

## **Grape extract could fight cancer**

1st Jan 2009

The Independent

A supplement made from grape seeds can destroy leukaemia cells, according to scientists at the University of Kentucky in Philadelphia.

In laboratory experiments, grapeseed extract forced the cancer cells to self-destruct. Within 24 hours, 76 per cent of leukaemia cells exposed to the extract died through a process called apoptosis. Healthy cells were unharmed. The researchers believe the discovery could lead to promising new treatments, but warned it was too early to justify recommending that people take grapeseed extract to stave off cancer.

Grape seeds contain a number of antioxidant plant chemicals including resveratrol, which is known to have anti-cancer properties.

Professor Xianglin Shi, who led the research, published in the journal *Clinical Cancer Research*, said: "These results could have implications for the incorporation of agents such as grapeseed extract into prevention or treatment of haematological [blood] malignancies. What everyone seeks is an agent that has an effect on cancer cells but leaves normal cells alone, and this shows that grapeseed extract fits into this category."

## **Cheers! Red Wine Keeps You From Aging**

8th Jan 2009

ABC News

Anti-aging properties may be the latest reason to toast red wine.

A group of scientists at the University of Wisconsin at Madison says there is a new reason to toast to the benefits of red wine.

Scientists have long thought a natural compound called resveratrol, which is found in some red wines, could help slow the aging process by helping to protect tissues inside the body. The question has been whether just a glass or two of wine could really make a difference.

The Wisconsin researchers announced today that it doesn't take as much red wine as many researchers had previously thought.

And at wine bars in New York City, they were already fielding calls.

"This morning I started getting phone calls saying, 'we heard about the red wine that prolongs your life. Which wine has it?'" said Nikos Antonakeas, owner of Morrell Wine Bar and Cafe.

Scientists at Harvard Medical School who have studied the impact of resveratrol on mice showed ABC News images of two rodents. Both were the same age, but the one on resveratrol was much more agile and running much more quickly than the other.

Many scientists are convinced that humans could see the same kind of anti-aging benefits, but there is a catch. How much resveratrol would it take?

In previous studies, mice had been given the equivalent of what they would have gotten from 100 bottles of wine a day.

But that's what is different with the findings in the Wisconsin study released today. The researchers used much lower levels on their mice and still had positive results.

"The precise number of glasses of wine or bottles of wine are difficult to predict," said Wisconsin-Madison professor Richard Weindruch, the author of the study.

As the research continues, some scientists are already popping corks, wondering if it is possible to put resveratrol in a pill.

David Sinclair of Harvard Medical School is trying, and just this week, his start-up company was sold to a pharmaceutical giant for \$720 million.

"I used to think it was probably 100 years in the future that we'd see these anti-aging drugs come around," Sinclair said. "Now, I'm optimistic that we'll see these within the next few years."

Still, many in the medical community say "not so fast," and warn that there is plenty of research to come.

Even so, red wine lovers have already been given another reason to toast.

## **Pittsburgh research explores resveratrol**

14th Jan 2009

Post gazette

The query under way in the nutrition world is, how great are grapes? Resveratrol, found in grape skins and red wine, has stirred interest in animal studies that show potential to lengthen life span, reduce heart disease, counter cancer, and prevent neurological disorders, among other health benefits.

While some critics dispute its potential for humans, research is planned to see whether the polyphenol -- a chemical substance in plants that also exists in peanuts, mulberries and knotweed -- has the same impact in people as occurs in yeast, worms, rats and apes.

And should resveratrol match its advertisements, Pittsburgh could become the seat of research and the center for development of supplement forms that include other polyphenols to multiply the effects of red wine on human health.

"I think this is the most interesting and compelling story of our adult lives," said Dr. Bryan Donohue, chief of the Division of Cardiology and medical director of the Cardiac Catheterization Laboratory at UPMC Shadyside. "There's an incredibly auspicious group

of people, all accomplished in their own gigs, who have come together because of a mutual interest in resveratrol. However this comes out, it will have a Pittsburgh stamp on it."

Dr. Donohue said he's ready to begin human clinical trials on resveratrol's impact on heart contractions and heart disease.

Another local player is Dr. Joseph Maroon, a University of Pittsburgh Medical Center neurosurgeon, whose new book, "The Longevity Factor: How Resveratrol and Red Wine Activate Genes for a Longer and Healthier Life," acknowledges its potential to extend life span. Atria Books is the publisher.

"The longevity factor may literally have been under our noses all the time and activated in the very same plants with which we have coexisted and coevolved for millions of years," his book's introduction says. "This is one of the most absorbing stories in contemporary biology and the latest chapter in that search, and in the exciting emerging research that may significantly contribute to a longer, stronger and healthier human life span."

But not everyone agrees, due in part to high quantities of resveratrol used in animal studies, the lack of human clinical trials, dosage uncertainty and the small percentage of resveratrol that ends up in the blood when taken orally. Dr. Maroon said blood levels are low because it goes straight from the gut into the liver, where it produces metabolites.

Roger Mason of Youngagain.com, a supplement retailer who says he sells only supplements supported by scientific evidence, describes resveratrol as "useless junk with zero science based on overdosed rats." Noting high prices for low concentrations of the supplement, he said the growing market for resveratrol might exploit people's hopes for profit.

But Dr. Maroon, former president of the Congress of Neurological Surgeons and team neurosurgeon for the Pittsburgh Steelers, said he helped conduct one of the first human trials in May that provided resveratrol, quercetin and other grape polyphenol compounds to 90 sedentary adults. Results of the blind study, presented to the American College of Sports, showed the mixture improved endurance, verbal memory and reaction time.

Dr. Maroon said resveratrol shows no toxicity nor problems with human tolerance. He's been taking 500 milligrams of it each day for two years, while Dr. Donohue said he takes 1,000 milligrams a day.

Dr. Maroon, 68, has competed in more than 50 triathlons, including three Ironman Championships in Hawaii. He said resveratrol seems to have enhanced his memory, endurance and reaction time.

"For yeast, worms and mice and all species tested, it shows positive results," he said. "It's not a stretch that we will see the same effects in humans, but that clearly needs to be proven in human studies."

In laboratory tests resveratrol prevented development of various types of cancer and reduced plaque buildup in arteries and inflammation, which could make it valuable in treating Alzheimer's and diabetes.

But its greatest potential is longevity through the same mechanism as calorie restriction. Both reportedly activate the SIRT1 gene in mammals to lengthen life span.

Dr. Maroon's book offers history, research, pros and cons of resveratrol and an evaluation of available products. Careful not to encourage alcohol abuse, he recommends a daily glass of wine to benefit health.

Resveratrol's potential has prompted a Pittsburgh-based company, Xenomis, to develop a supplement that combines a form of resveratrol with other polyphenols. The company plans to sell the supplement online in coming months. Dr. Donohue said he's involved with the company.

"There are reasons to be hopeful that this line of natural therapy addresses aspects of illness that had not been perfectly addressed through traditional means," he said.

### **Red wine prevents heart disease: Indian research**

9th Feb 2009

Indian express

Even while health benefits of red wine remain debatable, a study claims to have discovered a process inside the human body which gives those fond of this drink a valid reason to say cheers!

"It has often been observed that the French do not develop heart disease despite bad eating habits. This phenomenon, referred to as French Paradox has often been attributed, even by scientific studies, to the consumption of red wine which contains a chemical compound resveratrol which is beneficial for the heart and has anti-cancer properties," the study conducted by the Bio-chemistry department of Allahabad University says. Prof Syed Ibrahim Rizvi, the author of the study, which was presented at the National Symposium on Advances in Clinical Biochemistry held in Aligarh in November, 2008, said "it has been baffling for scientists that under laboratory conditions, resveratrol is required in much higher amounts to show effects similar to what is observed under normal conditions".

"For example, the amount of resveratrol ingested through a glass of wine or a serving of red grapes, another important source of the compound, has not been sufficient to elicit health benefits in studies conducted under laboratory conditions," he said.

"The key to this phenomenon may be found in an enzymatic system present in the red blood cells, known as plasma membrane redox system (PMRS). The resveratrol that is ingested into the body through any source, donates electrons to the PMRS which is

present in the red blood cells. These electrons are used by the PMRS to maintain the levels of ascorbic acid (Vitamin C) in the plasma," said Rizvi.

"Vitamin C is essential to regenerate Vitamin E which plays a very important role in preventing atherosclerosis, or hardening of the arteries, which in turn gives rise to several diseases related to the heart," Rizvi added.

"This phenomenon offers a possible explanation to the health-promoting effects of resveratrol, even when consumed in moderate concentrations. With this, people may also be rest assured that for health benefits, they need not consume large amounts of resveratrol-rich food like red wine, red grapes or pomegranate," he added.

Another important finding of the study has been that the rate of red blood cell PMRS increases during human aging. "It appears that the increase in PMRS activity is a defence mechanism of the human body to cope with increased oxidative stress during aging. Thus any compound which displays PMRS activating effect has a potential anti-aging effect," he added.

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## **Red Grapes "Wonder Cure" for High Cholesterol, Blood Pressure**

17th Feb 2009

Natural News

An extract made from components of red grapes that are regularly discarded by vineyards may dramatically reduce the risk of heart disease, above and beyond the well-known health benefits of red wine, researchers have found.

In a study published in the journal Nutrition, researchers from Complutense University of Madrid, Spain, produced an extract called Grape Antioxidant Dietary Fiber (GADF) from the seeds and skin of red grapes. For 16 weeks, they added the GADF extract to the meals of 34 non-smoking adults.

