



Natural Health & Nutrition Newsletter



Natural Food-Based Toxins

Part 5 - Resveratrol - Concerns About Bioavailability and Metabolism

*We live in deeds not years
In thoughts not breaths
In feelings not figures on a dial.*
-Aristotle

In April of 2008, drug giant GlaxoSmithKline announced plans to purchase Sirtris, a small Boston-area pharmaceutical company focused on developing drugs which activate supposed “anti-aging” genes called sirtuins. Thanks to widespread media exposure, Sirtris is now well-known for its research involving the red-wine component, resveratrol, and for producing novel resveratrol-related chemicals.

Glaxo’s well-publicized purchase for the whopping sum of \$720 million dollars has been criticized by Wall Street and academia alike as a notably risky endeavor. While it is true that a large (and growing) amount of *in vitro* research has shown that resveratrol-related compounds may be of some therapeutic benefit in diseases such as cancer and heart disease, the biological effects of such chemicals in humans are still largely unknown.

Because resveratrol itself is a component of food, it can freely be sold as a dietary supplement – and largely because of the media exposure generated by Sirtris, many people have begun taking such resveratrol in pill form. But this trend seems driven largely by the public’s inability (or unwillingness) to recognize

the biological differences between drugs, and the natural substances from which drugs are sometimes *derived*.

As a natural substance, resveratrol lacks the patent-protection which makes pharmaceuticals so profitable; and currently, we can find dozens of resveratrol-supplement promoters citing *in*

vitro (e.g., test tube) and animal studies in an attempt to sell this “natural” compound as an “anti-aging” nutrient. But only very rarely do we hear the honest admission that resveratrol supplements are highly *unlikely* to live up to their current hype – first and foremost, because of their extremely *poor* bioavailability in humans.



And the question of bioavailability is just the tip of the iceberg. Even if resveratrol *were* bioavailable, we don't know whether it would activate sirtuin genes in humans. Even if it *were* to activate sirtuin genes, we don't know whether this effect would be beneficial or harmful. We also don't know if the effects of resveratrol on detoxicative enzymes are beneficial or harmful (although resveratrol is almost certain to significantly alter the metabolism of other drugs). We don't know whether resveratrol acts as an estrogen agonist or anti-estrogen (there's evidence to suggest both effects), and as such, whether it would inhibit or stimulate different types of cancer, or negatively impact fertility. In addition to the effects of resveratrol which are generally deemed beneficial, some evidence suggests that resveratrol has the potential to *inhibit* the production of protective hormones, *stimulate* neurons to the point of death, and *impair* the functioning of the beta cells which produce insulin.

With its many biological effects, it's almost certain that drug companies will be able to chemically manipulate the resveratrol molecule in such a way as to produce targeted pharmaceuticals. But the mere fact that a drug seems to improve the symptoms of a *disease state* does not *ipso facto* make similar substances viable "anti-aging supplements" for regular use in healthy individuals. The use of insulin by a diabetic, or chemotherapy drugs by a cancer patient can, in each case, be life-saving (and, by implication, life-extending) – but the use of these same drugs by a healthy person would be a different story entirely. The current research on resveratrol and related compounds already shows that these substances are likely to exhibit drug-like, and not nutritive, effects – despite some early life-extending successes in certain species, resveratrol has, so far, failed to extend the lifespan of healthy, genetically normal animals.

Many supplement companies are profiting greatly by espousing an "overly-optimistic" stance on how applicable the current resveratrol research will turn out to be for humans. But despite the hype, resveratrol supplementation as an anti-aging strategy has infinitely less scientific justification than many people are being led to believe. There are numerous reasons to believe, in fact, that long-term resveratrol supplementation may very easily do more harm than good.

