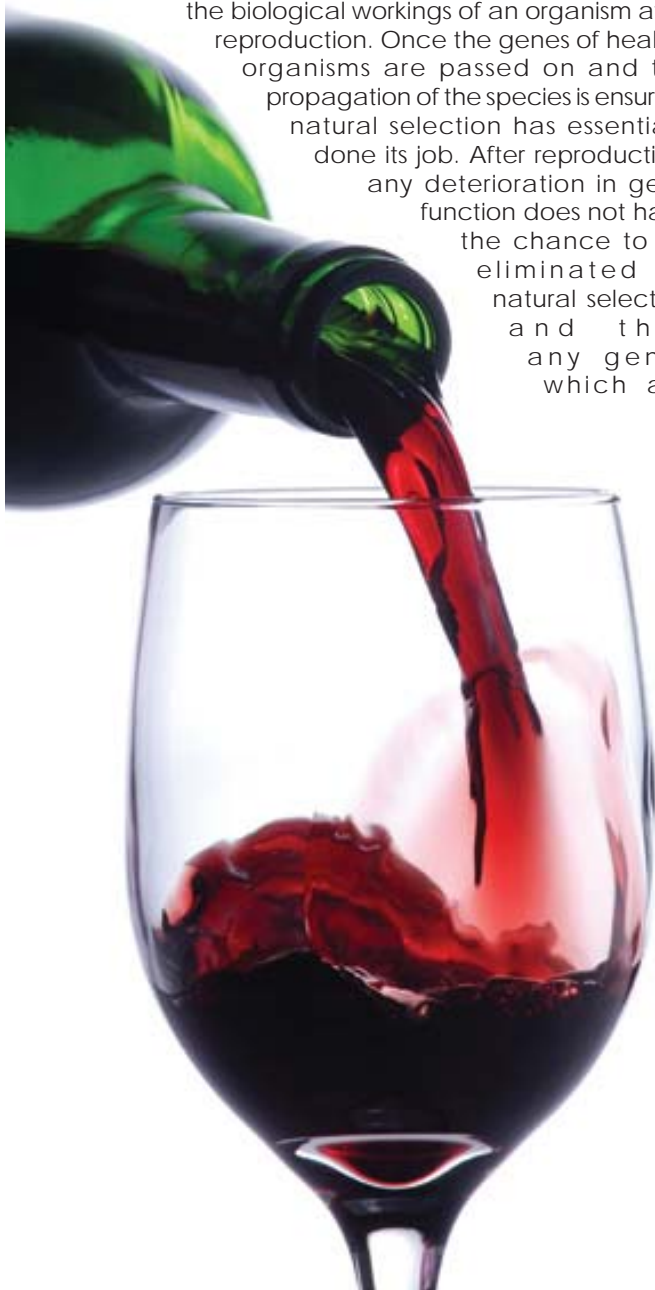


# A Modern Philosopher's Stone? A Molecular Look at Preventing Aging

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Since the beginning of civilization, people have been interested in developing an elixir of life to grant immortality or delay aging. Although such a potion has never been discovered, modern biologists might be well on their way to identifying mechanisms of aging and potentially curtailing them. Aging is a difficult concept to approach scientifically, not to mention emotionally. There have been a variety of theories that explain why organisms age, ranging from simple "wear-and-tear" to the Rate of Living Theory in which it is proposed that a faster metabolic rate implies a shorter lifespan. These theories are now considered unlikely and research instead backs the evolutionary theory of aging.

Evolutionary biologists explain aging as a decline in the biological workings of an organism after reproduction. Once the genes of healthy organisms are passed on and the propagation of the species is ensured, natural selection has essentially done its job. After reproduction, any deterioration in gene function does not have the chance to be eliminated by natural selection and thus any genes which are



advantageous for reproduction but fail thereafter are conserved and even favoured (1). So if aging is just a result of evolution, how can scientists delay its occurrence? One such way to slow aging, pioneered by Clive McKay at Cornell University, is 'caloric restriction', a diet in which an organism consumes a bare minimum of food and nutrients (2,3). From an evolutionary standpoint, the effects of caloric restriction are logical because in the event of a famine, organisms that can delay aging and survive until after the famine is over can successfully reproduce once resources become plentiful again (1).

## Molecular Basis of Caloric Restriction

Scientists have recently been interested in how caloric restriction (CR) works on a molecular level. One early theory suggests that CR delays aging by reducing the metabolic rate and oxidative processes in the body that damage cells over time (1). However, recent research has shown that caloric restriction is more complex than previously thought. In yeast, CR activates stress pathways that in turn regulate a gene known as Sir2. The Guarente laboratory at MIT carried out studies in both yeast and *C. elegans* in order to compare their lifespans with their Sir2 expression levels. In both cases high expression of Sir 2 correlated positively with longevity (2). The pathway that connects caloric restriction to Sir2 is intricate and the complete mechanisms for it are not yet fully understood, but research has indicated that Sir2 is required for prolonged life in yeast (4). In a reduced calorie diet, the Sir2 is activated to greater levels of expression, and consequently acts to suppress aging and leads to an overall increase in lifespan (5). The mechanisms of Sir2 action vary by species: in yeast, Sir2 functions by controlling rDNA genes, while in roundworms it controls insulin genes (1). To put it simply, Sir2 is an integral part of a complex emergency braking system that prevents aging during a time of stress, such as reduced food intake.

