

Wine & Health

A look at the latest research and most promising discoveries

From *Wine Spectator* magazine, [May 31, 2009 issue](#)

Each week seems to bring forward a new study on the health benefits of moderate wine consumption. Evidence continues to mount that wine drinking goes hand in hand with a healthy lifestyle and is a powerful means of preventing heart disease. In addition, there has been solid research over the past few years regarding how [wine may help prevent or relieve the effects of dementia, diabetes and even osteoporosis](#).

Many of the recent discoveries involve a compound in wine called resveratrol. What began as research into the unexplained health benefits of wine has turned into a fascinating quest to realize one of mankind's greatest dreams: [to prolong the human life span](#). For more on scientists' efforts to unlock the potential power of resveratrol, see "[Harnessing Wine's Healing Powers](#)," beginning on page 54.

As in any area of scientific inquiry, the findings presented in this report should be viewed in context. The conclusions of any single study or group of studies are always subject to ongoing research. With that in mind, we interviewed six leading researchers and physicians for their advice on how to incorporate wine into a healthy diet; their collected responses, "[Doctors Roundtable](#)".

As always, however, you must ultimately be your own advocate. Use this guide as a broad outline to help inform your decisions about wine and your health, and be sure to consult your physician before embarking on any new lifestyle regimen.

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Wine & Health: Research and Findings: A User's Guide to Wine Science

Summaries of recent findings and what they may mean for wine drinkers

By [Kim Marcus](#)

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TENDING TO THE HEART

The most important factor in gleaning health benefits from wine appears to be the amount of wine consumed. Many studies have shown that regular and moderate consumption (one to two glasses per day) of red wine is associated with the greatest amount of benefits, such as better circulation and overall heart health.

A fascinating new angle of study is being pursued by researchers at Stanford University, who have discovered that one of the factors behind alcohol's effect on the heart is that it activates an enzyme called aldehyde dehydrogenase 2. The enzyme, which helps process alcohol, also eliminates toxic byproducts created by the breakdown of fats in cells during a heart attack. Eliminating the byproducts prevents additional damage to the heart cells.

DELAYING DEMENTIA

Several studies have not only amassed evidence that moderate wine-consumption may help delay the onset of Alzheimer's disease and other forms of dementia, but are also now detailing the complicated physiological processes at play.

Two proteins known as amyloid-beta peptides are associated with Alzheimer's. These long protein strands tend to clump together, forming plaques that kill surrounding brain cells. Researchers at the University of California, Los Angeles, and the Mt. Sinai School of Medicine in New York have found that grape seed polyphenols block the formation of the plaques. "If the amyloid-beta proteins can't assemble, toxic aggregates can't form, and thus there is no toxicity," says David Teplow, a UCLA neurology professor. "Our work in the laboratory suggests that administration of the compound to Alzheimer's patients might block the development of these toxic aggregates, prevent disease development and also ameliorate existing disease."

PREVENTING ARTHRITIS

Researchers in Sweden have found that drinking an average of five to 10 glasses of wine per week may cut the risk of developing rheumatoid arthritis by up to 50 percent, compared with the risk to nondrinkers.

In addition, other studies have found that moderate wine-drinking is linked to increased bone density in elderly women, possibly lowering their risk of osteoporosis.

DEMYSTIFYING WINE HEADACHES

What causes some people to suffer headaches after drinking wine? Frederick Freitag, associate director of the Diamond Headache Clinic, says identifying the specific triggers that cause these headaches can be tricky, as there are different types of headaches that people experience when they drink wine. "There is a unique headache associated with red wines, which is different from the headache some people get from drinking wine of any sort, which is different still from the migraines some patients experience related to wine ingestion," he says.

Still, some conjectures can be ruled out. Freitag believes histamines, which are found in higher amounts in red wine, are an unlikely cause of headaches, as they exist in greater levels in other frequently consumed foods. "There is more histamine in 4 ounces of fish or a serving of eggplant than in 4 ounces of red wine," he notes, adding that a more common allergic reaction to histamines is a stuffy nose.

Similarly, the small amount of sulfites found in wines is often mistakenly identified as a headache-causing agent. These sulfites are also found in other food sources, such as dried fruit, baked goods and pickled vegetables. A serving of dried apricots, for example, contains almost 10 times the amount of sulfites of a serving of wine. And an allergic reaction to sulfites usually involves breathing trouble and rashes, not headaches.

Headaches could be triggered by the alcohol in wine, says Freitag, which would explain why red wine, which is generally higher in alcohol, seems to pose more problems for certain people. Another possible culprit is tyramine, an amino acid derivative that is produced during fermentation. Tyramine is especially suspected "for triggering migraine in up to about 40 percent of the migraine population," according to Freitag. (For more on information on tyramine, see "[Doctors Roundtable](#)".)

HEADING OFF A COLD

The Mayo Clinic recommends avoiding alcohol when you have a cold, because alcohol can contribute to dehydration. The good news, however, is that wine drinkers may be less likely to come down with colds in the first place. One Spanish study showed that participants who regularly drink eight to 14 glasses of wine a week are half as likely to develop a cold as those who drink beer, spirits or no alcohol at all.

KEEPING THE FLU AWAY

Researchers at the University of South Carolina say that a chemical found abundantly in red wine, apples and onions helps protect against influenza, especially after a rigorous respiratory workout, when the body is more susceptible to infection. The chemical, a polyphenol called quercetin, is a known anti-inflammatory found in the skins of fruit and vegetables.