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Resveratrol Bioavailability and Metabolism

Much of the excitement over resveratrol supplementation seems misplaced considering that the compound is so poorly bioavailable in humans. While its *absorption* is high, the human body rapidly "detoxifies" resveratrol in the bloodstream by conjugating (chemically complexing) it with sulfate and glucuronic acid. These processes (called sulfation and



glucuronidation respectively) render the substance more water-soluble for excretion in the urine.

Studies have shown that, in humans, a 25 milligram dose of resveratrol (roughly, the amount of resveratrol found in 4 to 12 liters of red wine, depending upon the grape cultivar) was unable to elevate plasma levels of unaltered resveratrol beyond trace levels:

Study Link - High absorption but very low bioavailability of oral resveratrol in humans.

Quote from the above study:

The most important question in this study was whether unmetabolized resveratrol could be detected in plasma. The rather intense UV absorption of resveratrol, in addition to the use of radioactive doses, provided a reasonably good experimental approach for this question. However, all attempts to find measurable levels of resveratrol in plasma after the oral dose at any time point in the six volunteers failed. Only trace amounts of less than 5 ng/ml could be seen.

Similarly, other studies have found that the resveratrol from wine is rapidly conjugated in the bloodstream – leading the researchers to reason that the health benefits of wine consumption may *not* be due to resveratrol, but to the overall combination of antioxidant substances and alcohol in wine:

Study Link - Bioavailability of trans-resveratrol from red wine in humans.

Quote from the above study:

The finding in human serum of trans-resveratrol glucuronides, rather than the free form of the compound, with a high interindividual variability, raises some doubts about the health effects of dietary resveratrol consumption and suggests that the benefits associated to red wine consumption could be probably due to the whole antioxidant pool present in red wine.

For resveratrol to exhibit its much-touted anti-cancer activity *in vitro*, levels of resveratrol of at least 5 micromols/liter are needed. But when ingested by humans, even in incredibly-high doses, levels of free (non-conjugated) resveratrol simply haven't been shown to reach these levels.

British researchers have recently found that even a **5 gram** (5,000 milligram) dose of resveratrol was only able to elevate human plasma resveratrol-levels to around

2.4 micromol/liter:

Study Link - Phase I dose escalation pharmacokinetic study in healthy volunteers of resveratrol, a potential cancer chemopreventive agent.

Quote from the above study:

Peak plasma levels of resveratrol at the highest dose were 539 +/- 384 ng/mL (2.4 micromol/L, mean +/- SD; n = 10)... The results presented here intimate that consumption of high-dose resveratrol might be insufficient to elicit systemic levels commensurate with cancer chemopreventive efficacy.

Other studies have shown, similarly, that orally-ingested resveratrol doesn't lead to the levels in human plasma that are thought to be necessary to mimic resveratrol's *in vitro* effects. For this reason, the researchers who conducted the following study went so far as to deem resveratrol's *in vitro* anti-cancer and anti-inflammatory effects irrelevant.

Study Link - Absorption of three wine-related polyphenols in three different matrices by healthy subjects.

Quote from the above study:

*The absorption of these three polyphenols [including resveratrol] is broadly equivalent in aqueous and alcoholic matrices but, at peak concentrations of 10 to 40 nmol/L, is inadequate to permit circulating concentrations of 5 to 100 micromol/L consistent with *in vitro* biologic activity. The voluminous literature reporting powerful *in vitro* anticancer and antiinflammatory effects of the free polyphenols is irrelevant, given that they are absorbed as conjugates.*

It's possible that the resveratrol conjugates themselves may exert biological activity, or that enzymes in certain tissues may be able to liberate free resveratrol from its conjugates, but, to date, none of the *in vitro* effects of resveratrol are at all applicable to the effects possible with supplementation – and oral resveratrol has yet to show any meaningful biological benefit in humans.

But because the body uses a portion of its detoxifying ability to rid the body of ingested resveratrol, the polyphenol is very likely to impair the body's ability to metabolize **other** drugs, hormones, and environmental toxins. For example, drugs which are sulfated for removal from the body have often been shown to deplete the body of sulfur compounds:

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Study Link - Serum concentration and renal excretion by normal adults of inorganic sulfate after acetaminophen, ascorbic acid, or sodium sulfate.

