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REPORT

Growing Evidence Links Resveratrol to Extended Life Span

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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%.1-3 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.4 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 under-lying 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.5 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.5

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.5

Resveratrol’s positive impacts on insulin sensitivity and survival were apparent after only six months of treatment.5 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.5 The obese resveratrol-supplemented animals experienced all of these benefits without a significant reduction in body weight.5

“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.”5

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.6 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 powerhouses 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.7

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 resvera-trol may offer "new approaches for treating obesity-related disorders and diseases of aging."7

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.5

Scientists believe that caloric restriction increases life span in part through its effects on the sirtuin genes.5 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 SIRT2.5,8-10 In the Harvard study, resveratrol helped counteract changes in SIRT2 expression induced by a high-calorie diet.5

"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.11

RESVERATROL AND EXTENDED LIFE SPAN: WHAT YOU NEED TO KNOW

- 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 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 under way.
- 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.

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.16,17

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.18-21 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.22-24

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.12,13 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.14

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.15

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%.

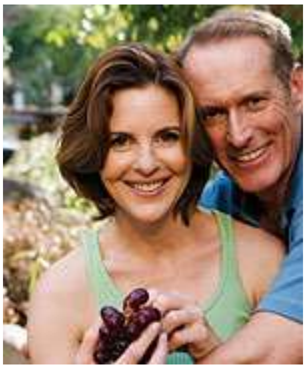
CANCER

In addition to its cardioprotective effects,25-27 resveratrol exhibits a range of anti-cancer properties.28 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.29,30

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.30,31 Through these mechanisms, resveratrol may enhance the anti-cancer effects of chemotherapeutic drugs and radiation.29 With its potent antioxidant capabilities,32,33 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.34

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.29

“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.



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.35,36

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.37

NEUROPROTECTION

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.38-40 This has led several research teams to propose that resveratrol may be a useful treatment for Alzheimer’s disease.41-43

According to a recent report, resveratrol demonstrated a protective effect against Huntington’s disease in animal models.44 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.24

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.

BIOMARKER PHARMACEUTICALS: PIONEERING LIFE EXTENSION RESEARCH

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."

EXTENDING HUMAN LIFE SPAN

Based on his study of experimental life-span extension in mice,45 Dr. Richard A. Miller of the University of Michigan suggests that resveratrol may extend the human life span.

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.

ENGINEERING BIOLOGICAL IMMORTALITY

When we discuss the ability of nutrients like resveratrol, drugs like metformin, and experimental regimens such as caloric restriction to induce favorable changes in gene expression in experimental animals, most people do not realize the ultimate objective of this type of research.

While the DNA in the nucleus of our cells includes thousands of genes, it appears that relatively few of these genes control functions that are critical to optimal health and longevity.

As mammals (including humans) age, beneficial genes are "turned down," whereas genes that are detrimental to cellular function are "turned up." Some genes may be turned off and on with advancing age, and others may have positive influences in youth, but negative influences as we grow older.

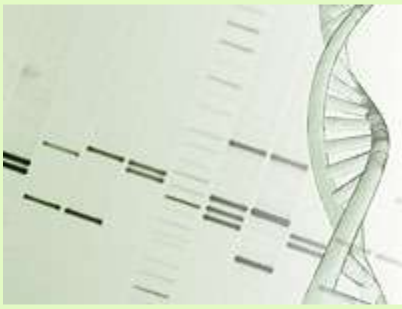
Examples of beneficial genes that are "turned down" during normal aging are genes that:

1. suppress aberrant cellular proliferation
2. induce DNA repair
3. enable insulin to assist glucose uptake into cells
4. facilitate production of beneficial high-density lipoprotein (HDL).

Examples of detrimental genes that are "turned up" during normal aging include those that:

1. induce excess production of potentially harmful low-density lipoprotein (LDL) and cholesterol
2. override normal patterns regulating cell division
3. promote excess production of insulin and inflammation
4. interfere with apoptosis (programmed cell death) of cancer cells.

By causing the genes involved in aging to function as they did in youth, it may become possible in the future to reprogram our genes to keep us alive in a state of perpetual youth, which could lead to biological immortality.



Just consider: although caloric restriction was discovered to extend maximum life span in mammals in the 1930s, only recently have scientists begun to identify the molecular mechanisms that may explain the benefits of caloric restriction, as well as potential caloric-restriction mimetics such as resveratrol and metformin. The implications of these findings—which have made headline news around the world—is that it may someday be possible to engineer our genes in a way that will make us invulnerable to atherosclerosis, cancer, dementias, arthritis, and all other age-related disorders, as well as aging itself. The net effect would be a radical extension of the healthy human life span.