Assuming that the Sir2 pathways observed in other organisms hold true for people, caloric restriction has the potential to prolong human lifespan. Mammals do indeed possess sirtuin family genes and the specific ortholog to Sir2 in humans is known as SIRT1 (1). Recent research in mice has revealed that SIRT1 is in fact implicated in metabolic processes, including CR, and that sirtuins are important regulators of metabolism (6). Other studies have found that SIRT1 controls aging through the regulation of processes such as insulin production, cell survival, and fat metabolism (7,8). This is not only promising for aging research but also for research concerning diseases such as diabetes. Leonard Guarente saw enough potential in SIRT beyond caloric restriction to co-found Elixir Pharmaceuticals in 1999, a company that now utilises sirtuin pathways to treat metabolic diseases.

## Resveratrol: A Miracle Compound?

Through multiple studies, sirtuins have emerged as powerful regulators of metabolic processes and, when activated in times of stress, are capable of slowing down the aging process tremendously. However, even with the knowledge

of the mechanism linking CR to sirtuin activity and longevity, it would be difficult to increase the lifespan of people in a society where large amounts of food are consumed. With this in mind, scientists undertook the task of looking for an

## So if aging is just a result of evolution, how can scientists delay its occurrence?

alternative method of activating Sir2 in non-mammalian organisms by using a pathway that did not involve CR. In other words, they wanted to discover a way to trick an organism into behaving as though its food intake was restricted, when in fact its diet was normal. After extensive screening of many molecules, resveratrol, an antioxidant compound produced by plants in response to stress and found in red wine, was identified as a promising candidate based on its interaction with the sirtuin family (2, 7). Resveratrol was found to increase longevity in *C. elegans*, *S. cerevisiae*, *Drosophila*, and species of vertebrate fish (7). In a corresponding study, resveratrol was found to be potent enough to extend the lifespan of yeast cells by 60% (9).

In order to extend the previous results to mammals an important experiment was carried out by the Sinclair laboratory at Harvard to test the effects of resveratrol on mice - an organism that comes close to modelling the effects of resveratrol on humans. The scientists found that due to a daily intake of resveratrol, the physiology of middle age mice on a high calorie diet began to closely resemble that of mice on a standard diet. Resveratrol not only increased the life expectancy of the high calorie mice to match those of the standard diet but also had other beneficial effects. It improved motor function, improved insulin sensitivity, and had a positive effect on organs such as the liver and heart. The liver was especially affected: resveratrol seemed to prevent the build-up of fat and thus the livers of overweight mice on resveratrol and standard calorie mice were similar (7). The result was that while the high calorie mice did not lose any weight, many of the adverse effects of obesity such as heart disease were greatly reduced by resveratrol.

### Future of Resveratrol and Aging

The results from the resveratrol studies provide hope to scientists and, more generally, to a world in which obesity is a serious epidemic and people want to live longer. As we have been shown many times, obesity can drastically reduce a person's lifespan due to the increased risks of heart disease, stroke, and cancers of the breast, kidney, colon, liver, pancreas, and gallbladder. In fact, obese people

tend to have insulin resistance and consequently higher levels on insulin in their bloodstream, which can cause cells to proliferate uncontrollably, causing cancer (10). Resveratrol, as mentioned above, reduces insulin resistance and is also involved in many metabolic pathways in humans. It seems that it is a good candidate for dealing with - at least in part - the issues of obesity in humans and increasing lifespan. If the studies on yeast and vertebrate fish hold up for mammals, resveratrol could also prolong the lives of normal weight humans by mimicking caloric restriction and thus delaying aging mechanisms.

However, it is important not to regard resveratrol as a panacea: even if resveratrol can delay aging, scientists still have to tackle other aging-related problems, such as brain degeneration. In addition, resveratrol's effects on humans are still mostly undocumented, and while it does demonstrate promise in extending the human lifespan, it is possible, as with all new drugs, that it has unforeseen side effects. As an example it was found that lifespan actually decreased for yeast that were given very high doses of resveratrol (11). Despite potential risks, a company called Sirtris Pharmaceuticals hopes to harness the power of resveratrol and caloric restriction to reduce aging and treat metabolic diseases. In addition, resveratrol is already being sold as a nutritional supplement in the form of capsules and powders. If the hype of resveratrol increases further, problems could arise if people decide to take resveratrol without learning about its effects or consulting their doctors. Furthermore, nutritional and pharmaceutical companies are not responsible for the education of consumers regarding potential side-effects of Resveratrol. In conclusion it is advisable for governments and various agencies to question the safety of resveratrol and, when necessary, to better regulate such products. In an age where an elixir of youth might be just around the corner,

scientists and policymakers must advance cautiously to protect the health of the public while learning to take full advantage of the powerful substances at their fingertips.



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