Quote from the above study:

Serum inorganic sulfate concentrations (mean +/- SD), 0.410 +/- 0.043 mM in the control period, were decreased after acetaminophen (0.311 +/- 0.043 mM, P less than 0.001).

Because these sulfur compounds are both important components of the detoxicative system **and** major structural components of connective tissue, drugs which are metabolized via sulfation have been shown to sometimes compromise the structural integrity of cartilage and other sulfur-rich tissue:

Study Link - Effects of drug-mediated serum sulfate depletion on glycosaminoglycan synthesis.

Quote from the above study:



Drug-induced changes in the serum sulfate concentration might result in an altered synthesis of cartilage glycosaminoglycans and eventually interfere with the pressure resistant functions of cartilage.

Note: Empirically, some users of resveratrol supplements have noted disorders of connective tissue (e.g., tendonitis, tendonopathy) as possible side effects. The connection or cause is unclear, but one wonders if the possible effect of resveratrol on sulfur status is partially responsible.

Due to a lack of research, it remains unclear what effect resveratrol has on sulfur status *per se*, but some evidence **does** suggest that resveratrol can negatively impact the body's ability to bind and deactivate estrogen via sulfation:

Study Link - Effect of Resveratrol on 17β-Estradiol Sulfation by Human Hepatic and Jejunal S9 and Recombinant Sulfotransferase 1E1.

Quote from the above study:

Resveratrol inhibited E2 sulfation with estimated Ki values of 1.1 μM (liver), 0.6 μM (jejunum), and 2.3 μM (SULT1E1), concentrations that could be pharmacologically relevant. The results suggest that these phytoestrogens can potentially alter the homeostasis of estrogen levels. These findings also imply that resveratrol may inhibit the metabolism of other estrogen analogs or therapeutic agents such as ethinylestradiol or dietary components that are also substrates for SULT1E1.

Another mechanism by which resveratrol may impair the proper metabolism of estrogen (and other substances) is via inhibition of the detoxifying enzyme known as CYP3A4:

Study Link - Resveratrol, a red wine constituent, is a mechanism-based inactivator of cytochrome P450 3A4.

Quote from the above study:

...[I]nactivation of CYP3A4 by resveratrol may cause clinically relevant drug interactions with CYP3A4 substrates.

Similar to resveratrol, compounds in grapefruit impair CYP3A4, which is responsible for the well-known "grapefruit effect" – i.e., the observation that drug metabolism is often dangerously altered

when taken with grapefruit, or grapefruit juice. As testament to the fact that natural components of food can have negative consequences insofar as they alter detoxification of estrogens, some (but not all) studies have found an increased risk of breast cancer among postmenopausal women who consume grapefruit juice:

Study Link - Prospective study of grapefruit intake and risk of breast cancer in postmenopausal women: the Multiethnic Cohort Study.

Quote from the above study:

Grapefruit intake may increase the risk of breast cancer among postmenopausal women.

Marketers in the supplement industry usually posit resveratrol as some sort of “anti-estrogen,” but the fact that resveratrol is likely to have a negative impact on the body’s ability to *deactivate* endogenous estrogen usually isn’t mentioned. It’s likely that resveratrol supplementation will have some complex and unpredictable effects on the hormonal system. To assume that resveratrol will have only positive hormonal effects is simply wishful thinking given all that is currently known (and all that is currently unknown) about resveratrol metabolism in humans.

It should be recognized that resveratrol’s ability to alter the metabolism of other substances is due to the fact that, biologically speaking, resveratrol is simply another toxin – it competes for the same enzymes and substances which the body uses to inactivate and excrete hormones, drugs, and environmental chemicals. For this reason, it’s been proposed that resveratrol may inhibit the metabolism of pharmaceuticals which are detoxified by the same mechanism as resveratrol itself. Such drugs could include statins, anti-arrhythmic agents, blood pressure medications, and benzodiazepines. Resveratrol could cause a potentially-dangerous increase in the bioavailability and toxicity of these drugs:

Study Link - Inhibition of CYP3A, CYP1A and CYP2E1 activities by resveratrol and other non volatile red wine components.