We at Life Extension hope that you are as excited as we are to be part of this fantastic voyage into the outer frontiers of medical research. We urge you to continue to support us so that we can play an ever-increasing role in funding this type of revolutionary scientific research.

RESVERATROL AND OTHER HEALTH-PROMOTING GRAPE CONSTITUENTS

The Life Extension Foundation constantly surveys the scientific literature in order to utilize the most important findings in promoting health and extending life. Mounting evidence demonstrates the broad-spectrum effects of biologically active molecules such as resveratrol, which is derived from natural plant extracts. In nature, molecular compounds like resveratrol are found in complex mixtures containing a diverse array of physiologically relevant molecules. Many of these constituents may be required in order to provide phytomedicinal agents with optimal bioavailability and synergistic action. Scientists must consider these points when conducting studies using either a single phytochemical (such as resveratrol alone) versus resveratrol combined with grape skin and grape seed extracts.

Classes of molecules found in natural whole grape, grape skin, and grape seed extracts include potent effectors like proanthocyanidins (in grape seed), anthocyanins (which give purple and red grapes their color), and single molecular entities such as resveratrol and quercetin. Scientific studies document the multiple health effects of these components, which can be characterized as antibiotic, anti-tumor, anti-diabetic, anti-ulcer, cardioprotective, anti-inflammatory, and anti-brain aging.7

The cardiovascular health benefits of grape seed extract include favorable effects on blood pressure, enhanced endothelial function, and decreased oxidative stress.8 The potent antioxidant activity of grape seed extract may be responsible for its reported neuroprotective effects, as observed in animal models of Alzheimer's disease.9,10 Recently, grape seed extract combined with calcium was found to be more effective than calcium alone in building healthy bone mass.11 Grape seed extract has effectively inhibited the growth of human colorectal tumor cells in the laboratory and in animals.12

Recent findings on resveratrol's effects in experimental animal models are attracting a great deal of interest from the scientific community, while raising many questions about resveratrol's applications in humans. One of the most intriguing questions is what dose of resveratrol may help humans achieve the beneficial health effects that have been observed in animals. While extrapolating animal dosage to human dosage is difficult at best, scientists are using several approaches to address this question. The accumulating data from gene-expression studies in mice provide some clues. These findings are also helping to illuminate the molecular basis of the biological effects of resveratrol and grape extracts.

The Harvard Study generated a great deal of enthusiasm by showing that mice fed high-fat diets (60% of calories from fat) avoided numerous diet-related health problems when supplemented with res-veratrol. Compared to mice that were not given resveratrol, the supplemented mice exhibited increased survival, increased insulin sensitivity, decreased organ pathology, and in-creased numbers of mitochondria.1 Resveratrol was also responsible for shifting the gene-expression patterns of mice on the high-fat diet towards those of mice on a standard (moderate-fat) diet. These results were achieved by feeding the mice a daily resveratrol supplement equivalent to 22.4 milligrams per kilogram of body weight.* In preliminary studies of this type, scientists often choose relatively high individual doses that are likely to generate an observable effect. Typically, more formal dose-ranging studies would be conducted later to identify optimal doses to attain specific effects. This is partly responsible for the controversy in the popular press regarding the relatively high dose of resveratrol used in this study.

While the Harvard study was under way, BioMarker Pharmaceuticals had already completed an eight-week controlled feeding study in which mice received either resveratrol (a synthetic version) or grape extract (containing resveratrol and other constituents), along with a "normal" diet. Gene-expression profiles were completed on these animals and compared to those of a group of calorie-restricted mice. Genes affected by either resveratrol formulation (synthetic or natural grape extract) or by caloric restriction were then compared. Importantly, the resvera-trol dosage used in this study was much lower—approximately 12-fold lower—than that used in the Harvard study (see Table 1).

TABLE 1. RESVERATROL DOSAGE IN MICE

Study	Dose (mg/kg/day)
Harvard study1 (high dose)	22.4
BioMarker study (low dose)	1.45,a 1.74b

a. Synthetic resveratrol

b. Grape extract resveratrol (obtained from Grapeseed Extract with Resveratrol).

RESULTS OF GENE-EXPRESSION ANALYSIS

Mice on normal diets were fed a daily, relatively low dose of resveratrol obtained from either a synthetic source or from a whole-grape extract enriched with resveratrol. A control group of mice fed a normal diet without resveratrol supplementation and a calorie-restricted group were also evaluated. Total calorie intake was identical in the resveratrol, grape extract, and control groups, and 40% less in the calorie-restricted group.