By the end of the study, the blood pressure of participants who had taken the GADF extract had gone down by as much as 5 percent, while their total cholesterol levels had decreased by up to 14 percent. Levels of LDL ("bad") cholesterol had also decreased significantly. The GADF extract also appeared to improve participants' lipid profile, which is a measure of heart disease risk based on a variety of cardiovascular tests.

Among the 13 participants with high cholesterol, the cholesterol reductions were even more striking. High cholesterol patients who took GADF extract experienced a 14.2 pc reduction in total cholesterol and an 11.6 pc decrease in LDL levels.

These cardiovascular benefits were not seen in nine control participants, whose diet was not supplemented with GADF extract.

"GADF showed significant reducing effects in lipid profile and blood pressure," researcher Jara Perez Jimenez said. "The effects appear to be higher than the ones caused by other dietary fibers, such as oat fiber or psyllium, probably due to the combined effect of dietary fiber and antioxidants."

Most heart health supplements are high in either antioxidants or fiber, both of which are known to lower the risk of cardiovascular disease. GADF extract, however, contains high levels of both. A single 7.5 gram supplement taken daily, Perez Jimenez said, could increase the average dietary fiber intake of the Western diet 5 to 10 grams over its current average of 20 grams per day.

"Further research on the relative contributions of fibers and flavonoids to prevent cardiovascular disease is needed," Perez Jimenez said.

Red grapes have long been praised as a heart superfood, largely due to their high content of the antioxidant chemical resveratrol. Studies have linked resveratrol to increased life span, decreased risk of heart disease and cancer, and reductions in levels of inflammation and blood sugar. However, resveratrol alone has never been enough to explain the health benefits of diets that include significant quantities of red wine, such as the Mediterranean diet.

The so-called Mediterranean diet is high in whole grains, legumes, fruits and vegetables and fish, and monounsaturated fats. It contains low to moderate levels of alcohol - particularly red wine - and low levels of red meat, poultry, dairy products and saturated fat. Numerous studies have shown that people who regularly eat a Mediterranean diet tend to live longer and have a lower risk of cardiovascular disease than those who eat a Western diet low in fruits and vegetables and high in meat, dairy and saturated fat.

## **Anti-aging pathway enhances cell stress response**

19th Feb 2009

BlogBiotech

People everywhere are feeling the stress of a worldwide recession. Our cells, too, are under continual assault from stress.

Hidden from sight, our cells battle challenges such as their environment, bacteria, viruses, too much or too little oxygen, and physiological stressors. Molecular systems protect cells under assault, but those systems can break down, especially with age.

To better understand how cells are protected from stress and damage, a team led by Northwestern University researchers studied the effect of resveratrol, a beneficial chemical found in red wine, on human cells in tissue culture.

The findings may help explain what happens in neurodegenerative diseases, which are age-related, when cell protection fails, proteins misfold, lots of damage accumulates and the system falls apart.

The researchers discovered a new molecular relationship critical to keeping cells healthy across a long span of time: a protein called SIRT1, important for caloric restriction and lifespan and activated by resveratrol, regulates heat shock factor 1 (HSF1), keeping it active. HSF1 in turn senses the presence of damaged proteins in the cell and elevates the expression of molecular chaperones to keep a cell's proteins in a folded, functional state. Regulation of this pathway has a direct beneficial effect to cells, the research shows.

This role of SIRT1 -- a protein already of great interest to pharmaceutical companies -- was not previously known. The results will be published in the Feb. 20 issue of the journal Science.

"When SIRT1 levels are high, you are in a high-protection mode," said Richard I. Morimoto, Bill and Gayle Cook Professor of Biochemistry, Molecular Biology and Cell Biology in Northwestern's Weinberg College of Arts and Sciences. He led the research team.

"Ironically, triggering the stress response and perhaps maintaining the cell in a protective state over a long period of time can keep cells healthy," said Morimoto. "The cell is protected against an accumulation of damage when HSF1 is more active."

SIRT1 levels decrease as humans age, Morimoto explains. Cells can't respond to stress as well. This decrease in SIRT1 may help explain why protein misfolding diseases, such as Alzheimer's, Parkinson's, Huntington's and adult-onset diabetes, are diseases of aging.

"We now have a powerful way to think about addressing neurodegenerative diseases," said Morimoto. "We have identified a pathway that can be manipulated to alter lifespan. Discovering this new basis for therapeutics is very exciting."

## **Red Wine Extract "Could Hold The Key" To Weight Loss And Muscle Gain**

6th March 2009

Webwire

A new commercially available supplement based on red wine extract from Biotivia Bioceuticals LLC ([www.biotivia.com](http://www.biotivia.com)) could hold the key to weight loss, according to cutting edge research.

New York, USA (6 March 2009) - Two new supplements available from Biotivia Bioceuticals LLC ([www.biotivia.com](http://www.biotivia.com)) could hold the key to weight loss and muscle gain respectively, according to leading edge medical research.

Biotivia Bioceuticals LLC has based its natural weight loss supplement on the so-called "miracle molecule" Resveratrol, which has been linked with weight loss, improved health and resistance to diseases of obesity and old age.

James Betz, CEO of Biotivia Bioceuticals LLC ([www.biotivia.com](http://www.biotivia.com)), believes the properties of Resveratrol are of particular benefit to those looking to lose weight and build muscle naturally without the use of stimulants or steroids.

"Dr. Sinclair of Harvard first discovered that resveratrol contained in red wine has some pretty extraordinary health and longevity properties. Resveratrol has been strongly linked with weight loss, improved immunity to certain conditions and general all round good health, by some of the world's leading scientists"

Biotivia Bioceuticals has developed two new and unique products off the back of these latest scientific developments, based on Resveratrol. Bio Shape, the weight loss supplement is designed to aid those looking to lose weight through a combination of suppressing the appetite and improving the metabolic rate.

"Likewise, our Bio Forge Natural Bodybuilding supplement works to aid muscle-gain and bodybuilding naturally. Both products are especially potent, and can deliver real value to the health-conscious in the fight against disease, obesity and ill-health"

Biotivia Bioceuticals LLC stock a wide range of unique all-natural extract products, such as the Bio Forge and Bio Shape ranges, designed to provide a healthier alternative for those seeking better health and longer life.

## **One for the ages**

23rd March 2009

Boston Globe

The lure of eternal youth has produced a multibillion-dollar-a-year global marketplace full of potions and pills that, the manufacturers claim, can offer life-extending benefits. Amid the dizzying array, one substance is capturing prime time attention: resveratrol.

Resveratrol advertisements - Reverse your biological clock! A miracle molecule! - are popping up everywhere, from the Internet to local health food stores. The stuff is even showing up in anti-wrinkle creams.

Ever since Harvard University molecular geneticist David Sinclair announced in 2003 that resveratrol appeared to dramatically extend the life span of yeast and fruit flies, the race was on to prove it worked in people.

Six years later, scientists have yet to demonstrate the substance can extend the life of creatures bigger than a mouse. But that hasn't slowed the resveratrol rage or claims by some manufacturers that they have captured the secret to long life in a capsule.

Resveratrol, a compound found in grape skins and red wine, is the most requested type of anti-aging product at the Vitamin Shoppe in Harvard Square.

"We have about seven different company brands," said assistant store manager Koudjo Ala. Most of the requests, he said, come from middle-agers who have "done a lot of research on it and they know exactly what they want."

At Good Health Natural Foods in Hanover, new resveratrol items are "100 times more popular" than the long-sold products with red wine extracts, said manager Tony Latessa.

"A lot of wellness counselors and homeopathic counselors are recommending it," he said. "I even had one doctor recommend it to one of his cardiovascular patients."

After his tantalizing 2003 announcement about resveratrol's apparent impact on yeast and fruit flies, Sinclair cofounded a private company, Sirtris, headquartered in Cambridge, that is researching resveratrol-based drugs designed to target genes called sirtuins. Sirtuins trigger enzymes that help repair and protect against cell damage. Sinclair's early research showed that sirtuins could be switched on by resveratrol.

Scientists have known for decades that rats on severely restricted diets lived longer and suffered fewer maladies of aging, such as heart disease and cancer. The caloric restriction appeared to stimulate sirtuin activity. So scientists have focused on finding a substance, such as resveratrol, that could trigger this same effect in humans - without the famine-like diet.

Yet even Sinclair - who declined through a Harvard spokesman to be interviewed for this story - issued a recent reality check on the resveratrol front. Interviewed on the CBS News program "60 Minutes," Sinclair said he believed it would be "five years, to be conservative" before the public would see a pill that could help people not only live longer, but keep them healthy longer.

"This will happen within our lifetimes," he said. "I'm fairly certain about that."

Other scientists without a financial stake in the resveratrol arena are skeptical that a proven anti-aging product will be available anytime soon. For starters, they say, it is easier to prove that a product is treating a specific disease, such as diabetes, than it is to show - in a measurable way - that one is retarding the aging process.

"It will be 30 years before we know whether resveratrol is actually working on aging - to change the rate at which people age," said Steve Austad, a professor of cellular and structural biology at the University of Texas and the deputy scientific director at the American Federation for Aging Research.

But Austad said he believes that resveratrol's benefits for treating certain diseases may be established more quickly. Sinclair's company, for instance, recently reported a lowering of blood sugar levels in diabetic patients treated with a resveratrol-like substance in early clinical trials.

