COMMENTARY ON RESVERATROL AND HORMESIS: RESVERATROL – A HORMETIC MARVEL IN WAITING?

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ABSTRACT

Hormesis is a phenomenon in which adaptive responses to low doses of otherwise harmful factors (also called mild stressors) make cells and organisms more robust. In their review, Calabrese et al. provide evidence for resveratrol acting hormetically in different types of human cell lines. The effects of resveratrol represent a "two-edged sword" in that it has contrasting effects at low and high doses in healthy and cancerogenous cells. What demarkates a low and a high dose needs to be clarified. Concentrations tested in cell cultures, moreover, may not be relevant to whole organisms. And data from animal models need not apply to humans. Co-morbidities should also be considered. More research is needed to understand the action of resveratrol on all cell types and conditions, and the optimum therapeutic concentration that applies to each of these. Future research needs to determine the dynamics of the effects of resveratrol in different subcellular compartments and the interactions of these. In addition, the interactions between resveratrol, environmental factors, other compounds and medications, diseases and the genetic background of the individual will need to be appreciated in order to gain a complete understanding of the hormetic response of resveratrol.

Keywords: hormesis, resveratrol, doses, co-morbidities, interaction.

COMMENTARY

Hormesis refers to the phenomenon by which benefits are seen for low doses of external stressors that at higher concentrations are noxious.[1,2] Resveratrol, a natural polyphenolic flavonoid found in grapes, red wine, berries, knotweed, peanuts and diverse other plants, mediates the beneficial effects of mild environmental stressors on lifespan and health. Its potent antioxidant effects might explain some of its diverse health benefits.[3-5] One well-established effect of resveratrol is its potential to inhibit the initiation and growth of tumours in different cancer models in mice and rats.[6,7] But an immense number of other health benefits have also been reported.[3-5]

In the present issue of Human & Experimental Toxicology, Calabrese et al.[8] have reviewed the evidence for resveratrol acting hormetically and find in favour of this possibility. The effects of resveratrol therefore represent a "two-edged sword" in that it has contrasting effects at low and high doses. At low doses, it appears to stimulate the proliferation of healthy and cancer cells, and has therapeutic effects on healthy cells. These effects include enhancement of metabolism and cardiovascular function, and improvement of osteoporosis. High doses, were, however, found to be able to inhibit proliferation of cells, healthy or not, so highlighting the potential of resveratrol as a new treatment for cancer. At these same doses, nevertheless, resveratrol had adverse clinical effects on other conditions. Its adverse effects included increased toxicity, suppression of immune response, and delayed healing. The extensive review by Calabrese et al.[8] gives numerous examples of such a biphasic response of resveratrol, a property not evident when assessing only individual studies. As highlighted by the authors, most of the mechanisms underlying the effects of resveratrol remain to be elucidated completely. The idea that res-

veratrol is a direct activator of sirtuins arose from a technical problem with the assay, and no longer holds.[9] Sirtuin activation is in fact probably indirect. Interestingly the most studied sirtuin, SIRT1, also has a dual role in cell death and survival.[10] More research is, however, needed to understand the action of resveratrol on all cell types and other conditions, and the optimum therapeutic concentration that applies to each of these.

Although there are well-known cardiovascular benefits of resveratrol, we consider that the authors' contention that the resveratrol present in red wine could be responsible for the "French Paradox" might be a little too simplistic. An optimistic estimate of the amount of resveratrol consumed in one glass (185 ml) of red wine (5 mg/l of resveratrol) is 13.5 μg/kg in a 70 kg person.[6] This is much lower than the low doses used in the cell culture experiments referred to in the review. Thus low and high doses should be better defined, because the low doses used in the cell experiments reported in their review[8] might be high doses if extrapolated to whole organisms. Resveratrol is available in natural foods at a low concentration,[3-5] and increased intake of fruits and vegetables may offer a small but protective effect against certain cancers.11 Its effects on vascular health and thus cardiovascular disease could be mediated at still lower concentrations, such as in red wine,[12] and might support the "French paradox". More evidence is, however, needed before this claim can be accepted.

The fact that low doses can stimulate cancer proliferation, however, should raise concerns. And how low? … especially given the fact that dietary intake is highly unlikely to provide enough to be dangerous – if anything, the reverse. The benefits on different diseases may involve different concentrations. Concentrations tested in cell cultures may not be relevant to whole organisms. And in whole organisms different doses can yield different effects. For example, in mice, low doses of resveratrol increase body weight, intermediate doses have no effect, whereas high doses decrease body weight.[13] Of course, data from animal models may or may not apply to humans. One disease might benefit, but the dose used could fail to affect another condition, or even make it worse. Thus co-morbidities should be considered.

There are considerable potential risks of resveratrol supplements available over the counter in pharmacies or on the internet. Origin, purity, and age of the product are often not known. On the top of this, resveratrol has low water solubility and is sensitive to light and heat, so customers may be purchasing an inactive product or a product that will not be absorbed. In this way, novel formulations of resveratrol, with improved oral bioavailability and pharmacokinetic properties, such as SRT501,[14,15] and new chemicals which also activate, directly or indirectly, sirtuins, such as SRT1720,[15] should be studied, and the risk of cancer should be re-evaluated. The potential of resveratrol, and perhaps the new compounds, to increase the risk of cancer in naïve consumers, however, should be of concern.

Considering the low solubility of resveratrol in water, it would be interesting to know how it was diluted in the experiments cited in the review, and if proper controls containing the same vehicle were used. Our own experience, based on the recommendations of the supplier, is to dilute resveratrol in absolute ethanol or dimethylsulfoxide (DMSO). But these chemicals could have adverse effects on cells during culture, and this would likely include cancer cells. DMSO, for example, increases proliferation of ovarian carcinoma cell lines.[16]

Future research needs to determine the dynamics of the effects of resveratrol in different subcellular compartments and the interactions of these. In addition, the interactions between resveratrol, environmental factors, other compounds and medications, diseases and the genetic background of the individual will need to be appreciated in order to gain a complete understanding of the hormetic response of resveratrol. In a practical sense, it is hoped that gaining such an understanding will assist in improvements in health at the cellular and organismal level, so reducing cancer rates, and preventing or treating metabolic, neurological, cardiovascular and other diseases. It would be wonderful if resveratrol and compounds with similar beneficial effects become novel therapeutic agents and thereby enhance lifespan and/or healthspan. As a general principle, however, the potential adverse consequences of introduction of new treatments based on benefits that any compound may have at

low-doses, but that is noxious at higher doses, means we must end with a note of caution pending the outcome of much more research in this fascinating area.

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