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## Wine's wonder drug?

### Benefits of resveratrol supplements questioned

*By Melissa Healy*  
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In August 2003, when scientists revealed the life-extending powers of trans-3,4,5-trihydroxystilbene — also known as resveratrol — its earthly form had all the allure of an apple in the garden of Eden.

Ruby red, delicately fragrant, shapely in a rounded nest of glass, red wine can deliver as much as 1.5 milligrams of the plant compound resveratrol per 4-ounce serving. At concentrations present in a person's blood after two glasses of red wine, resveratrol has been found to suppress the formation of blood clots and boost the efficiency of immune system cells.

Much larger doses of resveratrol increase the life span of yeast, flies, fish and roundworms, studies have shown. A feeding regimen that includes the good stuff found in red wine makes obese mice just as healthy, spry and long-lived as those who have been raised on near-starvation diets.

So leave it to American entrepreneurs to gin up a thriving market for a resveratrol supplement rather than urge consumers to enjoy the food — or in this case, savor the drink — linked to better health and longer life, says Dr. Gerald Weissmann, director of New York University's biotechnology study center.

In the blinking come-ons of some resveratrol pitches and in the subtext and testimonials of others, remarkable claims for resveratrol supplements abound: They will forestall or prevent such age-related scourges as cancer, diabetes, arthritis and Alzheimer's disease; they will restore vitality, endurance and strength to the middle-aged and older; they will make aging brains sharper and more agile.

But the business of selling the supplement touted as an "anti-aging miracle" rests on a foundation of science that is as incomplete as it is promising. In fact, the marketing frenzy surrounding resveratrol is a prime example of how science can be distorted when it is mingled with hope, amplified for buzz and spun for profit.

"I am surprised at the interest, if you consider that the long-term effects in humans are not known," said David Sinclair, the Harvard Medical School pathology professor who has pioneered research on resveratrol and the family of genetic pathways on which the plant compound acts. "The short-term effects are fine. But we don't know what happens if you take this for two decades."

The research on resveratrol is in its infancy.

To date, its most exciting possibilities have been demonstrated only in experiments conducted in petri dishes, on organisms such as yeast and roundworms, and in mice. A single study on rhesus monkeys is almost a year from completion.

## Human trials

A dozen human trials on resveratrol (or on drugs derived from it) are under way or have recently been completed. But only two are in the third and final phase of testing, in which an agent's effectiveness in treating or preventing a specific disease is measured.

Meanwhile, two small studies — neither of which has been published in a scientific journal — have pointed to the possibility that resveratrol might improve exercise endurance and regulate blood sugar in diabetics. And scientists are likely years away from establishing the safety of using large quantities of resveratrol for long periods of time.

The drug giant GlaxoSmithKline, having paid \$720 million last year for the commercial rights to some of the earliest research on resveratrol, is seeking ways to mimic its broad spectrum of effects in a compound created in the lab rather than grown on a vine.

Sinclair, who heads the company's efforts, called resveratrol "an interesting proof-of-concept molecule" — a crude but useful vehicle to activate a class of enzymes called sirtuins, which influence the cellular aging process in organisms as diverse as yeast and humans. But Sinclair said his research now focuses on some 4,000 synthetic versions of resveratrol that may more powerfully engage the sirtuins, blunting inflammation, blocking tumor growth and boosting the removal of toxins and cellular debris.

But science is slow. Sinclair said in an interview that it could be five to seven years before a drug based on resveratrol could get a nod from the Food and Drug Administration.

## Window of opportunity

For the purveyors of vitamins, minerals and herbal remedies, that is a five- to seven-year opportunity not to be missed. Consumers' dreams of forestalling the ravages of age have been engaged, and they will buy and swallow anything that gleams with the luster of science.

While they wait for science to flesh out resveratrol's promise, consumers' demands for the stuff can be built, tapped and satisfied with products that offer plenty of promise but tread lightly around the preliminary state of the scientific evidence.

Compared with the markets for many other dietary supplements — Omega-3, CoQ10, vitamin D and calcium — the market for resveratrol supplements is tiny. James Betz, founder of Biotivia, one of the leading suppliers of resveratrol products, estimates that the worldwide market for resveratrol supplements may stand at just \$20 million per year — making it a modest newcomer on the dietary supplements block.

"But our sales are ticking up rather dramatically now," Betz said. The market for resveratrol "does have an almost logarithmic rate of growth at this point," he added. "I think it could become as popular as, let's say, multivitamins."

The supplements themselves sell on the Internet and in stores for prices that range from about \$15 to close to \$150 per bottle (typically a one- or two-month supply, since dosage recommendations vary widely).

What does it do?

The flurry of commercial activity has taken off despite the fact that researchers don't know exactly what resveratrol does.

Betz and others vying for a share of that market say there is no need to wait until slow-moving clinical trials have established resveratrol's life-extending powers in humans, not to mention its safety, to encourage the use of large doses.

"I feel there is virtually no evidence so far — and resveratrol has been around for quite a while — of harm," he said. "And I feel, given the data we have now, which concludes it has benefits in terms of so many diseases ... that it will do more harm than good not making it available."

But until clinical trials provide the answers to questions on, among other things, the proper dose, Rafael de Cabo, a National Institute on Aging investigator who has co-written most of the pioneering studies on resveratrol, said he wouldn't consider taking a resveratrol supplement. And he certainly

would not recommend them.

"We need to understand exactly how these molecules work, at what doses and for what disease" before offering them on the open market, he said. "Unless you have scientific evidence, you're a snake oil seller."

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