Plant Polyphenols

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Resveratrol Still Has Something To Say about Aging!

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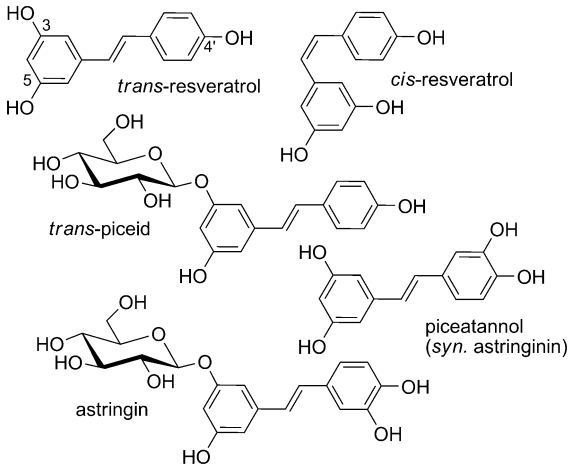
Resveratrol is without a doubt the most famous plant polyphenol, notably since the publication by Frankel et al.[1] in 1993 of its inhibitory effects against the oxidation of human low-density lipoproteins, a chemical event at the onset of the pathogenesis of atherosclerosis. Moreover, related earlier studies[2] had claimed the putative role of this wine ingredient in lowering lipid levels, thus possibly underpinning the so-called "French paradox", the observation of a lower incidence of coronary heart diseases among French people having a diet rich in saturated fats but drinking red wine on a regular basis.[3] Notwithstanding that Frankel et al. clearly warned that resveratrol was a much less potent antioxidant than the flavonoids quercetin and epicatechin, which are found in red wine at much higher concentrations,[1] it is resveratrol that then monopolized the attention of scientists.

Resveratrol (3,5,4′-trihydroxystilbene) belongs to the polyhydroxystilbene subclass of plant polyphenols.[4] It is a natural plant antibiotic (or phytoalexin) that is produced through the phenylpropanoid/polyketide hybrid biosynthetic pathway. Most of its biological activities have been attributed to its *trans* isomer, but the *cis* isomer also occurs naturally, as do its glucoside piceid (both *cis* and *trans* isomers) and their catecholic variants piceatannol (*syn.* astringinin) and astringin (Scheme 1). Resveratrol and its congeners are found in many plant species and plant parts, including nuts and fruits used as food sources, such as peanuts, various berries, and, of course, grapes, hence, its presence in wine. The amount of *trans*-resveratrol can vary between about 0.1 and 14 mg L^{-1} in different varietal red wines, and the concentration of its glucoside *trans*-piceid can reach up to about 30 mg L^{-1}.[5]

Even though *trans*-resveratrol is only a moderate antioxidant compared to many other polyphenols found in grapes and wine,[6] it nevertheless really became a star among polyphenols after Pezzuto and co-workers published in 1997 their results on a series of assays related to its chemopreventive potential against cancer.[7a] Resveratrol was shown to be capable of inhibiting enzyme activities and related cellular events associated with tumor initiation, promotion, and progression.[7a] The extraordinarily high number of publications (nearly 2000 to this day) that have ensued over the last 15 years or so certainly attests to the star status of



Scheme 1. Structures of resveratrol and related polyhydroxystilbenes.

resveratrol.[7b] However, many and often opposing theories have been proposed regarding the mechanisms and target interactions through which resveratrol could express its diverse and pleiotropic biological responses, not only against cancer or cardiovascular diseases, but also against metabolic diseases such as diabetes and age-related neurodegenerations such as Alzheimer's disease.[4,8]