Prior studies have theorized that quercetin helps reduce lung inflammation and inhibits the growth of prostate cancer. The specific anti-viral properties of quercetin remain unknown, but researchers speculate that the compound may block the ability of the influenza virus to replicate itself.

LOWERING DIABETES RISK

People who consume moderate amounts of wine daily appear to be at an advantage when it comes to preventing type 2 diabetes; studies have shown that light to moderate drinkers may have a substantially lower risk of developing the disease. A Harvard School of Public Health study from 2003 found that women 25 and older who consumed a glass or two of alcohol a day were at a 58 percent lower risk of developing diabetes than nondrinkers.

Researchers speculate that alcohol consumption, and red wine specifically, might help regulate insulin sensitivity and blood glucose levels by slowing the passage of glucose through the digestive tract. Those diagnosed with diabetes may benefit from drinking wine as well—the risk of coronary heart disease was up to 55 percent lower in studies for diabetics who drank alcohol in moderation.

COUNTING CARBS

Wines vary somewhat in nutritional content, but the USDA National Nutrient Database for Standard Reference, which lists general nutritional information for table wines, reveals that the carbohydrate counts are lower than you might think. The average 5-ounce glass of Cabernet Sauvignon comes in at 3.82 grams of carbohydrates; Merlot is similar, at 3.69 grams. A serving of non-light beer has more than twice the carbohydrates, and a sweetened soft drink may have up to 10 times the amount.

In addition, researchers in Spain report that the grapes used to make red wines contain significant levels of fiber. They've found that the fiber and antioxidants in Tempranillo in particular seem to reduce blood pressure and cholesterol better than other sources of dietary fiber, specifically oats and psyllium. The study is a follow-up to earlier experiments conducted by the same team that found that drinking 300ml of red wine per day increased soluble dietary fiber intake in Spanish men.

REDUCING THROAT CANCER RISK

Drinking wine in moderation may offer protection from the onset of Barrett's Esophagus, a precursor to esophageal cancer, according to a study released in March. Researchers found that subjects who consumed between seven and 14 glasses of wine weekly lowered their chances of developing the disorder by 56 percent. Barrett's Esophagus occurs when gastroesophageal reflux disease, or chronic heartburn, permanently damages the cells of the esophagus; the abnormal healing of the esophagus can lead to a cancer called adenocarcinoma. "Red wine and many foods, such as fruits and vegetables, contain antioxidants. It appears antioxidants may decrease the risk of getting Barrett's Esophagus," explains Douglas Corley, a gastroenterologist and one of the study's lead researchers.

EXERCISING AND WINE

According to Douglas McKeag, director of the Indiana University Center for Sports Medicine, it is not "bad" for your health if you have mildly imbibed prior to exercise; it does stimulate the heart somewhat, but so does a pre-workout warmup. Other

physiological effects of alcohol in moderation include dilation of the peripheral blood vessels and relaxation of the muscles.

But McKeag also warns of the unwanted, even potentially dangerous depending on the type of athletic pursuit, effects of too much alcohol, such as sedation and inhibition of judgment. If a meal with wine is scheduled prior to your exercise session, McKeag advises limiting your consumption to one glass.

MAXIMIZING MELATONIN

In a study published online by the Journal of the Science of Food and Agriculture, several winegrapes traditional to France and Italy were found to be rich in melatonin, a hormone that not only tells the body it's time to turn in for the night, but also acts as a powerful antioxidant and detoxifies cells. Eight varieties were tested in the study; Nebbiolo was found to contain the most melatonin, followed by Croatina, Barbera, Cabernet Sauvignon, Sangiovese, Merlot, Marzemino and Cabernet Franc. Alcoholic drinks before bedtime are discouraged by the National Heart, Lung and Blood Institute, however: "Alcohol robs you of deep sleep and REM sleep, keeping you in the lighter stages of sleep," the institute's healthy-sleep guide says.

PRODUCING FATTY ACIDS

European scientists have linked moderate alcohol consumption, especially wine drinking, to higher levels of omega-3 fatty acids in the blood. These fatty acids, prevalent in oily fish, have been found to help lower the risk of heart disease. While the body cannot manufacture these fatty acids, it can apparently synthesize omega-3 from everyday vegetable oils with the help of alcohol.

DRINKING FLAWED WINES

Concerned about those off scents coming from your wine bottle? They could be caused by TCA (2,4,6-trichloroanisole), a chemical that contaminates the corks, or by excessive growth of brettanomyces, a common yeast present in most fermented beverages. The former produces smells such as mold or wet cardboard, while the latter can be identified by aromas such as leather or barnyard.

Despite the unpleasant scents, enologist Pascal Chatonnet of the University of Bordeaux reports there is nothing dangerous about them. Regarding the safety of drinking either corked wine or wine showing brettanomyces, he says, "Don't worry about your health, there is absolutely no risk. However, there is also no pleasure in tainted wines."

WINE AND HEALTH GLOSSARY

ALCOHOL DEHYDROGENASE

Enzyme found in the digestive tract that helps the body break down alcohol. Women typically produce less alcohol dehydrogenase than men (and so metabolize alcohol more slowly).

