

Resveratrol Opportunism: What Is the Science Behind the Claims?

Jeffrey Bland, PhD, FACN, FACB

Resveratrol, a phytoalexin naturally produced by several plants when under attack by pathogens such as bacteria or fungi and found in foods such as peanut skins, grapes, and blueberries, has become the latest “darling” of the nutritional supplement industry. The foundation for its use was built upon the discovery work of David Sinclair, PhD, at Harvard University, who demonstrated that resveratrol influences activities of the sirtuin gene family (a group of 7 genes associated with the aging process, thus dubbed the “longevity genes”). As a result of his initial studies, there is a high level of interest in the preventive and therapeutic health potential of this compound.¹

The group at Sirtris Pharmaceuticals, a GlaxoSmithKline company working on developing small-molecule drugs that target the sirtuins, has engaged in detailed work on resveratrol's mode of action as a selective nicotinamide-adenine-dinucleotide-dependent histone deacetylase inhibitor, a process that activates expression of the sirtuin gene family.² When given to various test organisms and animals, resveratrol appears to increase longevity in a fashion similar to that of calorie restriction.³ This action seems to be a conserved function across the phylogenetic spectrum (ie, it is found across many species in evolution from yeast to mammals), suggesting that it is an ancient legacy from evolution.⁴

Resveratrol discoveries are encouraging, for they imply potential for new therapeutic agents to prevent and manage such age-related chronic diseases as type 2 diabetes, heart disease, and cancer. Certain questions, however, must be answered before we know how these recent findings eventually might translate into clinical applications. These questions include the following:

1. Will resveratrol be proven as clinically useful in humans as it appears to be in animals?
2. What dose of resveratrol is needed to produce positive effects in humans?
3. Is this effective dose safe when taken for a long period of time?
4. What side effects does resveratrol have at this effective dose?

Only when these 4 questions have been answered can we begin to evaluate the veracity of the current structure-function claims made for resveratrol-containing supplements. These claims include that resveratrol improves insulin action, reduces cancer risk, and improves cardiovascular function. As it stands, the basis of claims for the value of resveratrol-containing nutritional supplements derive principally from selective interpretation of science borrowed from published studies on resveratrol or on its methylated derivatives such as pterostilbene. However,

to determine whether these published studies support the claims that are made for specific resveratrol supplements, one must evaluate human data that indicate whether the percentages of resveratrol or pterostilbene in a specific nutritional supplement are within effective dose ranges.

Dose

The first issue of concern about available resveratrol supplements is the fact that the majority of these supplements actually contain a very low dose of resveratrol. The potency of most of the nutritional supplements labeled as resveratrol is in the range of 30 mg to 100 mg. This is 30 to 100 times lower than doses thought to be in the range for therapeutic effects in humans.⁵ At this point, the therapeutic dose for humans is not specifically known. Most of the feeding studies published on resveratrol have been in animals, and it is difficult to translate dosages in animal studies into human equivalents. However, a recently published human pharmacokinetic study of resveratrol indicated that a dose of 1000 mg to 5000 mg per day was required to bring the blood level of resveratrol into a range for being a potential cancer preventive.⁶

Some nutritional-supplement marketers have suggested that they have an improved “delivery system” for resveratrol in the form of the previously mentioned methylated resveratrol relative called pterostilbene. The claim is that this ingredient is many times more bioavailable than resveratrol itself, and, therefore, less of it is required for therapeutic benefits to accrue. Published literature that purportedly supports this claim has been cited, but closer scrutiny reveals that all but 1 of the studies used in vitro assays of specific cell lines in culture—which is not the same as evaluating activity in humans.⁷ A single human oral-administration study reported that when 450 mg of pterostilbene—extracted from *Pterocarpus marsupium* (the heartwood of the kino tree, an Ayurvedic medicinal plant)—was given, participants' blood levels failed to reach a point that had a measurable effect on inflammatory function (an assay for the physiological influence of resveratrol).⁸

In fact, animal studies have indicated that no oral dose of resveratrol (or of methylated derivatives of resveratrol) can attain blood levels necessary to influence expression of the sirtuin gene family.^{9,10} The bioavailability of resveratrol is low. In order to reach therapeutic blood levels that do affect the sirtuin gene family, Sinclair et al developed and patented an oral delivery system to increase bioavailability. However, this converts the nutritional ingredient into a drug by US Food and Drug Administration law. This leaves a critical question begging: Does this mean that, at this time, no resveratrol supplement is helpful in affecting the sirtuin gene?