Most resveratrol products range in strength from 10mg to over 200mg per tablet or capsule - 5 to 100 times the amount in a 5-ounce glass of dark red wine - and with nearly as many different sellers' instructions for suggested dosage. Prices also vary widely, from \$10 to nearly \$40 a bottle.

Yet consumers can't be really sure what they're getting when they buy resveratrol products. Unlike pharmaceuticals, dietary supplements, such as resveratrol, are not required by federal regulators to pass stringent safety and efficacy tests. That also means there is no independent assurance that what's listed on the label is actually in the bottle. A 1994 law requires only that supplements not claim to cure or treat any specific disease.

While the jury is still out on resveratrol, the consumer excitement it has generated has created interest in epigenetics, which is research on a wide variety of substances, including dietary supplements, that can trigger gene activity and perhaps affect diseases and aging.

The resveratrol phenomenon has created a "parallel interest in other substances, such as curcumin," said Douglas MacKay, a licensed naturopathic doctor in New Hampshire and vice president of scientific and regulatory affairs at the Council for Responsible Nutrition, a trade association of the dietary supplement manufacturers.

Curcumin is the main ingredient of turmeric, a bright yellow spice used in curry that has shown powerful anti-inflammatory and antioxidant properties in lab and animal studies. Preliminary human studies have indicated potential for use of curcumin in managing high cholesterol and heartburn, but more research is needed.

The 36-year-old MacKay, a cycling and surfing enthusiast, takes curcumin. He doesn't take resveratrol because, he said, the research hasn't yet proved that it can slow aging in humans.

But even some skeptics say they believe science eventually will figure out how to turn back the biological clock.

Austad, the University of Texas biologist, placed a \$300 bet in 2001 with University of Illinois demographer Jay Olshansky that there will be at least one spry 150-year-old person alive by the year 2150. Olshansky bet against that. Each put \$150 into a blind trust, with the understanding that the descendants of the winner would inherit the riches.

"That [150-year-old] would," Austad said, "be at least 9 years old right now."

## **Red wine 'could help you think'**

1st April 2009

Telegraph UK

Drinking red wine could help you think, according to the latest in a series of research projects into the health benefits of the tippie.

Men and women performed better in mental arithmetic tests after being given resveratrol, the ingredient in red wine associated with other advantages including burning off junk food and reducing the risk of heart disease.

It is thought resveratrol, which is also found in raspberries, blueberries and cranberries, works by increasing blood flow to the brain.

Researchers at Northumbria University found adults who had taken resveratrol performed better in a series of tests, according to a report in the Daily Mail.

Last year, researchers unveiled a drug based on resveratrol that was said to allow people to eat as much junk food as they liked without putting on a pound. The drug – known only as SRT1720 – fools the body into thinking it has to burn off fat to survive.

Other studies have linked resveratrol with fighting old age, cancer, obesity, diabetes and Alzheimer's.

It is also claimed that just half a glass of red wine a day can greatly cut the odds of death from heart disease.

White wine does not have the same benefits because is not made with grape skins and therefore lacks the necessary antioxidants.

Along with other types of alcohol, both red and white wines are associated with higher risks of breast cancer.

## **Researchers Increase Longevity of Mice Genetically**

10th April 2009

Food consumers

Research performed by the Healthy Aging University College in London is showing that gene manipulation can increase the longevity of mice.

Many scientists concur that a low calorie diet can lead to certain genetic changes that also increase longevity. The production of a protein called S6K1 is halted when a person goes on a low calorie diet; it changes in response to a reduction of caloric intake.

In the study, however, the researchers were able to genetically block production of the protein without altering the food intake of the mice. Several age related illness, such as Type 2 diabetes were circumvented and the life span of the mice was increased by 1/5.

There also seems to be an increase in the quality of life by halting the protein; the mice had improved motor skills and stronger bones. Additionally, the T-cells of the manipulated mice were more “youthful;” stronger T-cells help to slow down the natural aging process associated with declining immunity. Quality of life is just as important as longevity, as it affects mental health and a person’s overall sense of well being. We are not merely interested in prolonging our lives, but in making those additional years enjoyable by reducing illness.

Recently, scientists discovered that resveratrol, the anti-oxidant found in red wine, also helps to slow down the aging process by mimicking the biological changes that are manifested by lowering calorie intake.

## **Never Say Die**

20th May 2009

Forbes

Drug companies are mired in a slump. Their drugs are failing in clinical trials, and safety scandals have rocked the industry. Yet Harvard Medical School longevity researcher David Sinclair thinks pharmaceutical science is on the brink of a new generation of supermedicines that will prolong the human life span. "If we are right, the impact on society could be as great as the development of antibiotics by Alexander Fleming," he decrees.

Sinclair, aged a mere 39, is famous for discovering that resveratrol, a chemical found in red wine, helps fat mice live longer. He hopes his research will lead to pills that will treat or prevent numerous diseases simultaneously. "We have split the atom in this field," he proclaims. "It could be one pill for 20 diseases at once." He figures the compounds will save trillions in medical costs as people live to a ripe old age with few health problems. He is writing a book on his vision: *Just in Time*.

U.S. life expectancy soared in the first half of the 20th century with help from clean water and better medical care. It has grown slowly since to 78. An upward creep in obesity and diabetes could send it back down.

Sinclair hopes to restore the longevity curve to a steep upward trajectory. The key, he and a few others believe, is a group of enzymes called sirtuins that exist inside every cell. The theory is that sirtuins are master regulators that divert energy into cellular preservation in times of famine, in order to preserve the organism for reproduction later when times are better. "They are the body's natural defense against disease," Sinclair says.

Resveratrol activates one of the sirtuin enzymes. In 2006 Sinclair reported that large doses of resveratrol appeared to cancel out the ill effects of a poor diet in overweight mice. Minus the protective resveratrol, the bad diet (with 60% of calories from coconut oil) chopped away at a fat mouse's life span and clogged the animal's liver with fat. No surprise that Sinclair picked up some headlines with this experiment. It hinted that a pill would someday let you eat greasy cheeseburgers all day long with no health downside.

Last year Sinclair's lab showed that feeding resveratrol to healthy mice did not extend their lives. (It did prevent cataracts and improve bone strength.) Unlike his previous results, this finding got relatively little publicity. Sinclair is confidently redoing the experiment. He figures that the mice didn't start taking resveratrol early enough in life. Sinclair is so sure that he is on to something that he takes resveratrol himself, as do his wife and parents. He won't say where he gets it or what dose he uses. Numerous supplement companies sell the stuff, despite the lack of evidence it will boost human longevity.

Sinclair has wide eyes and a slight Australian accent. He speaks softly and earnestly, as if he is letting you in on a secret discovery. Phrases like "This was a unique moment in history" and "I told my wife something big has happened" pepper the conversation. He calls himself "one of these Benjamin Franklin types who want to put discoveries to practice." But just when you think he is about to go too far, he backs off, admitting that it is possible that the sirtuin research won't pan out in humans. "I don't know if it is me who is going to be successful," he says. A moment later he is insisting that if not he, then someone will eventually develop drugs against aging.

Balderdash, says veteran UCSF gerontologist Leonard Hayflick. Hayflick, 81, was the first to show, in the 1960s, that normal cells have finite life spans. He thinks life expectancy can't go much higher than 92. "The Sinclairs of the world appear every five years or so, and they have never been right yet," he says.

And then there are Sinclair supporters. "He is a bold scientist. He is willing to take chances and try risky experiments," says Sinclair's mentor, MIT biologist Leonard Guarente. Guarente first discovered the link between sirtuins and aging, but says it wasn't at all clear that one would be able to find effective compounds that activate sirtuins until Sinclair and collaborators did it.

Proving that sirtuin-boosting compounds can treat human disease will be up to GlaxoSmithKline. Last June it bought Sirtris Pharmaceuticals ( SIRT - news - people ), which Sinclair cofounded in 2004, for \$720 million. Sinclair got \$8 million from the deal, but he doesn't appear to be particularly focused on money. He drives a Toyota Camry.

Glaxo has concocted sirtuin boosters far more potent than resveratrol. Among other effects, the compounds lower blood sugar, and Glaxo is testing them to treat diabetes. But preliminary lab experiments suggest that sirtuins could have a role in everything from Alzheimer's disease to colon cancer. "We are talking about retarding the progression of certain age-related diseases," says Glaxo drug discovery head Patrick Vallance. "The application could be pretty broad."

Sinclair grew up in Australia and was fixated on death from an early age. "Most adults repress [thoughts about mortality], but I find it hard to put it in the back of my mind," he says. After getting a Ph.D. in yeast genetics from the University of New South Wales in 1995, he became a postdoctoral student with Guarente, who had just started searching for

yeast-longevity genes. Guarente's project "was what I had been waiting to hear my entire life," Sinclair says.

Even to others at MIT, Guarente's yeast aging project seemed a long shot. What could yeast possibly teach us about human aging? "Everyone else in the lab was saying this was crazy--how could you bet your career on it?" Sinclair recalls.

But the work slowly yielded results. Sinclair found one obscure cause of aging in yeast in 1997. In 1999 others in Guarente's lab found a second: they showed that yeast cells with high levels of a sirtuin gene called sir2 lived 30% longer than usual. It seemed this finding could be relevant to humans. Guarente theorized that sir2 might be responsible for the effects of calorie restriction, the decades-old finding that a near-starvation diet can extend the lives of various lab animals. Indeed, when Guarente and colleagues deleted the sir2 gene from the yeast and then restricted calories, the diet no longer lengthened life span.