In certain contexts, however, resveratrol’s ability to alter the body’s detoxicative ability could be construed as a beneficial effect. As a bit of background, the metabolism of potentially-toxic substances is divided into two phases. Phase I detoxification [involving P450 enzymes (CYPs) and flavin monooxygenases] alters chemicals in such

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a way as to make them more-easily acted upon by the Phase II enzymes – the ones that conjugate the substance with things like sulfate and glucuronic acid as we have seen. Many compounds, however, become *more* toxic (e.g., more carcinogenic) after being altered by Phase I enzymes (i.e., before they can be conjugated by the Phase II enzymes). For this reason, one avenue of cancer research involves manipulating detoxification via substances which can *inhibit* Phase I enzymes and/or *upregulate* Phase II enzymes. The pro-resveratrol camp is quick to point out that resveratrol may achieve both of these goals:

Study Link - Potent induction of cellular antioxidants and phase 2 enzymes by resveratrol in cardiomyocytes: protection against oxidative and electrophilic injury.

In some studies like the one above, resveratrol has been shown to “stimulate” some aspects of the metabolic machinery of detoxification leading to some wishful speculation that resveratrol may reduce the body’s overall toxic burden. But the effects of foreign substances on detoxifying enzymes are notoriously complex, and the *in vivo* benefits of resveratrol are apt to be seriously *compromised* by the very fact that resveratrol may alter detoxification pathways in this way:

Study Link – Therapeutic potential of resveratrol: the *in vivo* evidence.

Quote from the above study:

However, this same activity could make resveratrol as a potential therapeutic problematic because the inhibition of CYPs could alter the pharmacokinetics of other drugs.

Logically, it makes some sense that ingesting the resveratrol “toxin” will decrease Phase I metabolism of other substances (by direct competition and enzyme inhibition, as we have seen). It also makes sense that resveratrol would increase the enzymes responsible for driving Phase II metabolism (as a defensive measure in response to the ingested “toxin”). So, where the body’s response to resveratrol is, in a general sense, a defensive response to a toxic substance, it can’t in good conscious be said that these effects make resveratrol, in any way, beneficial or suitable for long-term use.

Case in point – research has shown that many of the same biological effects exhibited by resveratrol (i.e., inhibition of Phase I enzymes, upregulation of Phase II enzymes, and protection against the liver-toxicity caused by acetaminophen) have also been exhibited by alcohol:

Study Link - Protective effect of ethanol against acetaminophen-induced hepatotoxicity in mice: role of NADH:quinone reductase.

Quote from the above study:

These results suggest that ethanol inhibited not only the microsomal (CYP2E1 [a Phase I enzyme] mediated) formation of a toxic quinone metabolite from APAP, but also accelerated the conversion of the toxic quinone metabolite produced back to APAP by stimulating cytoplasmic QR [a Phase II enzyme] activity.

The above study gives some meaningful perspective on resveratrol (and how biological research is often conveniently misinterpreted to sell dietary supplements). While alcohol (aka ethanol – the alcohol in alcoholic beverages) may have some benefits when consumed moderately, its detrimental effects, when consumed in excess, are widely known. Nobody in their right mind would advocate a high intake of alcohol for health purposes, despite the fact that, in the above study, it showed a molecular-level benefit against, of all things, liver-toxicity.

In essence, people taking high doses of resveratrol (and many other plant chemicals, for that matter) are spending

hard-earned money to make their bodies filter out doses of chemicals which the human body simply wasn't built to handle. Resveratrol doesn't seem to be acutely dangerous, but, taking into account its poor bioavailability and its impact on the body's detoxifying mechanisms, supplementation seems to be a strange and potentially harmful practice driven more by wishful thinking than scientific evidence.