HDL CHOLESTEROL

High-density lipoprotein (HDL) cholesterol, aka "good cholesterol" in that it contains more proteins and less fat. A level of 60mg/dl of HDL is generally considered protective against heart disease by reducing inflammation in blood vessels and inhibiting the buildup of fatty deposits in the arteries. Low-density lipoprotein is known as "bad cholesterol"; an LDL of less than 100mg/dl is considered optimal. HDL cholesterol mops up LDL cholesterol and transports it to the liver, which breaks it down.

POLYPHENOLS

A class of chemical compounds found in plants, polyphenols fulfill a variety of functions, from providing color in fruits to fighting off infections; high levels are also found in the skins of grapes and other fruits. Polyphenols are divided into two classes: flavonoids and nonflavonoids. Flavonoids, which are abundant in wine, include flavonols, procyanidins (condensed tannins) and anthocyanins. The levels of these compounds greatly influence the overall taste, color and longevity of finished wines. Tannins are the most abundant polyphenol among the 4,000 found in the plant world. Several polyphenols, including procyanidins and quercetin, are being studied for their potential health benefits.

RESVERATROL

A polyphenol that functions as a plant's primary defense against damage from bacteria or fungi. Found in grape skins and red wine, resveratrol is the subject of intense study for its potential role in prolonging the human life span and in guarding against dementia, diabetes and cancer.

SIRT1

A human gene, part of a family of genes called sirtuins, being researched for its role in the aging process. SIRT1 may be activated by resveratrol and other polyphenols.

WOMEN & WINE

There is plenty of debate when it comes to balancing the potential health benefits of wine drinking with the particular issues that female drinkers face, some of which include pregnancy, breast cancer and even the way women metabolize alcohol differently than men. In the end, women should approach wine drinking with particular caution when it comes to these concerns.

PREGNANCY

Pregnant women have long been bombarded with conflicting medical advice on the subject of alcohol. While many countries where wine is viewed as part of a healthy lifestyle consider an occasional glass to be safe, doctors in the United States advise that the safest policy is no alcohol during pregnancy, as alcohol abuse has been linked to cognitive and developmental disorders in children, particularly fetal alcohol syndrome.

Yet some studies have indicated that not only can pregnant women safely drink a glass or two of wine per week, but that their children may perform better three years after birth when compared to children of women who did not drink at all. (It's yet to be determined whether this may be due to a correlation between wine drinking and demographic advantages.) Women who do decide to continue having wine during pregnancy should consume only minimal amounts, and always sipped slowly with food to avoid a rapid rise in blood-alcohol level.

CANCER RISKS

The medical community remains resolute in its warnings about an elevated breast cancer risk for women who drink. According to research conducted by the National Cancer Institute, women who consume between one and three drinks a day have a 24 percent increased risk of breast cancer compared with nondrinkers. Scientists theorize that alcohol affects the levels of hormones such as estrogen and progesterone in postmenopausal women, which may trigger breast cells to become cancerous.

A recent study from the Cancer Epidemiology Unit at Oxford University issued a warning to middle-aged women, finding that even light to moderate amounts of alcohol can increase the risk of certain cancers, including breast cancer. Wine drinkers, when measured separately from drinkers of beer and spirits, fared little better in the findings, except for colon cancer. Alcohol consumption did appear to decrease the risk of non-Hodgkin lymphoma, thyroid cancer and the leading form of kidney cancer. After reading the findings, other scientists argued that further research is needed.

According to R. Curtis Ellison, a professor of medicine and public health at Boston University Medical School, data increasingly shows that for women who do not binge drink, have adequate folate intake, and are not on hormone-replacement treatment, the risk of breast cancer appears to increase only for consumers of more than one and a half drinks per day (about 6 to 7 ounces). He adds that responsible wine drinking is not without benefits for women: "The net effects are striking, as small amounts of alcohol

lower the risk of the more-common causes of death among women, such as heart disease, stroke, hip fracture and dementia."

ONE DRINK PER DAY

Why do alcohol intake limit recommendations differ by gender? According to Tim Naimi, a researcher for the Center for Disease Control, "Part of it has to do with the fact that on average, women weigh less, but also women have less alcohol dehydrogenase per unit of body mass. Alcohol dehydrogenase is an enzyme that metabolizes ethanol. Even if you take a comparably sized woman and man, women will metabolize alcohol more slowly, which means they have a greater cumulative exposure to alcohol."

The Dietary Guidelines for Americans, published jointly by the Department of Health and Human Services and the Department of Agriculture, defines moderate consumption for women as one glass (5 ounces) of wine per day, reflecting research that suggests this amount delivers the most beneficial health effects and that greater amounts increase certain risks. Kim Marcus and Jacob Gaffney

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Wine & Health: A Body of Wine Research

A visual guide to wine's potential impact on your body

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BRAIN

Men who consume one to two glasses of red wine a day have a 40 percent lower risk of suffering an ischemic stroke, according to a 2003 Harvard study. Scientists have also found that grape seed polyphenols block and neutralize the toxic plaques that build up and kill cells in the brains of Alzheimer's patients. And one research team recently announced that a combination of wine, dark chocolate and tea, in moderate amounts, enhances cognitive performance in the elderly.

EYES

Moderate red-wine drinkers run roughly half the risk of developing cataracts as nondrinkers, according to a 2005 study in Iceland. And a 1998 survey in the United States found that wine drinkers are less likely to suffer from age-related macular degeneration.

