

Resveratrol: Cutting-Edge Technology Available Today

by Terri Mitchell



Wine. No other beverage has attracted the attention of modern medicine like this drink. Although it is most widely known for its benefits for the heart, wine has benefits against cancer, dementia, and other age-related diseases.

Researchers in Denmark recently looked at 25,000 people to find out what drinking alcohol does to mortality and discovered that wine drinkers slash their overall risk of dying from any cause by about 40%. [1]

Chemists took wine apart years ago to find out what makes it tick. Basically, it contains a host of plant compounds. Unfortunately, resveratrol and some of the other beneficial components got shelved as “toxicants,” and nobody paid much attention to them until a scientist tried to figure out why the French can eat so much fat and not get heart disease. It turns out that part of the answer to the “French paradox” is resveratrol found in red wine.

Resveratrol is naturally created by certain vines, pine trees, peanuts, grapes, and other plants. One of these plants (*Polygonum cuspidatum*) is an ingredient in traditional Asian medicines that are prescribed for liver and heart conditions. Resveratrol is classified as a polyphenol because of its chemical structure. Polyphenols make up a huge group of plant compounds that are further broken down into other classifications such as flavonoids, proanthocyanidins, and the like.

In the early '90s, after wine was pinpointed as the probable answer to the “French paradox,” researchers realized that the resveratrol content of wine might be the secret ingredient behind the healthy heart effects attributed to it and the traditional Asian heart medicines containing *Polygonum*. Research began in earnest, and just over a decade later, the accolades are enormous: “marked antioxidant activity,” “shows great promise for preventing cardiovascular disease,” “remarkable inhibitor,” “chemotherapeutic, little or no toxic effects in healthy cells,” “high efficacy against multiple sites.” Dozens of studies were published in this past year alone. Research has uncovered a diverse range of activities that may make resveratrol one of the most useful agents ever discovered for a wide range of human health problems.*

Heart/Blood Vessels and Resveratrol

When researchers deconstruct heart disease, they see many different things happening at the level of the cell. Cholesterol and other fat-related substances are one small part of a bigger picture that involves many other factors. Fortunately, many facets of heart disease can be controlled through dietary means. Resveratrol is a dietary agent that has powerful and diverse effects on the heart and blood vessels.*

The “French paradox” says that a person can eat a lot of fat, yet not get heart disease. Why? One of the reasons is that the wine they drink contains resveratrol, which is a powerful antioxidant. By now, many people have heard that oxidized low-density lipoprotein (LDL) is a problem in heart disease. This is why vitamin E helps prevent heart problems—it scavenges the radicals that oxidize this fat/protein. However, the kind of radicals that vitamin E blocks are not the only kind of free radicals people have to worry about. There are other types. In a study published in *Free Radical Research*, [2] resveratrol was put to the test against vitamin E and a synthetic antioxidant. All three were very good at scavenging artery-damaging radicals, but resveratrol emerged as the best defense against certain types of radicals. This points out the importance of using a multi-approach to antioxidants.*

One of the serious complications of free radical damage is hardening and thickening of arteries. A “vicious cycle” of radicals, artery damage, and narrowing due to scar tissue that, in turn, promotes more free radical activity and more damage, has been described. [3] Resveratrol, melatonin and Probuco are suggested as treatments for this progressive process. Resveratrol’s antioxidant action helps stop free radical damage and opens the arteries by enhancing nitric oxide.*

Nitric oxide is a critical component of heart/artery function. It allows blood vessels to “relax,” which enhances blood flow. In a recent study, a high-cholesterol diet decreased nitric oxide by about a third. Resveratrol supplements significantly reversed the trend.[4] In this respect, resveratrol is similar to Viagra, which also affects nitric oxide. However, whereas Viagra only affects small vessels, resveratrol affects the main arteries.*



Finally, resveratrol also stops the proliferation of cells in blood vessels that narrow the arteries,[5] and it also keeps blood cells from sticking together.[6] Both are very important for preventing heart attacks. The ability of resveratrol to keep blood cells from sticking together was investigated by Canadian researchers who wanted to know what role, if any, other components of wine might play in the process. They found that ethanol itself inhibited one type of stickiness-promoter (thrombin), and quercetin (another polyphenol) inhibited a different one (12-HETE), but nothing else they tested was active against this aspect of heart disease except resveratrol, which inhibited not only thrombin, but a host of other stickiness-promoting factors.[7]*

