylcysteine, also an antioxidant available in supplement form). Resveratrol treatment of the foam cells inhibited production of reactive oxygen species by greater than 90%, an important first step in breaking the cycle. Even more impressively, resveratrol partially restored the foam cells’ ability to move out of the entangling actin filaments, and migrate away from the endothelial lining!

This brings us back to Dr. Curtiss’s astounding initial observation that atherosclerosis is a reversible condition—through the use of powerful antioxidants such as resveratrol, we can now understand how oxidized LDL contributes to invasion of endothelium by inflammatory cells, and how prevention or reversal of LDL oxidation promotes mobilization of inflammatory cells and their emigration away from vessel linings.

As Dr. Park concluded, “[these studies] also provide additional mechanistic support for the atheroprotective effect of antioxidants.” Resveratrol is already well-known as a cardiovascular protective supplement—the work of Park and others is now showing us that resveratrol must also be considered a valuable cardiovascular therapeutic supplement, one that can literally “turn back the clock” on chronic vascular diseases of aging!
in part through beneficial, sirtuin-activating effects on mitochondria, the cellular powerhouses. Direct evidence of a resveratrol-mediated neuroprotective effect in Alzheimer’s disease was published in 2009 in a report by Cornell neuroscientists who studied mice given an experimental version of human Alzheimer’s. The mice were given resveratrol over a 45-day period; their brains were then examined for the damaging inflammatory beta-amyloid plaques characteristic of Alzheimer’s disease. Despite finding no resveratrol directly in the brain tissue, the scientists reported reductions in plaque formation of 48% to 90% in specific and important regions of the brain! These dramatic changes were accompanied by substantial increases in brain antioxidant molecules. The researchers concluded that “onset of neurodegenerative disease may be delayed or mitigated with use of dietary chemopreventive agents that protect against beta-amyloid plaque formation and oxidative stress.”

It’s not just in chronic degenerative diseases of the brain that resveratrol holds promise—neurosurgeons in Turkey found that resveratrol actually produced better biochemical outcomes in an animal model of spinal cord injury than did methylprednisolone, the steroid commonly given in high doses to trauma victims. And the mitochondria-preserving characteristics of resveratrol are now being explored by other neurologists and neurosurgeons as a means of preventing the devastating neurotoxic effects of restoring blood flow to brain tissue deprived of oxygen.

Cancer

Cancer is one of the most-feared scourges of humanity, and the risk of cancer increases progressively with advancing age. It is only in the past three years that significant attention has been paid by oncologists to the chemopreventive capacity of resveratrol—but that omission is being rapidly remedied through an outpouring of new research. Roman biologists have discovered, for example, that the most active form of the molecule, trans-resveratrol, causes human breast cancer cells in culture to commit the orderly suicide referred to as apoptosis, one of the most important and effective means of treating cancers and of preventing their progression. Scientists at the University of Nebraska Medical Center even found that they could utilize resveratrol to prevent damage to DNA caused by excess estrogen, effectively preventing the initiation of some breast cancers.

Because resveratrol acts by so many different mechanisms, it represents a true “multiple-prong” approach to prevention and treatment of cancers. These effects are especially notable in tissues with a high rate of natural cell turnover, where carcinogens can rapidly corrupt the DNA code and induce tumors—tissues such as the gastrointestinal tract and the skin. Oncologists at the Northeastern Ohio Universities Colleges of Medicine and Pharmacy in Ohio, for example, found that they could use resveratrol to inhibit liver cancer cells from proliferating, and cause them to undergo death by apoptosis, ultimately reducing the size and number of liver tumors in rats given a potent carcinogen.

A more profound understanding of resveratrol’s role in toxin-induced cancers (typical of the gastrointestinal tract and skin) has been revealed just this year, by Italian toxicologists studying the powerful enzyme systems involved in carcinogenesis. Remarkably, they have demonstrated that resveratrol inhibits the actions of certain “bioactivating” enzymes that inadvertently convert minor toxins into major carcinogens, and at the same time promotes activity of detoxifying enzymes that help prevent conversion of normal cells into cancerous tumors.

Indian toxicology experts also found that resveratrol prevented carcinous changes—this time in a rat model of skin cancer. Using resveratrol, they could delay the onset of tumor development, reduce the total number of tumors, and reduce tumor size in the skin of rats treated with a potent carcinogen. The scientists concluded that resveratrol regulates apoptosis and cell survival in mouse skin tumors and deserves consideration as a potent chemopreventive agent.

Finally, also early in 2009, another group of Indian scientists reported that they could block
toxin-induced colon cancers in rats by supplementing them with resveratrol before exposing them to a deadly carcinogen.\textsuperscript{64} Like the preceding group, they found reductions in both the occurrence rate and the size of tumors; importantly, both benign and malignant tumor types were suppressed. Though we are midway through 2009, a host of other new studies have already appeared, confirming and extending findings about resveratrol's astonishing chemopreventive capabilities.\textsuperscript{41,65}

Summary

The plant-derived polyphenol resveratrol, and especially its highly active form, \textit{trans-resveratrol},\textsuperscript{5,59,68} have been making big news in recent days. We've long known that resveratrol has potent antioxidant and anti-inflammatory effects, making it a key item in our armamentarium of supplements that can prevent age-associated chronic illness. The real news is that resveratrol continues to be linked to the life-extending effects of the powerful sirtuin molecules that control the fundamental processes associated with aging itself. By potently activating sirtuins, resveratrol stabilizes DNA to prevent cancerous changes, switches on antioxidant and anti-inflammatory defense mechanisms native to cells, and even instructs certain cells to commit organized suicide by apoptosis. The end result is an almost incredible array of health benefits, from reduction in cardiovascular risk factors to protection against neurodegenerative disease to cancer prevention. Indeed, resveratrol is being actively explored now by big pharmaceutical companies eager to cash in on its potency by creating new drugs derived from the natural molecule. But there's no need to wait, because highly purified forms of \textit{trans-resveratrol} are already available, waiting to provide their beneficial effects immediately.

If you have any questions on the scientific content of this article, please call a Life Extension Health Advisor at 1-800-226-2370.

References

47. \textit{BMC Gastroenterol.} 2008;8:40.
65. \textit{Autophagy.} 2009 May 19;5(4).
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