THROAT

A Kaiser Permanente study published in March found that people who consume between seven and 14 glasses of wine a week have a 56 percent lower risk of Barrett's Esophagus, a condition caused by chronic heartburn and often a precursor to esophageal cancer.

HEART

Two decades of research strongly suggests that alcohol, and red wine in particular, can reduce the risk of atherosclerosis and heart attacks by as much as 60 percent. In 2007, a Harvard team found that men with hypertension can lower their risk of a heart attack by 30 percent by drinking a glass or two a day.

BREAST

Few areas of wine and health research are more contentious. Several studies have shown that alcohol can increase the risk of breast cancer, but studies differ on whether one glass of red wine a day represents risk. And a 2008 study found that resveratrol suppresses the metabolism of estrogen, protecting cells from becoming cancerous.

LUNGS

California researchers announced last year that men who drink red wine have a lower risk of lung cancer compared with nondrinkers. Nonsmoking men who drank a glass or two per day were 4 percent less likely to get lung cancer than nondrinkers; smokers who drank this amount also had a lower risk, although still much higher than nonsmokers'.

STOMACH

Israeli researchers found that red wine helps the stomach remove potentially harmful substances found in red meats, aiding digestion and lowering the risk of atherosclerosis, type 2 diabetes and colon cancer.

LIVER

Alcohol abuse can have a devastating impact on the liver, but a 2008 study found that a daily glass of wine decreases the risk of nonalcoholic fatty liver disease. Another study found that alcohol and resveratrol reduced the amount of fat produced in the livers of mice fed dangerous levels of alcohol and appeared to help livers break down existing fat.

PANCREAS

Spanish researchers found that sticking to a Mediterranean diet, which includes moderate wine-consumption, helps reduce the risk of developing type 2 diabetes by up to 83 percent. The diet, rich in olive oil, grains, fruits, nuts, vegetables and fish, and low in meat and dairy products, also appears to help type 2 diabetes patients better regulate their metabolism.

COLON

A study from the University of California, Davis, last year found that anthocyanins extracted from Cabernet Sauvignon grapes aided digestion in pigs and could possibly prevent colon cancer in humans. A 2006 Stony Brook University study found that white-wine drinkers had a 12 percent lower risk of colon cancer, while red-wine drinkers had a 68 percent lower risk.

OVARIES

Women who drink a glass or two of wine daily show about half the risk of developing ovarian cancer compared with nondrinkers or women who drink beer or spirits, according to an Australian study.

LEGS

Peripheral artery disease is a form of atherosclerosis that cuts off the blood supply to the legs. A Dutch study at the Erasmus University Medical Center of people aged 55 or older found that one or two alcoholic drinks a day lowered the risk of this disease.

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Wine & Health: Harnessing Healing Powers

Researchers race to figure out how resveratrol and other polyphenols can help us live longer

By [Mitch Frank](#)

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It was the report that changed the world's perception of a glass of wine. In 1991, *60 Minutes* correspondent Morley Safer came on television screens and told viewers what many wine drinkers had always secretly believed—that wine is good for us. It was "the French Paradox," a story explaining how the people of France could enjoy a foie gras- and Camembert-laden diet yet still have lower cholesterol and heart disease rates than Americans. The key appeared to be red wine. Within weeks of the program's airing, sales of red wine in the United States shot up 40 percent as Americans took it to heart that red wine could improve health.

Earlier this year, Safer was back on TV, introducing a story headlined "Wine Rx." It explained how scientists are studying a chemical compound in wine called resveratrol in the hope that it could be the most potent antiaging medicine man has ever devised. And *60 Minutes* isn't the only news outlet hailing resveratrol as a possible wonder drug. Scientific journals have recently been filled with studies theorizing the compound's possible benefits, suggesting that it could be a treatment for Alzheimer's, cancer, heart disease, diabetes and other ailments.

David Sinclair, the scientific mind behind Sirtris Pharmaceuticals, a Cambridge, Mass.-based firm on the cutting edge of resveratrol research, believes that resveratrol-based drugs could turn back the clock on age-related diseases by targeting the genes that control the aging process. "People have been promised life-span extension before, but now the world's leading researchers are working on it," Sinclair says. "It's not fringe science anymore. This is not snake oil."

The Harvard Medical School researcher has been involved in antiaging genetics work for a decade, starting out under the tutelage of Massachusetts Institute of Technology's Leonard Guarente, a pioneer in the field. Sinclair struck out on his own and founded Sirtris in 2004, and the move has paid off; his research is promising enough that drug giant GlaxoSmithKline purchased Sirtris for \$720 million last year.

The firm recently finished clinical trials that gave resveratrol pills to diabetes patients, and more trials are in the works. Actual resveratrol-based medications are still years away, but in the meantime, scientists are convinced that the compound and other polyphenols in wine show great promise. "There is a huge upside possibility that there are specific entities in wine, such as resveratrol, that have a positive, beneficial health effect,"

says Charles Burant, an antiaging researcher at the University of Michigan who focuses on potential diabetes treatments.

But there are those who question the amount of attention devoted to resveratrol. "The focus on resveratrol, or any one component of wine, is unfounded," says Tedd Goldfinger, a senior cardiologist at the Tucson Heart Center in Arizona. "Studies have shown that the broad effect of wine is independent of any single compound."