In 1999 Sinclair snagged a job at Harvard Medical School and started competing with his old boss. Guarente had one theory of the biochemical mechanism behind sir2's role; Sinclair came up with a rival theory that contradicted it. "There was definitely a race. We drove each other forward at every step. It was hugely competitive," Sinclair says.

The next big thing was to devise drugs that affected sir2. A break came when biochemist Konrad Howitz made a serendipitous discovery: He found that resveratrol could activate sir2. He told Sinclair about the unpublished result. When Sinclair fed resveratrol to yeast cells, they lived 70% longer, Howitz and Sinclair reported in 2003 in the journal *Nature*. It also kept worms and fruit flies alive longer. Howitz says his role was minimized by Sinclair in some interviews. "He makes it sound like this was a project of his and he was thinking about this all along," says Howitz, at Enzo Life Sciences Intl. (Sinclair says he "always" credits Howitz.)

Sinclair's hope is that sirtuin-boosting drugs will first get approval for treating diseases like diabetes and cancer. As millions take the drugs, it will become evident if those on the drugs die less often from heart disease, Alzheimer's or other diseases of aging. This would be a sign the drugs influence the aging process.

University of Washington molecular biologist Matt Kaeberlein is dubious. He says his experiments show that sirtuins aren't responsible for the antiaging effects of calorie restriction. Another molecule, MTOR (mammalian target of rapamycin), plays a bigger role in the aging process, he says.

Sinclair concedes that multiple molecules are involved in aging. A successful drug may have to hit many of them. There are seven forms of sirtuin in the human body, and most studies to date have focused on only one. His laboratory is now furiously exploring the roles of the other six. "There will be a whole wave of new drugs coming from the field of aging research," he promises. "It is only a matter of time."

## Multiple Sclerosis

28th May 2009

Alternative Health

For the human body to correctly and normally operate, the brain and body must effectively communicate using the nervous system. The disease named Multiple Sclerosis, or nicknamed MS affects the paths of brain to body talking and can mildly or even completely stop normal functions in the body. The actions a person can perform that are commonly affected are coordination, balance, vision and muscle performance. Many cases of the disease are less severe and only affect the patient minimally. However, MS can cause total failure of walking, writing, speech and vision in extreme cases.

Multiple Sclerosis symptoms vary greatly for every patient. The disease is not specific to what communications pathways it targets in the body, so different functions are affected for each individual. The disease usually affects adults and the first steps for detection are a full physical exam, medical history review and blood tests. If MS is suspected, a Magnetic Resonance Imaging (MRI) scan may be ordered and focused on the spinal cord area. There are distinct MRI signatures that can be detected with a detailed analysis of the image by an expert. Additional diagnostic tools include removing a sample of the patient's spinal fluid for analysis. There are several proteins and chemicals detectable in the spinal fluid if MS is active.

MS stops or at least slows brain to body communications by directly irritating the lining of the nervous cells, called myelin, and other related cells of the nervous system. The severity of the irritation and inflammation caused by MS directly affects the flow of information along the nerve pathways. This disruption can affect any of the senses and functions of the body. Though much has been learned about how MS works, the root causes are unknown.

Modern medicine lists MS as a disease without a cure. Many Alternative Medicine or Naturopathic doctors view all diseases, including MS, as the body struggling to correct some problem related to the physical, emotional or mental states of the patient. They attack the problem first by strengthening the overall body and mind with time tested medicinal or mental treatments.

Often the next step is to seek herbal remedies to ease or eliminate the patient's symptoms. One supplement remedy is the widely acclaimed red wine compound, Resveratrol. Resveratrol has been shown to protect DNA damage that is known to be the cause of Multiple Sclerosis. Resveratrol rejuvenates and strengthens the body and mind, which can be the tipping point for recovery

Diet is always an important concern for naturopathic medicine, and there are several dietary regimens developed specifically to treat MS and its symptoms. Several of the dietary efforts have reported positive results including pronouncing the patient clear of all symptoms after several years of therapy. The diets usually target the fat content and nutritive value of a patient's food consumption. Extremely low fat diets have been

shown to slow or even halt the disease's progress. Studies demonstrate that if a person stops the diet, MS progression restarts until diet resumption.

There are specific standard drug treatments, mostly targeting the body's immune system, that are proven to slow the progress of MS. They can be taken for long term care and reduce the frequency of symptoms impacting the patient's lifestyle.

## **Red wine beneficial for health**

12th June 2009

Times of India

WASHINGTON: A polyphenol present in red wine, called resveratrol, has been found to have a large number of health benefits for drinkers, say researchers.

Red wine contains a complex mixture of bioactive compounds, including flavonols, monomeric and polymeric flavan-3-ols, highly coloured anthocyanins, as well as phenolic acids and the stilbene polyphenol, resveratrol.

Lindsay Brown, an associate professor in the School of Biomedical Sciences at The University of Queensland and corresponding author for the study, says that some of these compounds, particularly resveratrol, appear to have health benefits.

"The breadth of benefits is remarkable - cancer prevention, protection of the heart and brain from damage, reducing age-related diseases such as inflammation, reversing diabetes and obesity, and many more," said Brown.

"It has long been a question as to how such a simple compound could have these effects but now the puzzle is becoming clearer with the discovery of the pathways, especially the sirtuins, a family of enzymes that regulate the production of cellular components by the nucleus. 'Is resveratrol the only compound with these properties?' This would seem unlikely, with similar effects reported for other components of wine and for other natural products such as curcumin. However, we know much more about resveratrol relative to these other compounds," he said.

One of the main points of the review included that resveratrol exhibits therapeutic potential for cancer chemoprevention as well as cardioprotection.

"It sounds contradictory that a single compound can benefit the heart by preventing damage to cells, yet prevent cancer by causing cell death. The most likely explanation for this, still to be rigorously proved in many organs, is that low concentrations activate survival mechanisms of cells while high concentrations turn on the in-built death signals in these cells," said Brown.

The study suggests that resveratrol may aid in the prevention of age-related disorders, such as neurodegenerative diseases, inflammation, diabetes, and cardiovascular disease.

"The simplest explanation is that resveratrol turns on the cell's own survival pathways, preventing damage to individual cells. Further mechanisms help, including removing very reactive oxidants in the body and improving blood supply to cells," said Brown.

The researchers also said that low doses of resveratrol could improve cell survival as a mechanism of cardio- and neuro-protection, while high doses increase cell death.

"The key difference is probably the result of activation of the sirtuins in the nucleus. Low activation reverses age-associated changes, while high activation increases the process of apoptosis or programmed cell death to remove cellular debris. Similar changes are seen with low-dose versus high-dose resveratrol: low-dose resveratrol produces cellular protection and reduces damage, while high-dose resveratrol prevents cancers," said Brown.

She concluded that current scientific research is starting to explain reports from the last 200 years that drinking red wine improves health.

However, the researchers added that low to moderate drinking, especially of red wine, appears to reduce all causes of mortality, while too much drinking causes multiple organ damage.

The findings will be published in the September issue of *Alcoholism: Clinical & Experimental Research*.

### **Barbara Walter's Statement on Resveratrol**

19th June 2009

ABC news

You may have seen ads primarily on the internet for various products -- creams that supposedly remove wrinkles; pills or beverages containing an unknown amount of something called resveratrol.

These ads are often accompanied with my photograph, implying that I endorse the product. This is totally false. I have no idea if any of these products work and I rather doubt that they do.

This occurred because several years ago I presented a television special on longevity that featured research on the possibility of living longer. One such possibility was a pill with huge amounts of a substance called resveratrol, which is found in the skin of red grapes and extracted from red wine. But you would have to drink a tub of red wine to get the so-called benefits.

The actual pill containing massive amounts of resveratrol is still years away from being marketed, and it's not approved by the FDA. We do not know if there are any benefits.

In the meantime, I want to make it clear that I do not endorse any product.

## Researchers find new clues to biochemistry of 'anti-aging'

20th June 2009

Innovation reports

University of Wisconsin-Madison researchers have found that sirtuins, a family of enzymes linked to a longer life span and healthier aging in humans, may orchestrate the activity of other enzymes involved in metabolic processes in the body.

The finding, which shines a spotlight on enzymes only recently thought to play a role in the biochemistry of "anti-aging," has attracted the interest of biotechnology companies seeking to make drugs that delay the aging process and age-related diseases. The drugs could target the metabolic enzymes to produce health benefits.

"Sirtuins are very enticing because of their ability to slow the aging process," says John Denu, associate professor of biomolecular chemistry at the UW-Madison School of Medicine and Public Health (SMPH) and lead author on the study. "They also have great potential for promoting healthier aging by giving us a better understanding of - and possibly suggesting treatments for - metabolic diseases such as diabetes and neurological disorders such Alzheimer's and Huntington's diseases."

Scientists studying the genetics and physiology of sirtuins in organisms such as yeast, worms, flies and mice have shown that this enzyme family plays a role in a variety of cellular processes, including gene silencing, cell death, fatty acid metabolism, neuronal protection and life span extension.

"In humans, sirtuins have been implicated in the health benefits of calorie restriction, which is known to lengthen life span, and the enzymes are activated when they are exposed to resveratrol, a plant product found in red wine also known to extend life span," Denu says. "In addition, elevated levels of sirtuins somehow slow degeneration in nerve cells that have been damaged, and the enzymes affect aspects of metabolism responsible for controlling insulin secretion."