The Animal Studies

In some species, long-term caloric restriction (CR) has been shown to increase lifespan – but as we saw in the previous Integrated Supplements Newsletter, caloric restriction has not yet been proven to increase the lifespan of humans. Taking the conceptual leap of faith that caloric restriction *will* increase the health and lifespan of humans, some researchers have targeted resveratrol-related compounds as molecules which may mimic some of the genetic and cellular changes caused by CR. Realizing that almost no one possesses the discipline necessary to consume a life-long calorie-restricted diet, companies like Sirtris, are hoping that there will be a major market for chemicals which mimic its effects.

But even if resveratrol-related compounds do mimic *some* of the genetic effects of CR, it's unlikely that such chemicals would be suitable for long-term use by healthy individuals. Where some of the molecular-level mechanisms of action sought for resveratrol-based drugs are already known to be effects of currently-available medications, it's more likely that resveratrol research may simply lead to the development of "new" drugs for diabetes or cancer. The thiazolidinedione drugs, for example, in many ways, *already* exhibit some of the exact effects Sirtris is trying to achieve with resveratrol-based drugs:

Study Link - Energy restriction as an antitumor target of thiazolidinediones.

Quote from the above study:

Here, we identified thiazolidinediones (TZDs) as a novel class of energy restriction-mimetic agents in that they elicited hallmark cellular responses characteristic of energy restriction, including transient induction of silent information regulator (Sirt)1 expression, activation of the intracellular fuel sensor AMP-activated protein kinase, and endoplasmic reticulum stress, the interplay among which culminated in

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autophagic and apoptotic death.

But, again, there's a world of difference between drugs which treat disease states, and substances which are suitable for long-term consumption by healthy individuals.

To date, in fact, resveratrol has yet to extend lifespan when administered to healthy, genetically-normal animals eating a normal diet. In the study most-touted by resveratrol marketers, resveratrol was effective at *normalizing* lifespan only in obese mice consuming an excess of calories:

Study Link - Resveratrol improves health and survival of mice on a high-calorie diet.

In subsequent studies, in mice *not* consuming a high-calorie diet, no lifespan extension was noted from resveratrol:

Study Link - Resveratrol Delays Age-Related Deterioration and Mimics Transcriptional Aspects of Dietary Restriction without Extending Life Span.

Quote from the above study:

...[R]esveratrol does not seem to mimic all of the salutary effects of DR [dietary restriction] in that its introduction into the diet of normal 1-year-old mice did not increase longevity.

So, despite the current hype, it doesn't seem that either the nutritional supplement or pharmaceutical industries have yet developed anything even approaching a true "anti-aging" pill. Those consuming high-dose resveratrol supplements in the absence of long-term safety data have many reasons to be concerned not only

about the direct effects of resveratrol, but about the polyphenol's indirect effects on the metabolism of drugs, hormones, and environmental chemicals.

To truly reap the benefits from what the current anti-aging research shows, most of us would probably be well-served to simply eat a bit more modestly (though extreme caloric restriction is still a questionable practice). The case could certainly be made for the moderate consumption of red wine – which contains not only resveratrol, but small amounts of many health-promoting substances which are likely to work in synergy with one another. Outside of the dietary and nutraceutical realm, it's been found that building meaningful emotional relationships and managing stress are essential to longevity; and engaging in regular exercise and intellectually-stimulating hobbies are likely to be important strategies as well.

The science of gerontology is a rapidly growing field of study which is continually supplying us with important clues to unlocking the mysteries of aging and disease – yet, at this time, the ultimate keys to a longer, healthier life still remain unknown. Though many of us would like to believe that a simple pill will help to counter our modern dietary indiscretions, a more rational look at the anti-aging literature shows that this isn't likely to be the case any time soon.

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