Whether resveratrol proves to be a wonder drug or not, Glaxo's investment in Sirtris is just one sign of how far wine-and-health research has come since that first *60 Minutes* story aired in 1991. After two decades of serious study, a huge amount of scientific research has revealed that red wine—if consumed in moderate amounts and combined with a healthful diet and exercise—offers significant benefits. Although the debate rages on, the majority of health experts are confident that wine is good for you.

"Personally, I think wine should be consumed socially and not as a medicine," says Andrew Waterhouse, chairman of the enology department at the University of California, Davis. "However, the data shows a reduction in total mortality in people who drink wine responsibly." This July, physicians and researchers will gather in Washington's Walla Walla Valley wine region for the fifth International Wine & Heart Health Summit, a four-day conference that Goldfinger currently chairs. Speakers will present the latest wine and health research, and in between seminars, attendees will participate in organized wine tastings.

So the question is no longer whether moderate consumption of wine is healthy, but why and how. What substances in wine provide benefits? And what's the best way to harness their potential to prolong life?

Before *60 Minutes* turned a spotlight on the French paradox, most modern medical research on alcohol consumption was concerned with the damaging effects of alcoholism. A 1979 report by a British team found alcohol could reduce the risk of heart disease, but received little attention in the United States. After French epidemiologist Serge Renaud proposed the theory that wine has heart health benefits in Safer's report, he and colleague Michel de Lorgeril published an article in a research journal to back up the idea.

Researchers followed up on Renaud and de Lorgeril's work, and in 1996, the *British Medical Journal* published a review of 25 studies that focused on alcohol's effects on heart disease. Results in the studies varied, but evidence of some benefits was clear: People who drink moderate amounts of alcohol have a 20 percent to 60 percent lower risk of heart disease than people who abstain. Alcohol appears to reduce the amount of "bad," or low-density lipoprotein (LDL), cholesterol in the body and increase the amount of "good," or high-density lipoprotein (HDL), cholesterol. It also combats the buildup of fatty deposits in arteries.

Most early research did not distinguish between wine, beer and spirits. Then scientists began to wonder whether there was something particularly beneficial about red wine.

Two large studies published in the mid-'90s, one in Denmark and one led by Renaud in France, found that while beer and wine drinkers both had lower rates of heart disease, subjects who drank wine had a lower rate of death from all sicknesses. Moderate wine drinkers were the healthiest group in both studies. A 20-year study by Arthur Klatsky, a senior consultant in cardiology at Kaiser Permanente Medical Center in Oakland, Calif., and his colleagues, published in 2003, showed similar results.

With substantial evidence pointing to wine drinkers enjoying better health, scientists began to ask why. One possible explanation is simple coincidence—the data reveals that wine drinkers tend to eat healthier diets, smoke less and exercise more than others. But while lifestyle may be a contributing factor, the evidence suggested that something in the wine itself must be having an effect.

The average glass of wine is roughly 80 percent water. Alcohol makes up another 12 percent to 15 percent. The remainder is a mix of acids, proteins, sugars and other organic compounds: glycerol, acetaldehyde, esters, minerals and polyphenols such as procyanidins, quercetin and resveratrol.

Polyphenols, the focus of researchers' attention, are chemical compounds in plants. They include flavonols, tannins, anthocyanins and nonflavonoids and carry out all kinds of functions, such as providing the color in flowers and fruits and fighting off bacterial infections. Flavonols, tannins and anthocyanins are responsible for much of the color and flavor in wine. They're present mostly in grape seeds and skins, and as red wine ferments, the developing alcohol extracts the compounds into the wine. Other polyphenols are found in oak, and wine can absorb them while aging in oak barrels. (That vanillalike flavor? It's provided by the polyphenol vanillin.) Polyphenols also exist in other foods, including apples, berries, onions, tea and chocolate.

According to Waterhouse, there are about 1,800 milligrams of polyphenolic compounds in an average liter of red wine (compared with an average of 412 milligrams in a liter of apple juice, according to a Czech University of Agriculture study). White wine also contains polyphenolic compounds, but in lesser amounts. Scientists have long been interested in the effects these compounds have on the body. A steady diet of polyphenol-rich food and wine has been proven to have health benefits. Polyphenols are powerful antioxidants, but most research has shown that the body doesn't metabolize the compounds in high enough doses for them to act effectively in that capacity.

Polyphenols may serve the more interesting function of chemical messengers to our cells. The body's cells are capable of responding to a variety of different stresses or signals by increasing or decreasing the production of certain proteins. Polyphenols may tell the cells to produce particular proteins that could fight off illnesses—for example, ones that reduce inflammation in cells or regulate cell division to prevent the growth of tumors. If scientists could figure out which polyphenols send which signals, they could develop medicines to fight specific diseases. Some scientists believe the compounds might even be able to control how cells age.

Resveratrol was first isolated in the 1960s in Japanese knotweed, a plant used as a popular Asian herbal remedy. Japanese researchers later noted that a substance in knotweed seemed to prevent fatty liver deposits in lab rats; that substance turned out to be resveratrol. In 1991, Cornell scientist Leroy Creasy managed to isolate resveratrol in red wines. The compound is a phytoalexin, an antibiotic in grape skins that defends against attacking bacteria and fungi. In a study the following year, Creasy and Evan Siemann, a student of Creasy's and now a professor at Rice University, theorized that resveratrol was at least partially responsible for red wine's cardiovascular health benefits. Researchers began experimenting with it as a treatment for various ailments.