Alzheimer’s and Resveratrol

It was shown recently that resveratrol possesses a “novel mechanism” for scavenging radicals.[8] Might this novel mechanism protect the brain from free radical-driven diseases like Alzheimer’s?*

Although the research is very preliminary, studies indicate that resveratrol may be particularly important for those at risk for Alzheimer’s, or those who have it. It is theorized that free radicals might initiate the process that leads to the disease.[9] The brain is composed mostly of fatty acids, and just as the heart needs to be protected against oxidized fat, so does the brain.*

Alzheimer’s patients produce an abnormal peptide (a piece of a protein) known as “beta-amyloid” in their brains. Beta-amyloid provokes oxidative stress, and eventually cells are killed because of the abnormally high levels of free radicals. The killing of brain cells causes the gradual decline in Alzheimer’s patients. It has been proven that resveratrol can protect the brain against oxidative stress, and keep cells alive.[9,10] Research shows that adding vitamins C and/or E to resveratrol provides a greater degree of brain protection than any of the antioxidants alone.[11]*



Spinal Cord Injury, Stroke and Resveratrol

A recent study by Chinese researchers is notable.[12] If confirmed by other researchers, it could be very important for people who undergo serious brain/spinal trauma or stroke. In these types of injuries, the body’s response causes further injury, and for that reason, people are treated with drugs like cortisone, and in the case of stroke— aspirin. The idea is to reduce the body’s inflammatory response to the injury.

The study from China showed that resveratrol reversed the signs of inflammatory response to spinal cord injury on a level comparable to prednisone (a steroid used to reduce inflammation), but with better energy compensation and protection against free radicals, when injected immediately after injury. Besides helping to ameliorate this type of injury through free radical blockade, resveratrol actually inhibits specific enzymes that change the way individual cells respond to the injury. It’s possible that if a person regularly takes supplemental resveratrol, they will be more likely to withstand a stroke or other injury to the brain. This has been demonstrated in rodents pretreated 21 days with resveratrol.[13] Less motor damage, and less brain damage occurred post-stroke.*

Cancer and Resveratrol

Cancer is, perhaps, the most dynamic area of resveratrol research. Resveratrol is the first natural medicinal to have solid evidence behind it showing that it blocks or stops many stages of cancer. Resveratrol not only

prevents cancer, it's being proposed as an additional treatment.[14-16]*

The number of studies has exploded in the past three years, with the depth of knowledge about this polyphenol increasing with each report. Resveratrol is a broad-spectrum agent that stops cancer in many diverse ways, from blocking estrogen and androgens to modulating genes.[17-20]*

Some of the latest information about it shows that resveratrol causes a unique type of cell death,[14] and kills cancer cells whether they do or do not have the tumor suppressor gene, p53.[21] It also works whether cancer cells are estrogen receptor-positive or negative.[18,22]*

In addition to these findings, researchers are beginning to uncover the ability of resveratrol to augment other chemotherapies. For example, vitamin D3 converts to a steroid that inhibits the growth of breast cancer cells. Researchers at the University of Notre Dame have shown that resveratrol increases the effects of vitamin D.[23] Other research shows that it causes drug-resistant non-Hodgkin's lymphoma cancer cells to become susceptible to chemotherapeutic drugs (Gemcetabine, Navelbine, cisplatin, Paclitaxel, and TRIAL).[14]*

Researchers in Austria have done elaborate studies showing that resveratrol blocks the ability of cancer cells to metastasize to bone (30-71%).[24] The highest results were for pancreas, breast, and renal cancer. Prostate and colon cancers were also inhibited, but not as much.*

Resveratrol also acts against a component of the Western diet that promotes cancer cell growth: linoleic acid. Linoleic acid is converted to arachidonic, which is converted to hormone-like substances (such as prostaglandin E2 and leukotriene B4) that can promote inflammatory processes that stimulate cancer cell growth, among other things. It has been demonstrated that the Western diet can cause colon cancer in rodents without any other chemical or factor being necessary.[25] In a study from Japan, resveratrol in an amount easily obtained by supplementation, inhibited the growth of breast cancer cells, and blocked the growth-promoting effects of linoleic acid from the Western diet.[26]*