Denu and his team, which has published widely on sirtuins, conducted test tube studies using mouse cells to learn exactly which molecular players sirtuins act on directly. Previous studies suggested that sirtuins control genes indirectly in the cell nucleus. The first hint that sirtuins might directly control metabolic pathways came from earlier work in bacteria done by UW-Madison bacteriology professor Jorge Escalante.

The SMPH researchers found that sirtuins directly controlled the two-member class of enzymes called AceCSs (for acetyl-CoA synthetases) by activating these metabolic enzymes through the fundamental process of deacetylation. One form of sirtuin activated one type of AceCS, while another form of sirtuin activated the other AceCS. This reversible process transformed the AceCSs into a form that allows the body to utilize the small fatty acid called acetate.

"Acetate can be very important in animals as an energy source," Denu says, adding that cows and other ruminants use large quantities of it during digestion. "In humans, acetate can be obtained from the diet and as a by product of other metabolic processes. However, it is believed that we don't generally rely on it heavily as an energy source."

Denu says it's not clear what role acetate metabolism may play in the little-understood sirtuin molecular system that seems to confer so many advantages, but a connection to diabetes and aging does exist. Studies from the 1960s and early 1990s showed that diabetics and aged individuals exhibit a decreased ability to utilize acetate, he notes.

"Although the molecular links still must be established, appropriate control of our bodies' metabolic processes is essential to life extension and healthy aging," he says. "The observation that caloric restriction extends life span and appears to reduce the risk of diabetes in animal models only underscores the importance of metabolic pathways."

Denu plans to take advantage of the calorie restriction research program that has been under way for years at UW-Madison's National Primate Research Center under the direction of Richard Weindruch, SMPH professor of medicine.

Biotechnology companies are particularly intrigued by the Wisconsin team's discovery of sirtuin's direct effect on mammalian cells, in which the enzymes activate AceCS metabolic enzymes.

"This would be the easiest target, or hot spot, to aim for in developing a small molecule drug that could stimulate this process," Denu says.

## **Resveratrol supplements produce cardioprotecting, anti-inflammatory and antitumor effects**

22nd June 2009

BigNews

A review published in 2009 discusses the potential benefits of resveratrol supplements as they gives cardioprotection during heart diseases, hypercholesterolemia and diabetes. Stated by Guha and colleagues. Another study of 2009 conducted Pallàs M and coworkers supports the beneficial effects of Resveratrol on heart and stated as "Resveratrol is also suggested as a promising agent in promoting cardioprotection against coronary heart disease"

Gautam R and Jachak SM also concluded in their study "Recent developments in anti-inflammatory natural products" that Resveratrol supplements act as natural anti-inflammatory agent.

Kao and colleagues also have done a study in 2009 that demonstrates that use of Resveratrol supplements are good against tumors and also enumerate that they accelerate programmed death of tumor cells. Resveratrol supplements also safeguard and act as weapon against in certain type of cancers. It is specifically evident from the book "The Nutraceutical revolution" by Dr. Richard Firshein that Resveratrol helps body in

longstanding problems and help in all stages of cancer (initiation, promotion and progression).

Resveratrol is a flavonoid extracted from grapes skin having high concentration of cell protecting elements. Use of Resveratrol supplements act as barrier against cell jeopardizing to reduce the likelihood of cells for premature aging. Other effects include prevention of hardening of vessels, capillary fragility, easy bruising and varicose veins. Resveratrol supplements also promote wound healing and also help to restrict macular degeneration.

## **Natural Aromatase Inhibitors are Best Prevention of Breast Cancer in Postmenopausal Women**

29th June 2009

NaturalNews

One of the answers to breast cancer prevention has been right under our noses all along. When diets high in natural foods that inhibit the aromatase enzyme are eaten, breast cancers in postmenopausal women don't get a chance to start, according to research from the University of Munster in Germany. Scientists there have found that aromatase inhibitors are what keep normal cells from developing to the point where they can be classified as Grade 1 cancer.

Estrogen receptors (ER) alpha and beta are proteins found inside certain healthy cells of breast tissue. Estrogen binds with these receptors to stimulate tissue growth in young women during normal breast development. As women age these receptors play an important role in the development of breast cancer because they can continue to bind with excessive estrogen produced in breast tissue through the aromatization process, even after the ovaries no longer produce much estrogen. This can lead to the rapid growth and proliferation of mutated breast cells. If the process of aromatization is inhibited, excess estrogen will not be present in breast tissue to stimulate the growth of a cancer.

In a study designed to determine the effectiveness of aromatase inhibitors compared with anti-estrogen drugs, the German scientists analyzed 21 human breast cancer tissue samples for a change in the ER alpha /ER beta ratio during the malignant progression of breast cancers. They found that the transition from normal breast cells to grade 1 tumors was characterized by the down-regulation of ER beta, while the transition from grade 1 to grade 3 tumors was associated with the decrease in ER alpha expression. In stimulation assays they found that anti-estrogen drugs such as tamoxifen increased ER alpha expression and left ER beta unchanged. In contrast, aromatase inhibitors up regulated ER beta, and by doing so, blocked the initiation of cancer. (Anticancer Research, June) Nature has provided an abundance of aromatase inhibitors

You don't have to take drugs to inhibit aromatase. Nature has provided plants that will get the job done without harmful side effects. In April, Natural News ran an article about the powerful aromatase inhibiting ability of chrysin (<http://www.naturalnews.com/026086.html>), a flavonoid from the passion flower plant. Research showed that chrysin worked as well to inhibit the aromatase enzyme as a drug

designed for that purpose. Chrysin is normally taken as a supplement along with piperine which greatly enhances its bioavailability.

For those who would rather get their aromatase inhibiting flavonoids from whole foods, there are several good tasting choices. Beneficial compounds gotten from food have the added benefits of the perfect synergy found in a whole food as well as the other nutrients and compounds it contains.

Quercetin, naringenin, resveratrol, apigenin, genistein, and oleuropein are all powerful flavonoids from whole foods that inhibit aromatase while at the same time offering a treasure chest of other health benefits. When these foods are organically grown, they are higher in these flavonoids than produce grown conventionally.

Quercetin is the main reason an apple a day keeps the doctor away. It is a major antioxidant with important anti-aging benefits. It fights inflammation and reduces the cellular damage inflammation causes. By fighting inflammation, it also helps decrease swelling and pain, and keeps the circulatory system healthy. Quercetin helps prevent fatigue by helping to decrease damage from heavy exercise, and increase endurance. It is an anti-viral, and an immune system supporter and liver protector. Research has suggested that quercetin has other anti-cancer benefits aside from inhibiting aromatase in breasts and prostates. Cabbage, onions and garlic are other good sources of this powerful flavonoid.

Apigenin is a non-mutagenic flavonoid that has significant chemoprotective action against UV radiation. Research has shown apigenin reduces oxidative damage of DNA, inhibits the growth and induces differentiation in human leukemia cells, inhibits cancer cell transduction, and induces appropriate cell death. Like quercetin, apigenin acts as an anti-inflammatory and as an antispasmodic. Apigenin is found in good supply in celery, parsley, artichokes, basil, and chamomile.

Naringenin, is an antioxidant, free radical scavenger, anti-inflammatory, and immune system modulator. It has been shown to promote proper metabolism of carbohydrates. It was shown to reduce hepatitis C virus production by infected liver cells in cell culture and to inhibit the secretion of very low density lipoprotein by cells. As a cancer fighter, it reduces oxidative damage to DNA. Naringenin is found in all citrus and may be the reason that diets high in citrus are negatively correlated with heart disease. However, naringenin should not be obtained from grapefruit or grapefruit juice, which has an inhibitory effect on the human cytochrome P450 isofrom, another enzyme in the same complex as the aromatase enzyme. This enzyme is involved in breaking down and metabolizing sex hormones and preventing their excess accumulation in the body, so inhibiting it is not a good idea.

Resveratrol is a flavonoid gaining wide respect for its multitude of health benefits. Several recent research studies have revealed that resveratrol is highly effective against breast cancer by inhibiting ER positive and negative cell proliferation, cell cycle progression, and primary breast tumor growth. Resveratrol is protective of the liver even

against alcohol. It also keeps the central nervous system strong by protecting neurons from oxidative stress. Resveratrol is found to some degree in the skin and seeds of red grapes. Muscadine grapes have the largest content and are often used to make red wine. Although supplements of resveratrol are popular and widely available, getting resveratrol from red wine allows you to get the entire grape polyphenol group of nutrients, a group that has been shown to work much better synergistically. Breast tumor growth and metastasis to bone and liver were shown to be better inhibited by the complete grape polyphenol complex.

Oleuropein gives olive oil its distinctive flavor and is found in abundance in the leaves of the olive tree. It is one of the reasons olive leaf is such a powerful tool for wellness. Oleuropein helps the body fight off viruses, bacteria, and fungi. It is contained in every part of the olive tree and is the basis of its defense from insects. Oleuropein has been shown to boost the immune defense of people too, as well as fostering a healthy balance between friendly bacteria in the intestinal tract. In animal research, oleuropein was shown to enhance nitric oxide production. It is also a potent antioxidant and anti-inflammatory.

### **Queensland study backs red wine as healthy tipple**

6th July 2009

Courier mail

Undoubtedly, drinking any alcoholic beverage in excess causes problems. However, the scientific evidence about moderate quantities is stacking up in favour of a daily glass or two of your favourite red.

And the latest confirmation of this comes from the University of Queensland.

Work done by Dr Lindsay Brown and his colleagues (including associates from the UK, US and Germany) is detailed in a study to be published in the September issue of *Alcoholism: Clinical & Experimental Research*.