Some nutritional-supplement formulas blend a low level of

resveratrol (35-100 mg) with a low level of methylated resveratrol as pterostilbene (100-200 mg) along with the bioflavonoid quercetin (200-300 mg). Claims associated with these products suggest that the low-level combination of these 3 ingredients produces a synergy that makes the combination more effective. However, a review of 1 published study supporting this claim revealed that, when high levels of pterostilbene and quercetin were administered by intravenous injection to mice with liver cancer, only a modest additive effect, but not synergy, was detected.¹¹

Biochemistry and Bioavailability

Upon oral induction, both resveratrol and methylated resveratrol convert into glucuronide and sulfate forms—with methylated resveratrol being the slower of the 2 (the derivatives have been shown to remain longer in the blood before converting than resveratrol alone). However, the argument of improved bioavailability is somewhat misleading in that the glucuronide and sulfate forms of resveratrol also stay in the blood for some time. The question that recently has been raised is whether higher blood levels of the glucuronide and sulfate forms of resveratrol themselves have benefit, perhaps serving as a pool of “time release” sources of resveratrol between times when resveratrol is consumed.¹²

Whatever the case, the fact that resveratrol and methylated resveratrol have different rates of conversion into their glucuronide and sulfate forms does not necessarily mean that one form is preferable to the other in terms of potential health benefits. It is well known that many genes are influenced positively in vitro by both resveratrol and methylated resveratrol; therefore, it is premature to conclude that one form is more beneficial than the other.¹³ It is likely that resveratrol and its methylated derivatives such as pterostilbene have very different modes of action and physiological effects owing to their different chemical structures.

What can be said at this time is that recent discoveries surrounding resveratrol and its methylated derivatives have opened up a new chapter in our understanding of the role that phytochemicals have on gene expression and their potential influence on health and disease. The value of any resveratrol supplement is dependent on human clinical studies to demonstrate that a specific formula does safely, favorably, and reproducibly influence physiology in humans. Before resveratrol in supplementary form can support the enthusiasm that surrounds it, it must meet a standard of scientific validity.

Jeffrey Bland, PhD, FACS, FACC, is cofounder and former chairman of the Institute for Functional Medicine (IFM), a nonprofit organization dedicated to supporting the growth of patient-centered medicine. Dr Bland also developed and continues to oversee the Functional Medicine Clinical Research Center, a facility unrelated to IFM. In addition, he currently serves as chief science officer for Metagenics and president of its biotechnology unit, MetaProteomics. All of these organizations/companies are based in Gig Harbor, Washington. During his illustrious career, Dr Bland has been the clinical laboratory director for the Bellevue Redmond Medical Laboratory in Washington, the director of the Nutritional Supplement Research Laboratory at Oregon State University's Linus Pauling Institute of Science and Medicine, and president of the Seattle-based Northwest Academy of Preventive Medicine. He has also authored numerous books and peer-reviewed papers.

References

1. Baur JA, Sinclair DA. Therapeutic potential of resveratrol: the in vivo evidence. *Nat Rev Drug Discov*. 2006;5(6):493-506.
2. Milne JC, Lambert PD, Schenk S, et al. Small molecule activators of SIRT1 as therapeutic for the treatment of type 2 diabetes. *Nature*. 2007;450(7170):712-716.
3. Sinclair DA, Guarente L. Unlocking the secrets of longevity genes. *Sci Am*. 2006;294(3):54-57.
4. Morris BJ. A forkhead in the road of longevity: the molecular basis of lifespan becomes clearer. *J Hypertens*. 2005;23(7):1285-1309.
5. Reagan-Shaw S, Nihal M, Ahmad N. Dose translation from animal to human studies revisited. *FASEB J*. 2008;22(3):659-661.
6. Boocock DJ, Faust GE, Patel KR, et al. Phase 1 dose escalation pharmacokinetic study in healthy volunteers of resveratrol, a potential cancer chemopreventive agent. *Cancer Epidemiol Biomarkers Prev*. 2007;16(6):1246-1252.
7. Wen X, Walle T. Methylated flavonoids have greatly improved intestinal absorption and metabolic stability. *Drug Metab Dispos*. 2006;34(10):1786-1792.
8. Hougee S, Faber J, Sanders A, et al. Selective COX-2 inhibition by a Pterocarpus marsupium extract characterized by pterostilbene, and its activity in healthy humans. *Planta Med*. 2005;71(5):387-392.
9. Wenzel E, Soldo T, Erbersdobler H, Somoza Y. Bioactivity and metabolism of trans-resveratrol orally administered in Wistar rats. *Mol Nutr Food Res*. 2005;49(5):482-494.
10. Remsberg CM, Yáñez JA, Ohgami Y, et al. Pharmacometrics of pterostilbene: pre-clinical pharmacokinetics and metabolism, anticancer, antiinflammatory, antioxidant and analgesic activity. *Phytother Res*. 2008;22(2):169-179.
11. Ferrer P, Asensi M, Segarra R, et al. Association between pterostilbenes and quercetin inhibits metastatic activity of B16 melanoma. *Neoplasia*. 2005;7(1):37-47.
12. Wenzel E, Somoza V. Metabolism and bioavailability of trans-resveratrol. *Mol Nutr Food Res*. 2005;49(5):472-481.
13. Pan Z, Agarwal AK, Xu T, et al. Identification of molecular pathways affected by pterostilbene, a natural dimethylene ether analog of resveratrol. *BMC Med Genomics*. 2008 Mar 20;1:7.

Gain library access to 6 years of IMCJ back issues

SUBSCRIBE NOW!

Don't miss a single issue! Stay abreast of innovative research and cutting-edge information with peer-reviewed, scientifically accurate, practical articles on the integration of conventional and natural medicine.

**To subscribe, go to
www.imjournal.com**