Resveratrol works against a wide range of cancers, both at the preventive and treatment stages. Its ability to stop cancer is connected to its capability, first, to distinguish a cancer cell from a normal cell. Unlike chemotherapeutic drugs that affect normal as well as cancer cells, resveratrol does not damage healthy cells. Not only is it not harmful to normal cells, it protects them.[27,28] Second, resveratrol is sophisticated in its actions. It doesn't just scavenge free radicals, it activates and deactivates critical enzymes and genes, hormones and chemicals.[29-31,14,19]*

Resveratrol Activates a Longevity Gene

In a widely publicized report, researchers at Harvard Medical School and BIOMOL Research Laboratories have demonstrated that resveratrol activates a "longevity gene" in yeast that extends life span by 70%. The effects mimic those of calorie restriction, the only proven way of extending maximum life span. Resveratrol activates one of the same "sirtuin (SIR)" genes as calorie restriction. Although the research has only been done in yeast, flies and worms so far, humans have their own version of the same life span-extending gene.*

Cancers Inhibited by Resveratrol According to Published Research†
Colon
Neuroblastoma
Esophageal
Breast (all types)
Prostate (all types)
Leukemia (various types)

Resveratrol's ability to activate the gene has to do with its chemical structure, not its antioxidant potential. It works by increasing the rate of a reaction known as "deacetylation." Acetylation reactions affect whether a gene is "off" or "on." This is extremely important. In cancer cells, for example, genes are activated that aren't supposed to be, and vice versa. By controlling deacetylation, and augmenting the longevity gene, resveratrol is able to confer some serious life extension benefits—at least in lower critters. And, yes, acetylation modulators are being pursued for the treatment of cancer to restore the normal activation/deactivation of genes in cancer cells.*

Metastasis to bone
Skin
Pancreas
Ovarian
Melanoma
Liver
Lung
Stomach
Oral
Cervical
Lymphoma (various types)
Thyroid
†In rodents and/or cell culture

One of the known causes of aging and death is that older cells lose their ability to perfectly replicate DNA in every new cell. DNA "mistakes" accumulate and allow little pieces of DNA to become active and print themselves out, so to speak, creating a type of "DNA debris" that eventually stops a cell from functioning. It is similar to printing out a report and having a couple of pages at the end not contain any relevant information—so you throw them away. The cell can't throw away the extra "printed out" DNA; it accumulates and clogs up the cell. This build up of "debris" is connected to aging, and the death of individual cells. Resveratrol reduces the frequency of "DNA debris" by 60% through the longevity gene that it stimulates.*

How Much Resveratrol Is In Wine

In order to understand how much resveratrol is in wine, one must realize that resveratrol is a natural substance made by grapes and other plants in response to fungal infection. How much resveratrol is in a glass of wine depends, first, on whether the grapes were grown organically, and, second, how the wine was made. Grapes sprayed with pesticides that prevent fungal infection contain little, if any, resveratrol. Wines grown in dry climates have less resveratrol than those grown in humid areas. Red wines contain more than white because of how red wine is made. The end result of all of this is that organic red wines from certain areas of Europe contain the highest level of resveratrol. But most wines contain either no resveratrol at all, or very little (less than a milligram per glass).



The only sure way to obtain a certain amount of resveratrol daily is to take a standardized extract. Standardization ensures a consistent amount of resveratrol with consistent high quality. The finest resveratrol available comes from Europe. It is made from organic French grapes known for their high resveratrol content. The resveratrol is carefully extracted to retain other compounds (polyphenols) that naturally occur with it. This pharmaceutical wine extract is then enhanced with resveratrol extracted from the roots of a medicinal plant (*Polygonum cuspidatum*) used for centuries in Asia for the treatment of inflammation, heart, blood vessel and liver disease, skin and lipid problems. The result is a product that retains the active parts of wine in a natural balance with increased potency and consistent quality.

The Hidden Dangers of Alcohol

Although red wine has been shown to confer some benefits, it must be noted that excessive consumption of alcohol can be dangerous to one's health.

Alcohol is the most socially acceptable addictive drug that has life-threatening health hazards. Alcohol consumption is so ubiquitous that people often don't realize how dangerous it can be.