It all comes back to an apparently simple compound called resveratrol.

Resveratrol is found in the skin of grapes, which explains why any benefits from it are far more likely to be obtained by drinking red, rather than white, as the skins of red grapes are integral to the production of red wine.

Resveratrol is a phytoalexin – a compound produced by plants to ward off fungal infection.

Studies are ongoing but it appears resveratrol in low doses helps to protect cells, while in higher quantities, kills cancerous cells.

Dr Brown has said the breadth of benefits is remarkable: cancer prevention, protection of the heart and brain from damage, reducing age-related diseases such as inflammation, reversing diabetes and obesity, and many more.

The famous French Paradox has intrigued scientists and winelovers alike for 200 years.

The anomaly was first recorded by an Irish physician travelling through France in 1809, though it really came to prominence when an American television program reported on it in the early 1990s.

For those not familiar, the paradox is why the French, who drink and smoke more heavily than most, and whose diet contains far more fatty foods, enjoy a far lower rate of heart disease than other countries. It has long been attributed to their consumption of red wine.

Studies are continuing and one of the aspects of resveratrol is that it is shining a light on to the way the body's cells work.

At this stage, there is still much work to be done. There is some thought that pinot noir is better for you than cabernet sauvignon and that grapes from higher altitudes work best, but it is very early days. Also, what is the best quantity? Most seem to believe that around one to two glasses is ideal but again, it is too early to be definitive.

A further point which, as Dr Brown puts, it, sounds logical but is not proven: absorption of resveratrol is possibly much more effective through the mouth than through the stomach.

One thing that everyone will agree with is that a glass of red is a far more pleasant road to health than injections or pills.

It is not all good news. Dr Brown has also noted that old age begins at 27, which is when mental powers start to decline. The good news is that drinking red wine at 27 helps slow the process. It does seem worth raising a glass to resveratrol.

### **Tests begin on drugs that may slow aging**

20th Aug 2009

Taipei Times

In experiments with mice and other laboratory animals, certain chemicals, caloric restriction and the change of single genes have all brought noticeable increases in life span. Can the same be true for humans?

It may be the ultimate free lunch — how to reap all the advantages of a calorically restricted diet, including freedom from disease and an extended healthy life span, without eating one fewer calorie. Just take a drug that tricks the body into thinking it's on such a diet.

It sounds too good to be true, and maybe it is. Yet such drugs are now in clinical trials. Even if they should fail, as most candidate drugs do, their development represents a new optimism among research biologists that aging is not immutable, that the body has resources that can be mobilized into resisting disease and averting the adversities of old age.

This optimism, however, is not fully shared. Evolutionary biologists, the experts on the theory of aging, have strong reasons to suppose that human life span cannot be altered in any quick and easy way. But they have been confounded by experiments with small laboratory animals, like roundworms, fruit flies and mice. In all these species, the change of single genes has brought noticeable increases in life span.

With theorists' and their gloomy predictions cast in the shade, at least for the time being, experimental biologists are pushing confidently into the tangle of linkages that evolution has woven among food intake, fertility and life span.

“My rule of thumb is to ignore the evolutionary biologists — they’re constantly telling you what you can’t think,” Gary Ruvkun of the Massachusetts General Hospital remarked this June after making an unusual discovery about longevity.

Excitement among researchers on aging has picked up in the last few years with the apparent convergence of two lines of inquiry: single gene changes and the diet known as caloric restriction.

In caloric restriction, mice are kept on a diet that is healthy but has 30 percent fewer calories than a normal diet. The mice live 30 or 40 percent longer than usual with the only evident penalty being that they are less fertile.

People find it almost impossible to maintain such a diet, so this recipe for longevity remained a scientific curiosity for many decades. Then came the discovery of the single gene changes, many of which are involved in the body’s regulation of growth, energy metabolism and reproduction. The single gene changes thus seem to be pointing to the same biochemical pathways through which caloric restriction extends life span.

If biologists could only identify these pathways, it might be possible to develop drugs that would trigger them. Such drugs could in principle have far-reaching effects. Mice on caloric restriction seem protected from degenerative disease, which may be why they live longer. A single drug that protected against some or all the degenerative diseases of aging would enable people to enjoy more healthy years, a great benefit in itself, even if it did not extend life span.

The leading candidates for such a role are drugs called sirtuin activators, which may well be mimicking caloric restriction, in whole or in part. The chief such drug is resveratrol, a minor ingredient of grapes and red wine. Sirtris Pharmaceuticals, of Cambridge, Massachusetts, is now conducting clinical trials of resveratrol, in a special formulation, and of small-molecule drugs that also activate sirtuin but can be given in much lower doses. The resveratrol formulation and one of the small chemicals have passed safety tests and are now being tested against diabetes and other diseases. The Food and Drug Administration does not approve drugs to delay aging, because aging in its view is not a disease.

The sirtuin activators have a strong scientific pedigree. They emerged as the surprising outcome of a quest begun in 1991 by Leonard Guarente of MIT to look for genes that might prolong life span in yeast, a single-cell organism. Working with David Sinclair, now at Harvard Medical School, he discovered such a gene, one called sir-2. People and mice turned out to have equivalent genes, called sirt genes, that produce proteins called sirtuins.

Guarente then found that the sirtuins can detect the energy reserves in a cell and are activated when reserves are low, just what would be needed for a protein that mediates the effects of caloric restriction. Sinclair and colleagues screened a number of chemicals for their ability to activate sirtuin, and resveratrol landed at the top of the list. The chemical was already known as the suspected cause of the French paradox, the fact that the French eat a high fat diet without penalty to their longevity.

The two researchers and their colleagues thus argued that caloric restriction works by activating sirtuins, and so drugs that activate sirtuins should offer the same health benefits.

In 2004 Sinclair co-founded Sirtris with Christoph Westphal, a scientific entrepreneur. Helped by growing interest in the sirtuin story, Westphal was able to sell the company last year to GlaxoSmithKline for US\$720 million.

Sinclair says that “the results from the Sirtris compounds are promising and will be submitted for publication in coming months.”

But despite the high promise and strong scientific foundation of the sirtuin approach, it has yet to be proved that Sirtris’ drugs will work. The first of many questions is that of whether caloric restriction applies at all to people.

Two experts on aging, Jan Vijg of the Albert Einstein College of Medicine and Judith Campisi of the Lawrence Berkeley National Laboratory, argued recently in *Nature* that the whole phenomenon of caloric restriction may be a misleading result unwittingly produced in laboratory mice. The mice are selected for quick breeding and fed on rich diets. A low-calorie diet could be much closer to the diet that mice are adapted to in the wild, and therefore it could extend life simply because it is much healthier for them.

“Life extension in model organisms may be an artifact to some extent,” they wrote. To the extent caloric restriction works at all, it may have a bigger impact in short-lived organisms that do not have to worry about cancer than in humans. Thus the hope of mimicking caloric restriction with drugs “may be an illusion,” they write.

To decide whether life extension by caloric restriction is an artifact of mice in captivity, why not try it on wild mice? Just such an experiment has been done by Steven Austad of the University of Texas Health Science Center. Austad reported that caloric restriction did not extend the average life span of wild mice, suggesting the diet’s benefits are indeed an artifact of mice in captivity. But others interpret his results differently. Richard

Miller of the University of Michigan, says the maximum life span of the wild mice was extended, and so the experiment was a success for caloric restriction.

Laboratory mice are inbred, and researchers can get different results depending on the breed they use. To put the mouse data on a firmer footing, the National Institute on Aging has set up a program to test substances in three laboratories simultaneously. Its first round of candidate agents for reversing aging include green tea extract and two doses of resveratrol.

The resveratrol tests are still under way, but last month the results with another substance, the antifungal drug rapamycin, were published. Rapamycin was found to extend mice's lives significantly even though by accident the mice were already the equivalent of 60 years old when the experiment started.

Rapamycin has nothing to do with caloric restriction, so far as is known, but the study provided striking proof that a chemical can extend life span.

Another result, directly related to the caloric restriction approach, emerged last month from a long-awaited study of rhesus monkeys kept on such a diet. The research was led by Richard Weindruch of the University of Wisconsin. As fellow primates, the monkeys are the best possible guide to whether the mouse results will apply in people. And the answer they gave was ambiguous.

The monkeys who had spent 20 years on caloric restriction were in better health than their normally fed counterparts, and suffered less diabetes, cancer and heart disease, apparently confirming that caloric restriction holds off the degenerative diseases of aging in primates as well as rodents.

But as for life span, the diet extended life significantly only if the researchers excluded deaths that were apparently unrelated to aging, such as under the anesthesia necessary to take blood samples. When all deaths were counted, life span was not significantly extended.

Some researchers think it is perfectly valid to ignore such deaths. Others note that in mouse studies one just counts the numbers of dead mice without asking what they died of, and the same procedure should be followed with monkeys, since one cannot be sure if a death under anesthesia might have been age related.

With the rapamycin and rhesus monkey results, Sinclair said, "We have more weight on the side of people who think it's going to be possible." He emphasized the ability of both caloric restriction and sirtuin-activating drugs to postpone the many diseases of aging, at least in mice. To have one drug that postponed many degenerative diseases in people would be a significant advance, he said, even without any increase in longevity.

People may live so long already that no drug could make much of a difference. Probably because of reductions in infant mortality and other types of disease, human life

expectancy in developed countries has been on a remarkable, unbroken upward trend for the last 160 years. Female life expectancy at birth rose from 45 years in 1840 to 85 years in 2000.