In 1993, David Sinclair was studying biology at the University of New South Wales, not far from his childhood home in Sydney. During a lunch with a visiting lecturer, Leonard Guarente of MIT, Sinclair was inspired to pursue a career in Guarente's field, longevity research. He successfully applied for a postdoctoral research position in Guarente's Cambridge lab. "[At the time] people thought it was a ridiculous field to bet your career on," Sinclair recalls.

"In the early '90s, the idea of genes controlling life span was thought to be nuts," says Cynthia Kenyon, director of the Hillblom Center for the Biology of Aging at the University of California, San Francisco. Most experts believed that animals aged much like cars do: Over time, their parts broke down through wear and tear until they died. But longevity researchers suggested that aging might be encoded in our genes.

The same year that Sinclair met Guarente, Kenyon published a paper describing how she modified a single gene to double the life span of a species of roundworm. It was a huge breakthrough. Since that discovery, Kenyon has isolated other genes that have an impact on aging; she now has worms that live six times longer than normal. These genes appear to regulate cell functions, keeping cells healthy as they perform their daily tasks and cleaning up malfunctions.

In 1995, Guarente identified a gene in yeast that appeared to control aging, called SIR2. There are parallel genes in animals, including humans, who have a SIRT1 gene. The genes are part of a family called sirtuins. While Sinclair was working with him, Guarente postulated the theory that these genes are linked to diet. Scientists have found evidence that a nutritional diet containing 30 percent fewer calories than normal dietary guidelines can extend life span. They theorize that genes are programmed, when food is scarce, to slow aging, allowing an animal to survive until times are better and it can reproduce. Guarente believed caloric restriction might activate SIRT1. But because few people are willing to restrict caloric intake to the point of almost perpetual hunger, and because such a diet would cause other negative side effects, researchers set out to find a chemical compound that might activate the gene.

In 2003, several scientists at Biomol Research Laboratories in Plymouth Rock, Pa., discovered that SIRT1 was activated by certain polyphenols. Sinclair, by then working at Harvard Medical School, collaborated with scientist Konrad Howitz to identify one of the

polyphenols as resveratrol. They tested it in yeast, worms and fruit flies, and found that it extended their life spans.

By 2004, Sinclair was confident that resveratrol activated anti-aging genes, and he founded Sirtris to develop drugs based on the polyphenol that could treat specific diseases. Longevity researchers have theorized that many of the diseases we associate with growing older—heart disease, cancer, type 2 diabetes, dementia—are connected to cellular aging. So Sinclair focused on the fact that if resveratrol activates SIRT1, it could help cells fight off those diseases. "We all know that the body has very powerful self-healing properties," he says. "These sirtuin genes seem to be key regulators of the body's defenses against disease and aging. SIRT1 is kind of like the Pentagon—it controls the body's repair and defense systems."

In 2006, Sinclair, partnering with the National Institute on Aging in Bethesda, Md., published a study on mice and resveratrol. His team split the mice into four groups. Two were fed normal diets and two were fed high-fat diets. One group of fat mice and one group of normal mice were also fed high doses of resveratrol. At the end of the experiment, the fat mice on resveratrol were just as healthy as both groups of non-obese mice. They did not suffer from diabetes or heart disease. (Neither the obese mice on resveratrol nor the non-obese mice on resveratrol lived longer, however.)

Sinclair then moved on to tests of resveratrol on diabetes sufferers, announcing in April of last year that daily doses had lowered patients' glucose levels. Now, he's about to start trials with compounds that Sirtris has isolated that are similar to resveratrol but more potent. "Any drug development is risky, but I think the science is now at a point that it's not an 'if,' it's a 'when,'" he says. "If it's not in five years, it's 10."

Sinclair is an optimist, and many questions remain about resveratrol, its relationship to sirtuins, and whether sirtuins even control aging and aging-related diseases. Some members of the scientific community have had trouble reproducing Sinclair's results. Other scientists, including Kenyon and Stephen Helfand, a molecular biology professor at Brown University, have identified other genes that may control the aging process. (Kenyon helped found a rival company that develops drugs related to antiaging genes, Elixir Pharmaceuticals in Cambridge.)

The spotlight on resveratrol has raised another concern, however. Since the media began focusing on resveratrol as a potential wonder drug, it's become ingrained in the public imagination as the reason red wine helps keep people healthy. This has led to nutritional supplement firms eagerly touting products such as resveratrol pills. In Australia, one doctor recently released wines "enhanced" with extra resveratrol.

But crediting resveratrol for wine's health effects is like saying Ringo Starr is solely responsible for the Beatles' musical greatness. "I am always irritated by reports that suggest resveratrol accounts for the health benefit of red wine," says Roger Corder, a professor at the William Harvey Research Institute in London and author of *The Red Wine Diet* (Avery). "It has become something of an urban myth. Everybody should

recognize that the amount of resveratrol consumed in a glass of wine is about 1/1,000 to 1/10,000 of the amount required to show any effects in experimental studies."

It's true that most of the studies by Sinclair and others on resveratrol employ doses far larger than what's found in the average bottle of red wine. A 150-pound man would have to drink 1,500 bottles of Pinot Noir a day to get the same dose of resveratrol that Sinclair gave his mice.