Alcohol is a proven carcinogen, and those who drink have significantly higher rates of brain, esophageal, liver, breast, and other cancers.[32] About one-third of heavy drinkers develop peripheral neuropathy.[33]*

Most people associate drinking alcohol with liver cirrhosis. Mortality statistics, however, show that increased cancer risk may be the real concern.*

Smokers generally know that smoking is hazardous to their health. Yet most people are not aware of how dangerous alcohol is from a statistical standpoint. Epidemiological studies show lower heart attack rates amongst those who regularly consume moderate amounts of alcohol. Yet those same benefits—and more—may be obtained with polyphenols such as resveratrol, EGCG (epigallocatechin gallate) from green tea and aspirin.*

Summary

The research on resveratrol is so voluminous that it's not possible to cover it in one article. In addition to the benefits mentioned previously, resveratrol has been tested for its ability to stop pain,[34] stop the growth of the bacteria that causes stomach ulcers that can lead to cancer (*Helicobacter pylori*),[35] protect immune cells,[36] protect DNA,[37] protect against skin cancer,[38] and many other conditions. As pointed out earlier, recently resveratrol became the first-ever supplement known to activate a longevity gene.



While it is important to point out that a lot of the research on this wine extract has been done only in test tubes or rodents, the sheer volume suggests that resveratrol is one of the most versatile and effective plant compounds discovered so far. Resveratrol represents a novel solution to many common problems encountered by aging humans.

References

1. Gronback, M. et al. Type of alcohol consumed and mortality from all causes, coronary heart diseases, and cancer. *Ann. Intern. Med.* 2000;133:411-19.
2. Tadolini, B. et al. Resveratrol inhibition of lipid peroxidation. *Free Radic. Res.* 2000;33:105-14.
- 3 Simonini, G. et al. Emerging potentials for an antioxidant therapy as a new approach to the treatment of systemic sclerosis. *Toxicology* 2000;155:1-15.
- 4 Zou JG, et al. Effect of red wine and wine polyphenol resveratrol on endothelial function in hypercholesterolemic rabbits. *Int. J. Mol. Med.* 2003;11:317-20.
- 5 Haider, U.G. et al. Resveratrol increases serine 15-phosphorylated but transcriptionally impaired p53 and induces a reversible DNA replication block in serum-activated vascular smooth muscle cells. *Mol. Pharmacol.* 200;363:925-32.
- 6 Zbikowska, H.M. et al. Antioxidants with carcinostatic activity (resveratrol, vitamin E and selenium) in modulation of blood platelet adhesion. *J. Physiol. Pharmacol.* 2000;51:513-20.
- 7 Pace-Asciak, C.R. et al. The red wine phenolics trans-resveratrol and quercetin block human platelet aggregation and eicosanoid synthesis: implications for protection against coronary heart disease. *Clin. Chim. Acta.* 1995;235:207-19.
- 8 Burkitt, M.J. et al. Effects of trans-resveratrol on copper-dependent hydroxyl-radical formation and DNA damage: evidence for hydroxyl-radical scavenging and a novel, glutathione-sparing mechanism of action. *Arch. Biochem. Biophys.* 2000;381:253-63.
- 9 Draczyska-Lusiak, B. et al. Oxidized lipoproteins may play a role in neuronal cell death in Alzheimer disease. *Mol. Chem. Neuropathol.* 1998; 33:139-48.
10. Jang, J.H. et al. Protective effect of resveratrol on beta-amyloid-induced oxidative PC12 cell death. *Free*

Radic. Biol. Med. 2003;34:1100-10.

11. Chanvitayapongs, S. et al. Amelioration of oxidative stress by antioxidants and resveratrol in PC12 cells. *Neuroreport* 1997;8:1499-502.

12. Yang, Y.B. et al. Effects of resveratrol on secondary damages after acute spinal cord injury in rats. *Acta. Pharmacol. Sin.* 2003; 24:703-10.

13. Sinha, K. et al. Protective effect of resveratrol against oxidative stress in middle cerebral artery occlusion model of stroke in rats. *Life Sci.* 2002;71:655-65.

14. Cal, C. et al. Resveratrol and cancer: chemoprevention, apoptosis, and chemoimmunosensitizing activities. *Curr. Med. Chem-Anti-Cancer Agents* 2003;3:77-93.

15. Pervaiz, S. Resveratrol—from the bottle to the bedside? *Leuk. Lymphoma* 2001;40:491-8.

16. Ding, X.Z. et al. Resveratrol inhibits proliferation and induces apoptosis in human pancreatic cancer cells. *Pancreas* 2002;25:e71-e76.

17. Gusman, J. et al. A reappraisal of the potential chemopreventive and chemotherapeutic properties of resveratrol. *Carcinogenesis* 2001;22:1111-17.