An important difference among experts on aging is whether there is an intrinsic rate of aging. Supposing there were cures for all diseases, what would one die of, if one died at all? Vijg and Campisi believe there is a steady buildup of damage to DNA and to proteins like the collagen and elastin fibers that knit the body together. Damage to DNA means that the regulation of genes gets less precise, and this regulatory drift disrupts the stem cells that repair each tissue. Even if all disease could be treated, it is not clear that anything could overcome intrinsic aging.

Miller, on the other hand, said he believes that no clear distinction can be made between disease and other frailties of aging. "Anything a doctor can charge for we call disease, but wrinkled skin, white hair or not feeling good in the morning, these we don't call disease," he said.

He said he thinks that the idea of intrinsic aging is not well defined and that contrary to the theories of the evolutionary biologists, there may be simple ways to intervene in the aging process.

In the view of evolutionary biologists, the life span of each species is adapted to the nature of its environment. Mice live at most a year in the wild because owls, cats and freezing to death are such frequent hazards. Mice with genes that allow longer life can rarely be favored by natural selection. Rather, the mice that leave the most progeny are those that devote resources to breeding at as early an age as possible.

According to this theory, if mice had wings and could escape their usual predators, natural selection ought to favor longer life. And indeed the maximum life span of bats is 3.5 times greater than flightless mammals of the same size, according to research by Gerald Wilkinson of the University of Maryland.

In this view, cells are so robust that they do not limit life span. Instead the problem, especially for longer-lived species, is to keep them under control lest they cause cancer. Cells have not blocked the evolution of extremely long life spans, like that of the bristlecone pine, which lives 5,000 years, or certain deep sea corals, whose age has been found to exceed 4,000 years.

Some species seem to be imperishable. A tiny freshwater animal known as a hydra can regenerate itself from almost any part of its body, apparently because it makes no distinction between its germ cells and its ordinary body cells. In people the germ cells, the egg and sperm, do not age; babies are born equally young, whatever the age of their parents. The genesis of aging was the division of labor in the first multicellular animals between the germ cells and the body cells.

That division put the role of maintaining the species on the germ cells and left the body cells free to become specialized, like neurons or skin cells. But in doing so the body cells made themselves disposable. The reason we die, in the view of Thomas Kirkwood, an expert on the theory of aging, is that constant effort is required to keep the body cells going. "This, in the long run, is unwarranted — in terms of natural selection, there are more important things to do," he writes.

## **Resveratrol, a substitute of Aspirin for Heart Health**

22nd August 2009

24 medica

Resveratrol, an antioxidant, anti-inflammatory substance created by a variety of plants, starting from vines to peanuts and pine trees. Resveratrol has been used in Asian medicine for hundreds of years, especially in liver and heart problem treatments. Resveratrol helps lower cholesterol, and is as much as 10 to 20 times more potent than vitamin E in protecting against LDL oxidation. Further studies of resveratrol revealed that it helps prevent blood clots by keeping blood vessels open and pliable.

### Source of Resveratrol

Resveratrol is found in the stems, leaves, and skins of grapes. Although a glass or two of red wine each day may lower the risk of heart disease, one recent study shows that alcohol-free red wine works just as well. Resveratrol is also present in purple grape juice, red or purple grapes, and peanuts. However, because of the fermenting process, resveratrol levels are higher in red wine than other natural sources red wine has about three times as much resveratrol as grape juice.

### Resveratrol Benefits

Today resveratrol is being considered one of the main beneficial elements found in red wine. Studies have shown that red wine, especially resveratrol, can help prevent colds, increase the levels of HDL (good) cholesterol, lower the risk of Alzheimer's, reduce the size and number of fat cells in the body, reduce the risk of prostate cancer, and has anti-inflammatory properties to boot.

### Resveratrol and Heart Health

Resveratrol is known to have antioxidant, anti-inflammatory, antifungal, antimutagenic, anticancer, neuroprotective, and antiaging properties. As a bonus, it may also beat aspirin at its own game in terms of cardiovascular protection. Resveratrol protect heart health by limiting the effects of cardiac fibrosis, a hardening of the heart tissue, finds new animal research. However research showing that resveratrol has a major impact on heart health could see increasing interest in its use as a supplement.

### Resveratrol and Women's Health

Some studies in women regarding the consumption of alcohol and risk of breast cancer found an increase of this type of cancer in women who consume at least one drink daily. According to a report by the American Cancer Society in 2004 there was an increase of 30% in the death rate from breast cancer in women who would drink alcohol daily. This confounding information aside consumption of one or two drinks per day is associated

with a reduction in risk of approximately 30 to 50 percent in coronary heart disease. Heart disease being the overwhelming number one killer of woman annually makes it the major target. So wine consumption has an overall positive effect on death rates in the female population.

#### Resveratrol and Cancer

One of the other aspects that recommend resveratrol as a good anti cancer agent is the fact that it combats linoleic acid. The acid, found in most western diets, transforms to hormone like substances that stimulate cancer growth. Resveratrol enhances the ability of the vitamin D to inhibit the fast rate growth of cancer cells, thus stopping the spread of the disease.

Resveratrol remains a new ingredient to the supplement industry and is not currently supplied by European grape products companies. There are some resveratrol supplements available in the US although European industry remains wary over its regulatory status. Resveratrol supplements are also now available, and are usually combined with grape extracts or other antioxidants. To get the health benefits of red wine without the negative impact of alcohol, you can purchase resveratrol and mixed red wine polyphenols in capsules. One capsule of red wine polyphenols is approximately equal to the polyphenol content of one bottle of wine.

### **A future of miracle pills that can slow down aging**

12th Sept 2009

The Standard

We all grow older and – hard to admit it – ultimately die. It is strange, even funny how age creeps up on you. Bill Cosby, the venerable American stand-up comedian wrote a hilarious book about aging when he turned 50. It was titled Time Flies. In Time Flies, he tells a classic Cosby joke about how to know your downhill journey has begun. You spend hours looking everywhere for your eyeglasses; finally you are exhausted and drenched in irritating sweat. As you try to wipe off the sweat with the back of your hand, you discover the glasses had been patched above your forehead all along.

That is funny and familiar if you are, like me, north of 40 and rapidly approaching the half- century point.

Aging and dying have no direct correlation, of course, except in a linear, terminal way – aging eventually leads to death but we age all the time. Aging is a journey while death is a destination.

Michael Jackson died at 50 even though he had access to all the healthcare money could buy. My father, and before him, my grandmother, stretched it to their 90s before quitting – without the benefit of modern medicine.

It is a cruel irony that Michael Jackson, who at one point is said to have tried to live in an oxygen bubble in an attempt to escape the impurities of the world, may have died from polluting his body with 'too much medication'.

We try to cheat our aging bodies – through diet, exercise, medication, and yes, even surgery – but the inexorable inner clock has its ultimate revenge. Sooner or later, we wither away – 'check out of here', as Bill Cosby would say.

### Scientific breakthroughs

It is why any topic about reversing or delaying aging is guaranteed to get lots of attention. It is why human beings – from emperors to ordinary people – have for millennia sought a mysterious so-called elixir of life, a mixture that bestows on the drinker the gift of eternal youth.

If recent scientific breakthroughs in aging have to be believed, our long quest for youthful longevity may be coming to a happy end. Scientists have known for about 70 years that limiting calorie intake extends the life spans of many mammals – in some cases by as much as 50 per cent. Limiting calorie intake or burning off excess calories is not easy, as any obese person will testify. The trick is to limit the intake of energy-rich food while ensuring the body receives nutrition that is complete and balanced. So, how does one slow the aging process in humans without imposing a strict diet? It turns out, unsurprisingly, that it is a matter of genetics.

But how do you turn on this gene in the body? What is the trigger? Resveratrol, a molecule found in the skin of red grapes and therefore a constituent of red wine, appears to be one of the triggers.

Sirtris, a company owned by the pharmaceutical giant, GlaxoSmithKline, is working on a chemical compound 1,000 times more potent than resveratrol. According to Sirtris,

Imagine a future of miracle pills that can treat obesity and slow down aging. Imagine a future where the onset or progression of age-related diseases are delayed or vanquished. It is not beyond the realm of possibility.

### **Scientists find path to 'fountain of youth'**

2nd Oct 2009

The Gazette

The fountain of youth may exist after all, as a study showed that scientists have discovered means to extend the lifespan of mice and primates.

The key to eternal -- or at least prolonged -- youth lies in genetic manipulation that mimics the health benefits of reducing calorie intake, suggesting that aging and age-related diseases can be treated.

Scientists from the Institute of Healthy Ageing at University College London (UCL) extended the lifespan of mice by up to a fifth and reduced the number of age-related diseases affecting the animals after they genetically manipulated them to block production of the S6 Kinase 1 (S6K1) protein.

Scientists have shown since the 1930s that reducing the calorie intake by 30 percent for rats, mice and -- in a more recent finding -- primates can extend their lifespan by 40 percent and have health benefits.

By blocking S6K1, which is involved in the body's response to changes in food intake, similar benefits were obtained without reducing food intake, according to the study published in the US journal *Science*.

The results corroborated those of other recent studies.

"Blocking the action of the S6K1 protein helps prevent a number of age-related conditions in female mice," explained UCL professor Dominic Withers, the study's lead author.

"The mice lived longer and were leaner, more active and generally healthier than the control group. We added 'life to their years' as well as 'years to their lives.'"