So if resveratrol alone isn't responsible for red wine's health benefits, what is? The specifics remain unanswered for now, but there are several possibilities. Some early research focused on quercetin, although that polyphenol also comes in low doses in wine. Other researchers, including Corder, believe that another family of polyphenol, procyanidins, is responsible, at least for red wine's impact on heart health. Procyanidins come mainly from the outer coating of grape seeds, and red wines—especially tannic reds—contain far larger amounts of procyanidins than they do resveratrol.

Still others think that it's the combination of various polyphenols that gives red wine its healthful properties. Sinclair himself believes this, despite his focus on resveratrol as a drug. "I think that the cocktail of molecules in red wine is what's important, and resveratrol is one component," he says. "The combination of molecules in red wine could be synergistic and provide health benefits you would not otherwise see if you just took a single pure substance."

Sinclair thinks that red wine is more like a preventative medicine. "Drinking red wine over the course of your life is so different from [a doctor] hoping to see a treatment's effect on a patient in three weeks," he says. At Sirtris, Sinclair is developing treatments for people who are already ill, for example with diabetes or osteoporosis.

And that may be the most important distinction. Whatever substance or combination of substances in red wine is responsible for its health benefits, the evidence suggests that drinking red wine moderately can prevent sickness over the course of a life. And it's one of the reasons most of the doctors referenced in this story drink it regularly. "I drink wine every day," Kenyon says, "because I know it's good for me."

Frequent contributor Jacob Gaffney assisted in researching this report.

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Wine & Health: Roundtable

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There is a wealth of information linking wine and a healthy lifestyle. Some of it can be confusing or even conflicting. To help guide you through all the data and gain an overall vision of the best course of action when it comes to your personal health decisions, *Wine Spectator* interviewed several leading researchers for their take on some popular topics. Along with having knowledge of the latest clinical studies and firsthand experiences with patients, all of these doctors are wine drinkers, so they practice what they preach. — Jennifer Fiedler, Jacob Gaffney and Kim Marcus

R. CURTIS ELLISON, M.D.

Professor of medicine and public health

Boston University School of Public Health, Boston

In 1994, Ellison, 75, established BU's Institute of Lifestyle and Health, whose research includes the role of moderate wine-consumption in a healthy lifestyle. He is also a senior researcher with the Framingham Heart Study, a 60-year study investigating risk factors for heart disease and other illnesses.

MARY JACOBSON, M.D.

LYNN GRETKOWSKI, M.D.

Clinical assistant professor and assistant residency director

Department of OB/GYN Stanford University, Palo Alto, Calif.

Adjunct clinical assistant professor

Department of OB/GYN; Stanford University, Palo Alto, Calif.

Jacobson, 46, and Gretkowski, 44, are Bay Area-based OB/GYNs and the founders of Wine Doctors.com, a site dedicated to compiling information from medical studies and finding a consensus on alcohol and health issues.

MITCHELL KRUCOFF, M.D.

Director of cardiac safety, ECG Services

Duke University Medical Center, Durham, N.C.

Krucoff, 55, a professor of medicine and cardiology, joined the Duke medical staff in 1988. He oversees a wide range of cardiology-related programs at Duke and at the Durham Veterans Affairs Medical Center, and is co-director of the Cardiac Safety Consortium, a joint initiative between Duke and the FDA.

ARTHUR KLATSKY, M.D.

Senior consultant in cardiology and adjunct investigator

Division of research Kaiser Permanente Medical Center, Oakland, Calif.

In 1974, Klatsky, 79, published one of the first studies to show a link between light to moderate alcohol intake and decreased heart attack risk. He has also been a principal investigator on population studies involving alcohol consumption and its relationship to stroke, cancers and liver cirrhosis.

ANTONIA TRICHOPOULOU, M.D.

Associate professor of nutrition and preventative medicine

University of Athens Medical School, Athens, Greece

Trichopoulou, 69, is a researcher in the field of nutritional health. Her studies focus primarily on how dietary choices can increase longevity, including reducing the risk of cancer and heart disease. She also directs the World Health Organization Collaborating Center for Nutrition.

Wine Spectator: What is your definition of a healthy lifestyle and is wine a part of it?

Ellison: A healthy lifestyle has four or five components. Not smoking. Not being obese. Eating a reasonably healthy diet—a Mediterranean-type diet seems to be the ideal. Getting some exercise. And [moderate wine drinking], unless it is contraindicated because of previous abuse.

Klatsky: A healthy lifestyle includes a number of habits. Probably the single most important one is regular exercise of some sort. Staying thin or close to ideal weight is important. Diet is involved, of course, not only in terms of total calories [consumed] but also in terms of the components of the diet. A healthy lifestyle emphasizes fruits, vegetables and grains and deemphasizes animal fat. It involves having unadulterated foods as much as possible and a total avoidance of tobacco. It definitely includes regular amounts of light to moderate drinking, which could be in the form of red wine, white wine or beer. It doesn't have to be red wine. There is evidence that above and beyond all of the other aspects of a healthy lifestyle, small amounts of alcohol on a regular basis reduce the risk of a cardiovascular problem.

Krucoff: Wine is at the core of some of the most balanced human lifestyles. I'm sure you've heard the Mediterranean [diet] cited many times. I think as much as the chemistry is interesting ... at the end of the day, the real message is where does [wine] fit in your lifestyle? How does it help balance this very amped-up, stress-riddled culture that we all live in, with the ability to feel relaxed, to feel balanced, to breathe and to actually enjoy what God has given us?