18. Lu, R. et al. Resveratrol, a natural product derived from grape, exhibits antiestrogenic activity and inhibits the growth of human breast cancer cells. *J. Cell. Physiol.* 1999;179:297-304.

19. Serrero, G. et al. Effect of resveratrol on the expression of autocrine growth modulators in human breast cancer cells. *Antioxid. Redox. Signal* 2001;3:969-79.

20. Mitchell, S.H. et al. Resveratrol inhibits the expression and function of the androgen receptor in LNCaP prostate cancer cells. *Cancer Res.* 1999;59:5892-5.

21. Narayanan, B.A. et al. Interactive gene expression pattern in prostate cancer cells exposed to phenolic antioxidants. *Life Sci.* 2002;70:1821-39.

22. Pozo-Guisado, E. et al. The antiproliferative activity of resveratrol results in apoptosis in MCF-7 but not in MDA-MB-231 human breast cancer cells: cell-specific alteration of the cell cycle. *Biochem. Pharmacol.* 2002;64:1375-86.

23. Wietzke, J.A. et al. Phytoestrogen regulation of a vitamin D3 receptor promoter and 1.25-dihydroxyvitamin D3 actions in human breast cancer cells. *J. Steroid Biochem. Mol. Biol.* 2003; 84:149-57.

24. Ulsperger, E. et al. Resveratrol pretreatment desensitizes AHTO-7 human osteoblasts to growth stimulation in response to carcinoma cell supernatants. *Int. J. Oncol.* 1999;15:955-59.

25. Lipkin, M. et al. Dietary factors in human colorectal cancer. *Annu. Rev. Nutr.* 1999;19:545-86.

26. Nakagawa, H. et al. Resveratrol inhibits human breast cancer cell growth and may mitigate the effect of linoleic acid, a potent breast cancer cell stimulator. *J. Cancer Res. Clin. Oncol.* 2001;127:258-64.

27. Zhuang, H. et al. Potential mechanism by which resveratrol, a red wine constituent, protects neurons. *Ann. N.Y. Acad. Sci.* 2003;993:276-86.

28. Floreani, M. et al. Oral administration of trans-resveratrol to guinea pigs increases cardiac DT-diaphorase

and catalase activities, and protects isolated atria from menadione toxicity. *Life Sci.* 2003;72:2741-50.

29. Ferguson, L.R. Role of plant polyphenols in genomic stability. *Mut. Res.* 2001;475:89-111.

30. Casper, R.F. et al. Resveratrol has antagonist activity on the aryl hydrocarbon receptor: implications for prevention of dioxin toxicity. *Mol. Pharmacol.* 1999;56:784-90.

31. Hsieh, T.C. et al. Cell cycle effects and control of gene expression by resveratrol in human breast carcinoma cell lines with different metastatic potentials. *Int. J. Oncol.* 1999;15:245-52.

32. Bagnardi V. et al. A meta-analysis of alcohol drinking and cancer risk. *BR. J. Cancer.* 2001;85:1700-1705.

33. Agelink, M.W. et al. Alcoholism, Peripheral neuropathy (PNP) and cardiovascular autonomic neuropathy (CAN). *J. Neurol. Sci.* 1998 Dec 11;161(2):135-42.

34. Torres-Lopez, J.E. et al. Comparison of the antinociceptive effect of celecoxib, diclofenac and resveratrol in the formalin test. *Life Sci.* 2002;70:1669-76.

35. Mahady, G.B. et al. Resveratrol and red wine extracts inhibit the growth of CagA+ strains of *Helicobacter pylori* in vitro. *Am. J. Gastroenterol.* 2003;98:1440-1.

36. Yen, G.C. et al. Effects of resveratrol and 4-hexylresorcinol on hydrogen peroxide-induced oxidative DNA damage in human lymphocytes. *Free Radic. Res.* 2003;37:509-14.

37. Revel, A. et al. Resveratrol, a natural aryl hydrocarbon receptor antagonist, protects lung from DNA damage and apoptosis caused by benzo[a]pyrene. *J. Appl. Toxicol.* 2003;23:255-61.

38. Adhami, V.M. et al. Suppression of ultraviolet B exposure-mediated activation of NF-kappaB in normal human keratinocytes by resveratrol. *Neoplasia* 2003;5:74-82.