The genetically altered female mice lived 20 percent longer -- living a total of 950 days -- or over 160 days more than their normal counterparts.

At age 600 days, the equivalent of middle age in humans, the altered female mice were leaner, had stronger bones, were protected from type 2 diabetes, performed better at motor tasks and demonstrated better senses and cognition, according to the study.

Their T-cells, a key component of the immune system also seemed more "youthful," the researchers said, which points to a slowing of the declining immunity that usually accompanies aging.

Male mice showed little difference in lifespan although they also demonstrated some of the health benefits, including less resistance to insulin and healthier T-cells. Researchers said reasons for the differences between the two sexes were unclear.

"We are suddenly much closer to treatments for aging than we thought," said David Gems of UCL's Institute of Healthy Aging, one of the authors of the study, which was primarily funded by the Wellcome Trust.

"We have moved from initial findings in worm models to having 'druggable' targets in mice. The next logical step is to see if drugs like metformin can slow the aging process in humans."

Other studies have also found that blocking S6K1 were channeled through increased activity of a second molecule, AMPK, which regulates energy levels within cells.

AMPK, also known as a master "fuel gauge," is activated when cellular energy levels fall, as takes place when calorie intake is reduced.

Drugs, such as the widely-used metformin, that activate AMPK are already being used in human patients to treat type 2 diabetes.

Recent studies by Russian scientists suggested that metformin can extend mice's lifespan.

Another drug, rapamycin, was found to extend the lifespan of mice, according to a study published in the British journal Nature.

As rapamycin is already used in humans as an immunosuppressant -- to prevent a patient from rejecting an organ after transplant -- it could not be administered as an anti-ageing drug in its current form.

But rapamycin blocks S6K1 activity and could thus extend lifespan through its impact on S6K1.

Seizing on the potential, US firm Sirtris Pharmaceuticals uses resveratrol, a powerful anti-oxidant found in red wine, as well as other fruits than raisin.

Sirtris scientists -- including co-founder David Sinclair, also a researcher at Harvard Medical School -- have found that resveratrol activates the production of sirtuin proteins, which also unleash the same physiological effects as reducing calorie intake.

Sirtris has produced highly concentrated doses of resveratrol and is currently leading clinical trials with diabetes patients and others suffering from liver and colon cancer.

## **Red Wine Chemical May Treat Diabetes**

14th Oct 2009

CBS News

The much touted compound resveratrol shows some promise as a future treatment for type 2 diabetes, but drinking wine or taking resveratrol supplements isn't likely to do diabetic people much good, researchers say.

Resveratrol, found in red wine, was found to lower blood sugar levels and improve insulin levels when injected directly into the brains of mice fed very high-calorie diets in a study conducted by researchers at the University of Texas Southwestern Medical Center (UTSW).

The finding suggests that the brain plays a key role in resveratrol's beneficial effect on diabetes and that the benefits may occur independently of diet and body weight.

If this is true, new type 2 diabetes treatments targeting the brain may be possible, lead researcher Roberto Coppari, PhD, tells WebMD.

But drinking red wine is not likely to improve blood sugar and insulin levels because resveratrol does not cross the blood-brain barrier very efficiently.

"We don't want to send the message that you can treat diabetes by drinking red wine," Coppari tells WebMD. "Two or three glasses a day wouldn't be nearly enough for the brain to accumulate the amount of resveratrol delivered in our study. It would take many, many bottles, and clearly that wouldn't be good for you."

**Resveratrol: Fountain of Youth?**

Resveratrol first made headlines several years ago when researchers identified it as the substance likely responsible for the health benefits to the heart attributed to red wine.

The buzz became almost deafening early this year, when the news program 60 Minutes aired a story suggesting that resveratrol-based drugs may one day succeed in slowing aging in humans.

Found mostly in the skin of red grapes and other dark fruits, resveratrol has been shown to protect against diabetes in studies involving mice, although very high doses of the molecule have been needed.

In the newly published study, Coppari and colleagues examined whether injecting resveratrol directly into the brains of diabetic mice would activate a group of proteins known as sirtuins, which have been shown to have anti-diabetes properties in earlier animal studies.

The UTSW researchers injected one group of diabetic mice with resveratrol, while a second group was given saline-containing placebo injections.

All the mice were fed a very high-fat diet throughout the study.

Despite this, insulin levels in the resveratrol-treated mice dropped significantly and were halfway to normal by the end of the five-week study. Insulin levels among the placebo-treated mice continued to rise.

**Resveratrol Activates SIRT1**

The resveratrol injections were found to activate SIRT1 proteins in the brain and they reduced brain inflammation related to the mice's high-calorie diets.

The study was published this week online and it will appear in the December issue of the journal *Endocrinology*.

"The brain appears to be a major player in diabetes," Coppari says. "The treatments we have for diabetes target other organs like the liver. The brain hasn't really been on the map."

If the findings are confirmed, Coppari believes the brain could become a target for not only diabetes treatments, but treatments for cardiovascular disease and obesity as well.

The study is not the first to show that resveratrol can prevent the deleterious consequences of a high-fat diet. In November of 2006, researchers from Harvard Medical School and the National Institute on Aging reported that obese mice fed a diet containing 60 percent of calories from fat lived significantly longer if they were treated with resveratrol.

The resveratrol-treated mice lived as long as lean mice, with a much better quality of life, as measured by motor skills tests.

"After six months, resveratrol essentially prevented most of the negative effects of the high calorie diet in mice," study co-author Rafael de Cabo, PhD, of the National Institutes of Aging says in a news release.

## **What Exactly Does Resveratrol Do?**

5th Nov 2009

Corante

Resveratrol's a mighty interesting compound. It seems to extend lifespan in yeast and various lower organisms, and has a wide range of effects in mice. Famously, GlaxoSmithKline has expensively bought out Sirtris, a company whose entire research program started with resveratrol and similar compound that modulate the SIRT1 pathway.

But does it really do that? The picture just got even more complicated. A group at Amgen has published a paper saying that when you look closely, resveratrol doesn't directly affect SIRT1 at all. Interestingly, this conclusion has been reached before (by a group at the University of Washington), and both teams conclude that the problem is the fluorescent peptide substrate commonly used in sirtuin assays. With the fluorescent group attached, everything looks fine - but when you go to the extra trouble of reading things out without the fluorescent tag, you find that resveratrol doesn't seem to make SIRT1 do anything to what are supposed to be its natural substrates.

"The claim of resveratrol being a SIRT1 activator is likely to be an experimental artifact of the SIRT1 assay that employs the Fluor de Lys-SIRT1 peptide as a substrate. However, the beneficial metabolic effects of resveratrol have been clearly demonstrated in diabetic animal models. Our data do not support the notion that these metabolic effects are mediated by direct SIRT1 activation. Rather, they could be mediated by other mechanisms. . ."

They suggest activation of AMPK (an important regulatory kinase that's tied in with SIRT1) as one such mechanism, but admit that they have no idea how resveratrol might activate it. Does that process still require SIRT1 at all? Who knows? One thing I think I do know is that this has something to do with this Amgen paper from 2008 on new high-throughput assays for sirtuin enzymes.

One wonders what assay formats Sirtris has been using to evaluate their new compounds, and one also wonders what they make of all this now at GSK. Does one not? We can be sure, though, that there are plenty of important things that we don't know yet about sirtuins and the compounds that affect them. It's going to be quite a ride as we find them out, too.

### **New research: resveratrol improves diabetes by affecting the brain**

7th Nov 2009

Natural news

(NaturalNews) Think of a treatment for diabetes, and you probably think of a drug or natural therapy that targets the pancreas to help normalize blood sugar levels. Resveratrol, a phytochemical found in red grapes, has been shown to have a host of health benefits -- including improving diabetes in animal studies. But, it turns out, that's not necessarily because it benefits the pancreas. Instead, scientists have made an unexpected discovery: resveratrol's anti-diabetic properties appear to be mediated through the brain.

That's the conclusion of a new study conducted by scientists at the University of Texas Southwestern Medical Center in Dallas, Texas, that was just published in *Endocrinology*, a journal of The Endocrine Society. The researchers focused on sirtuins, a class of proteins activated by resveratrol that are thought to underlie many of the potential beneficial effects of calorie restriction, including promoting longevity and slowing down the aging process.

Early studies in mice have produced important evidence showing that when resveratrol activates sirtuins, diabetes is improved. While sirtuins are expressed virtually all over the body, until now researchers have remained in the dark about what tissues could be mediating resveratrol's beneficial effects on the disease.

"We know that sirtuins are expressed in parts of the brain known to govern glucose metabolism, so we hypothesized that the brain could be mediating resveratrol's anti-diabetic actions," said Roberto Coppari, PhD, of the University of Texas Southwestern Medical Center and co-author of the study, in a statement to the media. "To test the hypothesis, we assessed the metabolic consequences of delivering resveratrol directly into the brain of diabetic mice. We found that resveratrol did activate sirtuins in the brain of these mice which resulted in improving their high levels of blood sugar and insulin. These findings may lead to new strategies in the fight against type 2 diabetes."

Dr. Coppari and his research team found that long-term infusion of resveratrol into the brains of diet-induced obese and diabetic mice normalized the animals' hyperglycemia

(high blood sugar) and greatly improved the rodents' hyperinsulinemia (excess levels of circulating insulin in the blood). The scientists noted in their research paper that these beneficial effects were independent of changes in the lab animals' body weight, food intake, and circulating levels of leptin (a hormone that helps regulate appetite and metabolism).