Trichopoulou: Moderate amounts of ethanol appear to be beneficial against cardiovascular diseases. Moreover, antioxidant compounds, which are plentiful in red wines—but also present in white wines—may have wide-ranging beneficial effects. Evidence has emerged that wine may modulate the health effects of other nutritional compounds in the stomach. In this context, it is worth remembering that in the Mediterranean diet, alcohol is consumed mostly in the form of wine and mostly during meals.

WS: What do you recommend to your patients who ask about wine drinking and health?

Klatsky: The advice has to be individualized. It depends upon the individual's specific risks and benefits. For example, a 25-year-old woman who has no coronary disease risk

factors and a healthy lifestyle is not going to benefit in the short term from small to moderate amounts of alcohol, while a 65-year-old man with a history of high blood pressure, high cholesterol and who used to be a smoker and never had a problem with alcohol should definitely be a light to moderate drinker. It is certainly appropriate to advise people at a relatively high risk of heart attack—which is most middle-aged to older people—that light to moderate amounts of alcohol should be a part of their healthy lifestyle, unless they have some special risk.

Krucoff: The conversation about alcohol has to start with the recognition that too much of anything is bad for you, and alcohol can be quite toxic in chronic and overdosed forms. On the other hand, balanced and moderate amounts of alcohol, either epidemiologically or mechanistically, have very consistently been related to a longer life and fewer cardiovascular events. There are some cautions. Alcohol is metabolized in the liver, so if you are taking other drugs that are metabolized in the liver—blood thinners, for instance—you ought to be careful about interactions.

Trichopoulou: Diet is more important overall than wine. Studies evaluating the health effects of the traditional Mediterranean diet have been uniformly supportive of substantial benefits, while studies focusing on individual foods or food groups have generated equivocal results. All fats are not the same; olive oil, particularly extra-virgin olive oil, appears to have superb qualities and facilitates high consumption of good foods like vegetables and legumes.

Jacobson: I think it depends on the context. Personally I'm not recommending that people drink wine every day with respect to health. But part of the history I take includes alcohol consumption. I dovetail my recommendation off that. The American College of OB/GYN does not recommend any alcohol during pregnancy, and certainly we abide by that recommendation during pregnancy. We also have patients who have a history of breast cancer, and they are concerned about occurrence increased by drinking alcohol.

WS: What is your definition of moderate wine consumption?

Ellison: People vary tremendously. There is no average person. Don't ask me [how much you should drink], ask your spouse. If you are getting obnoxious after one drink, then drink a half. If you are drinking several drinks and functioning perfectly normally, then generally you are tolerating it better, unless you drink five, six or seven [drinks] or a bottle of wine a day—then you get to a level where you may be causing liver disease and other things. But it is so variable that it is hard to define moderation.

Jacobson: I go with the National Institute on Alcohol Abuse and Alcoholism definition. They define one alcoholic drink as 5 ounces of 12 percent alcohol for wine specifically. That would be 12 ounces of 5 percent beer. For women, it's one drink per day, and for men, it's two drinks. That's what defines moderate drinking.

WS: What is the most exciting area of research regarding the health benefits of wine?

Ellison: Well, for me, since I am getting so old, it's the dementia [chuckling]. No, I think that over the last five years, it's been the better elucidation of the importance of the pattern of drinking. The problem is that binge drinking is bad. We can both drink 14 drinks a week, but if I am doing two a day and you are doing it all Saturday night, I will get the full benefit and you'll get none of the benefits and all the adverse effects. The pattern of drinking, and the importance of that, is getting clearer and clearer.

Klatsky: The evidence [that alcohol consumption] is beneficial for [preventing] coronary heart disease, which I think is quite compelling, has been the most exciting thing. It's solidly established. In recent years, there's been evidence that alcohol protects against diabetes, which is a very common problem and becoming increasingly common as we have this obesity epidemic. The evidence is also beginning to grow—but is not as solid yet as it is for diabetes—that alcohol may reduce the risk of dementia, particular Alzheimer's dementia, which, quite frankly, [is exciting to me] now that I'm getting to be an old timer.

WS: What causes wine headaches?

Gretkowski: A lot of people think it's the sulfites that cause these headaches. The data couldn't [disagree more]. Tyramine is thought to be a vassal active substance that causes the dilation and contraction of blood vessels—the squeezing and relaxation component of headaches. There are different tyramine compounds in wine that have been calculated. Younger wines, wines that have not been racked extensively, unfiltered wines—these have higher rates of tyramine. It's important to know this because a lot of patients that we see say, "I used to like red wine and I don't drink it anymore because it gives me a headache." That generalization is flawed because not all red wines will give you a headache.

WS: What is the next big discovery?

Gretkowski: I think that the SIRT1 gene [which plays a role in the aging process] with regards to resveratrol is very interesting. There may be an interplay between exposure to resveratrol and flipping that gene on and off. We're [researching] at the molecular level now, and that might be promising. The nitric oxide pathway in smooth muscle relaxation continues to be the hot topic as it relates to cardiovascular research and wine consumption. We also hope to hear more about that.

Jacobson: I think it's fascinating that wine has been consumed since [antiquity]. In other cultures, it was consumed in lieu of water because the water supply wasn't safe. [Wine was] also used in religious rituals and in treating diseases. People around the Mediterranean grew up with wine as part of their daily diet. Our country developed differently—alcohol was always related to moralism. Now we're coming around and we need science to show what the impact of alcohol is on health.