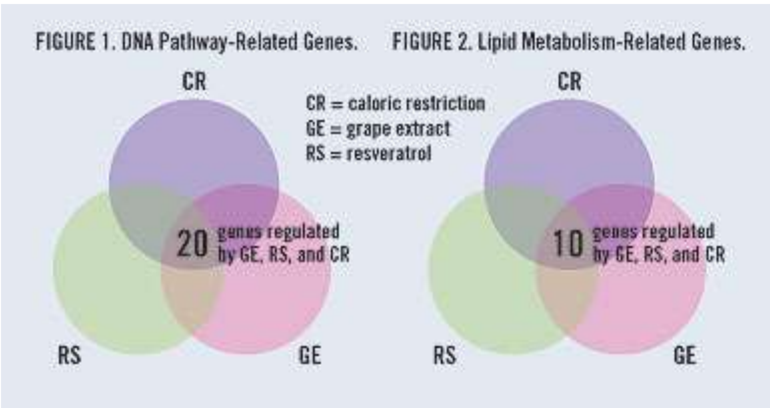
At the end of an eight-week feeding schedule, the animals' livers were harvested in order to prepare RNA (the biochemical cousin of DNA) for gene-expression profiling. The samples were specially prepared for analysis with DNA microarrays, or "gene chips," containing a full set of characterized mouse genes (the Affymetrix GeneChip® contains a total of over 45,000 probe sets, representing a complete set of over 34,000 genes of the mouse genome). Gene-expression levels were determined using statistical methods that ensure a high degree of confidence in the data.*

Both mouse groups that received resveratrol showed significant changes in the expression of key genes, confirming that even at the relatively low doses used in this study, there was a notable biological effect. The differentially expressed genes control over 100 different molecular pathways, including those related to metabolism (primarily metabolism of carbohydrates and lipids), DNA repair, and the regulation of cell death. Since the genes involved are in key biological pathways, they are likely to be responsible for at least some of resveratrol's biological effects. Furthermore, significant results were achieved using a dose of synthetic resveratrol that was more than 10-fold lower than that used in the Harvard study.

Animals fed grape extract received resveratrol and other components of whole-grape extract.** Their gene-expression response would therefore be expected to reflect effects of both resveratrol and other grape components. Genes that significantly changed in expression in the grape extract group are found in molecular pathways involved in carbohydrate metabolism and biosynthesis (such as the creation of blood sugars), and lipid metabolism and biosynthesis (such as the creation or reduction of cholesterol and fatty acids).

Interestingly, scientists noted a significant overlap—about 65%—when they compared the gene-expression patterns of the resveratrol and grape extract groups. While expected, these results confirm the similar effects of pure synthetic resveratrol and grape extract-derived resveratrol on gene expression in animals.

The gene-expression effects of "low-dose" resveratrol were similar to those seen in calorie-restricted mice: about 55% similarity between the calorie-restricted and resveratrol groups, and 52% similarity between the calorie-restricted and grape extract-supplemented groups.



A method known as molecular pathway analysis can be applied to the gene-expression profiling results in order to identify the key regulatory pathways affected by the various treatments of resveratrol, grape extract, and caloric restriction. Displayed in Figures 1 and 2, these data show which pathways are specific to the different treatments, as well as pathways that are shared between or among the treatments.

Figure 1 shows the results for genes in pathways that are related to biological processes involving DNA; as shown by the overlap, 20 differentially expressed genes involved in DNA-related processes are regulated in the same fashion in animals receiving synthetic resveratrol, grape extract, or caloric restriction. These data suggest that the three treatments share some common features with respect to how genes involved in DNA processing are controlled through gene expression.

A similar approach was used to analyze genes involved in lipid metabolism. As shown in Figure 2, 10 genes involved in pathways related to lipid metabolism are commonly regulated by resveratrol, grape extract, and caloric restriction. These data are just a subset of the entire analysis. In total, 159 different molecular pathways were found to be commonly regulated by these three different treatments.

Resveratrol and grape extract produce strongly similar effects, based on the gene-expression responses demonstrated in mice fed a relatively low dose of these compounds. Comparison of these groups with calorie-restricted mice shows a significant overlap in the three treatments' regulation of similar biological pathways. These data add to the accumulating evidence that resveratrol triggers a biological response in mammals that is similar to that observed with caloric restriction, an intervention that is known to extend life span and protect against age-related diseases.2-5 These effects are observed even at a relatively low dose of resveratrol, indicating that a human-equivalent dose can be obtained through dietary supplementation with high-quality resveratrol products.

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