The scientific popularity of resveratrol received another major boost with the 2003 publication by Sinclair and co-workers.[9] This study reported the ability of resveratrol to activate sirtuin 1 (Sirt1) and mimic calorie restriction. Sirt1 is a mammalian NAD^+-dependent protein deacetylase that promotes cell survival, notably by inactivating the proapoptotic tumor suppressor p53 protein. Calorie restriction is known to slow the pace of aging, and was said to be mimicked in *Saccharomyces cerevisiae* in the presence of resveratrol by the activation of Sir2 (the yeast homologue of Sirt1), while extending the average lifespan of the cells by 70%.[9] Resveratrol was later shown to extend the lifespan of the nematode *Caenorhabditis elegans* and the fruitfly *Drosophilia melanogaster*, also in a Sir2-dependent manner.[10] Remarkably, it could also shift the physiology of middle-aged mice on a high-calorie diet towards that of mice on a standard diet, which resulted in a significant increase in their survival.[11] Such results on aging and diet-dependent longevity have of course attracted a great deal of attention from the scientific community, and has come with a fair share of controversy, to say the least.[12] Thus, the link between resveratrol and the sirtuins has been heavily scrutinized and questioned, since

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data have shown that resveratrol would in fact not be a direct activator of these "longevity" proteins.[13] The controversy further increased last year when a detailed study was reported by Gems and co-workers.[14] Their results a) called into question the experimental robustness of some of the original studies on the impact of Sir2 overexpression on the lifespan of *C. elegans* and *D. melanogaster*; b) refuted the role of Sir2 in increasing the lifespan of *D. melanogaster* through calorie restriction; and again c) casted doubt over the role of resveratrol in activating Sir2.[14] The role of Sirt1 in mammals has not escaped the debates, and doubts also arose about whether Sirt1 is a lifespan determinant for mice.[15] It appeared that Sirt1 mediates metabolic adaptations to stress situations, including high-calorie diets that cause obesity, while protecting mice from aging-associated pathologies such as type 2 diabetes, neurodegeneration, and cancer.[15] Sirt1 would, thus, indirectly, but positively, affect the lifespan by ensuring healthy aging. But what about resveratrol? Its administration to mice has also been shown to protect against metabolic diseases by enhancing mitochondrial function in a Sirt1-dependent manner.[16] So how does it do it if not by directly activating Sirt1?[13c]

An answer came from Chung and co-workers, who reported last February that phosphodiesterases (PDEs) that degrade cyclic adenosine monophosphate (cAMP) are the primary targets of resveratrol.[17] A high cellular level of cAMP activates the exchange factor Epac1, one of its receptor proteins. This in turn activates a phospholipase C and results in an increase in the cellular Ca^{2+} level by activation of the ryanodine receptor 2 Ca^{2+}-release channel. This signaling cascade then goes on to activate the Ca^{2+}/calmodulin-dependent kinase kinase β (CamKKβ), which itself phosphorylates another kinase enzyme, the adenosine 5′-monophosphate (AMP) activated protein kinase (AMPK). This phosphorylation and the allosteric activation by AMP fully activate this kinase. This enzyme is known to be a major sensor and regulator of cellular energy by modulating the NAD^+ metabolism, as well as to be a master global regulator of metabolic homeostasis.[18] The activation of AMPK enhances the activity of the NAD^+-dependent sirtuin Sirt1 by increasing the cellular levels of NAD^+. Chung and co-workers showed that resveratrol can start it all by directly competing with cAMP in its PDE binding site. The resulting inhibition of PDEs (types 1, 3, and/or 4) causes an increase in the cellular cAMP levels, which triggers the above signaling cascade and leads to the activation of Sirt1, quod erat demonstrandum! Since an increase in the cAMP levels is also a consequence of calorie restriction, resveratrol would thus indeed mimic this dietary regimen with the same metabolic and health benefits.[17]

The modus operandi by which resveratrol exhibits its (indirect) action on Sirt1 would thus appear to be finally elucidated. Although this is probably not yet the end of the resveratrol/sirtuins affair, this study by Chung and co-workers nevertheless re-emphasizes the value of searching for direct activators of Sirt1. It also identifies inhibitors of PDEs as other possible agents for the prevention of diet-induced obesity, metabolic and other diseases associated with aging, perhaps simply by boosting the energy expenditure, aerobic and reactive oxygen species reduction capacities of mitochondria.[16–19]

To conclude, it remains somewhat intriguing that such a structurally simple molecule as resveratrol is capable of so many health-preserving wonders.[8] While some might be tempted to add it to their antiaging survival kit next to aspirin and vitamin C, others will chose to exercise more, eat less, and drink a glass or two of fine red wine a day … and life goes on!

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