Resveratrol (3,5,4’-trihydroxystilbene) is a polyphenol synthesized by several plants in response to adverse conditions (e.g., environmental stress or pathogenic attacks). It is classified as a phytoalexin, a class of plant-derived antibiotics that serves as part of a plant’s defensive arsenal.(1)

Resveratrol is found in numerous plant species such as mulberries, peanuts, and grape skin, and in less commonly known plants such as Japanese knotweed (Polygonum cuspidatum).(2)

The skin of the grape is used to manufacture red wine. Hence, resveratrol has been proposed to be the main cause of the so-called French “paradox”(3)—that is, that the French, despite a diet rich in fat and particularly saturated fat, experience far less heart disease than other Westerners. The difference is believed to be their higher consumption of red wine.

In recent years, resveratrol has attracted considerable interest due to its demonstrated biological activities against many of the chronic diseases of our time, including cardiovascular disease, cancer, and neurodegenerative disease.(4, 5) In addition, researchers are working diligently to gain a better understanding of how resveratrol influences the activity of genes associated with lifespan, with some early studies showing how resveratrol extends the lifespan of organisms such as yeast and select vertebrates.(6-9)

Cardiovascular Health

The effects of resveratrol on reducing cardiovascular disease in humans have been equated to the effect of a 25% calorie reduction over six years.(10) (More on this later.) These effects include antiatherosclerotic effects, dilation of blood vessels, reducing platelet aggregation, lowering of blood pressure, reducing endothelin-1 (a potent vasoconstrictor), and antioxidant effects.(7,11,12) Unlike other flavonoids, resveratrol has the ability to increase the expression of endothelial NO synthase, which contributes to vasodilation via an increase in nitric oxide.(13) Regulating the production of both vasodilators (nitric oxide) and vasoconstrictors (endothelin-1) is one mechanism whereby resveratrol promotes cardiovascular health.

Low-density lipoprotein (LDL) cholesterol oxidation is an established risk factor for heart disease. Oxidation of LDL particles is strongly associated with the risk of coronary heart disease and myocardial infarction.(12) Resveratrol helps prevent LDL oxidation by chelating copper and directly scavenging free radicals.(14) LDL also plays a role in the formation of arterial plaque and in the endothelial inflammatory pathway. The oxidation of LDL is a primary cause of endothelial damage and the release of pro-inflammatory mediators within the endothelial lining of blood vessels. The removal of LDL is an essential step in addressing the inflammatory component of atherosclerosis.(15) Resveratrol helps protect lipids from oxidative damage and inhibits, to some extent, the uptake of oxidized LDL in the blood vessel wall.(16) Several complex pathways are involved in the beneficial effects of resveratrol on cardiovascular health. Further research, including more clinical studies, are needed (some are in progress) to establish optimal doses for health.

Cancer

Back in 1997, Jang and colleagues reported the ability of resveratrol to inhibit carcinogenesis at
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multiple stages, including tumor initiation, promotion, and progression. Resveratrol affects all three discrete stages of carcinogenesis by modulating cell-signal transduction pathways that help control cell division and growth, apoptosis, inflammation, angiogenesis, and metastasis. Data from a number of studies point to the fact that resveratrol exerts antiproliferative effects via its ability to influence specific cell receptors involved in apoptosis (programmed cell death). Epidemiological studies show that long-term inhibition of cyclooxygenase activity significantly reduces the risk of developing many cancers. In fact, deletion of the gene for cyclooxygenase-2 (COX-2) was shown to be protective in a mouse model of colon cancer. Increased COX-2 activity promotes inflammation and cell growth. Resveratrol demonstrates an ability to reduce total cyclooxygenase activity of tumors and normal tissue through moderate inhibition of COX-1 activity and/or reduction of COX-2 gene expression.

Given the numerous mechanisms whereby resveratrol exerts its effects, many scientists believe it to be a promising anticancer therapy. Currently, several human clinical trials are underway. Scientists are hopeful that these studies will give us a better understanding of the mechanisms and clinical efficacy of resveratrol in specific forms of cancer.

Neurodegenerative Disease
The pathogenic processes involved in neurodegenerative disorders are similar and are related to the mechanisms that are part of aging. Cognitive decline is a prominent “symptom” of the aging process. Alzheimer’s disease (AD), the most common age-related neurodegenerative disease, is characterized by the presence of neurofibrillary tangles and beta-amyloid plaques in the cortex and hippocampus—areas of the brain responsible for memory and learning. In 1997, one of the first studies reported that moderate to mild wine consumption was associated with a low risk of AD. More specifically, moderate consumption of red wine was shown to reduce beta-amyloid levels in a mouse model of AD. Studies suggest that resveratrol has significant antiamyloidogenic and antifibril effects, suggesting that it may act as an antioxidant helping to prevent the production of toxic beta-amyloid proteins and precursors to the damaging neurofibrillary tangles.

As mentioned earlier (and again later on), resveratrol, like calorie restriction, has also been said to extend the lifespan of various organisms. It accomplished this by activating or “turning on” a family of genes known as sirtuins. By activating SIRT1, one member of the sirtuin gene family, resveratrol may help attenuate beta-amyloid deposition and associated neuropathology. Resveratrol is thought to offer promise for the treatment and prevention of Alzheimer’s disease, and, in addition, given its various biological effects, may also be of benefit in Parkinson’s disease, Huntington’s disease, and other neurological disorders.

Resveratrol and Lifespan
The ability of resveratrol to mimic the beneficial effects that calorie restriction has on the lifespan of yeast (S. cerevisiae) was first demonstrated by David Sinclair, PhD, and colleagues in 2003. Since that time, the effects of resveratrol on a number of different organisms such as the roundworm (C. elegans) and fruit fly (D. melanogaster) have been tested. In every case, resveratrol caused an increase in average lifespan of between 18% and 56%. Later studies in mice showed that high doses of resveratrol could prevent many of the ill effects of a high-fat diet by regulating some of the physiological and metabolic parameters involved in diabetes, cancer, and cardiovascular disease. Resveratrol has been shown to produce changes associated with longer lifespan, including increased insulin sensitivity, reduced insulin-like growth factor, increased mitochondrial number, and improved motor function. The researchers concluded that resveratrol may be able to reduce the negative health effects associated with a poor lifestyle.

Metabolism clearly plays a role in resveratrol’s mechanisms of action, which, similar to calorie restriction, may be linked to its role in the aging process. It is believed that high doses of resveratrol are required for maximum benefits. Richard Weindruch, PhD, and colleagues from the University of Wisconsin, Madison, demonstrated that even low doses (equal to about 4.9 mg/kg) of resveratrol are “as effective as calorie restriction in opposing the majority of age-related transcriptional alterations in the aging heart.” The collection of such alterations in gene expression is a biomarker of aging, and the results imply that similar to calorie restriction, resveratrol supplementation at low doses is likely an effective intervention in the retardation of cardiac aging.

The ability of resveratrol to activate sirtuins is one significant mechanism believed to account for its effects on metabolic physiology and lifespan. It is this mechanism that has led scientists to
vigorously pursue the study of resveratrol in some of the chronic age-related diseases such as diabetes, cardiovascular disease, and cancer. We are eagerly awaiting the results of ongoing clinical trials, which may give us even more insight into the mechanisms whereby resveratrol exerts its effects and possibly help determine dosing, safety, and efficacy in a wide variety of chronic conditions.

References:


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