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"Resveratrol improves health and survival of mice on a high-calorie diet"

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Here are the highlights of the original "Resveratrol paper", the one that shook the wine industry last December and got everyone talking about the health benefits of wine. So, judge for yourself! You can also choose to skip this one, as it deals with health -not winemaking or grapegrowing- even if this type of publicized research does impact consumers' attitudes towards wine.

• How to eat more healthily is a "hot topic" for medical science these days. Researchers have discovered a category of proteins, called *sirtuins*, that seem to regulate the physiological adaptations of mammals to a low-calorie diet (*caloric restriction)*. When they screened a large amount of compounds in search for molecules able to enhance sirtuin production, they stumbled upon one particular molecule, produced by a variety of plants in response to stress, which was particularly potent: *resveratrol.* [*Editor's note: In fact, the authors pulled two enhancing molecules out of some 20,000 tested. The fact that, out of such a vast variety of chemical structures, these two molecules happened to be in the same compound category- polyphenols- was what triggered the authors to expand their health research in the direction of phenolic comopunds*].

• Since experiments with simple organisms (yeast, fruit flies and fish) showed that resveratrol was effective in extending their lifespan and health, researchers asked whether it could have similar effects in mice. Could resveratrol shift the physiology of mice on a high-calorie diet to that of a standard diet and provide the associated health benefits without the mice having to reduce calorie intake?

• To find out, 1 year-old mice were provided a **standard diet** (SD), or a **high-calorie diet** of which at least 60% of calories came from fat (HC). To each of the diets, they added resveratrol: standard diet + resveratrol (SDR) and **high-calorie diet + resveratrol** (HCR). The researchers tested two concentrations of resveratrol, but because the effects were more prominent in the higher dose (22 mg/kg/day), the results presented here refer to this high dose.

• 1) **Increased survival.** At 15 months of age, the survival curves of the HC (high-calorie diet) and HCR (high-calorie diet + resveratrol) groups began to diverge. At 2 years of age, resveratrol had reduced death from the HC diet mice by a statistically significant 30%. In addition to lifespan, researchers wondered whether "quality of life" was maintained as well. In mice, you do that by measuring balance and motor coordination. So they tested the ability of mice to perform on a *rotarod* (those rods you see hanging from the cage where mice run endlessly without going anywhere). Surprisingly, resveratrol-fed mice improved their motor skills as they aged, to the point of being undistinguishable from the SD group. Researchers made sure this was not just due to the fact that resveratrol-fed mice weighed less, as they found no correlation between rotarod performance and body weight.

• 2) **Decreased diabetes**. In humans, high-calorie diets cause increased glucose and increased insulin, leading to diabetes. The HC mice had increased plasma levels of both glucose and insulin, as well as other markers that predict the onset of diabetes. In contrast, the HCR group had much lower levels, paralleling the SD group. Also, we know that when mice are fed high doses of glucose, blood glucose levels do not

remain high for more than 60 minutes in young mice, even though a longer persistence is typical in older mice. The persistence of glucose and insulin in blood was significantly decreased in the resveratrol-fed HC mice. The authors go on next about the potential mechanism involved.

• 3) **Decreased organ pathology**. At 18 months of age, the high-calorie diet greatly increased the size and weight of the mice livers, and resveratrol prevented these changes. Histological examination revealed loss of cellular integrity and accumulation of large lipid droplets ("fatty liver") in the HC but not the HCR groups. Pancreas damage was also elevated in the high calorie group but not the resveratrol-fed group. Other organs studied did not show differences.

• 4) **Increased mitochondria number**. Mitochondria are particles within the cells (*organelles*) where food molecules are converted into energy; they are the "cellular power plants". There is evidence that exercise and reduced caloric intake increase hepatic mitochondrial number, so the authors wondered whether resveratrol might produce the same effect. The answer is yes: the livers of resveratrol-fed mice had considerably more mitrochondria than those of HC controls. To their surprise, they also noticed less (not more) mitochondrial genes being activated. So, even though mitochondrial numbers are higher in a resveratrol-rich diet, their turnover is less.

• 5) **Metabolic pathway analysis**. Through RNA hybridization experiments, the researchers looked at what genes had the highest levels of expression in the mice liver cells. They found that resveratrol caused a significant alteration of 127 pathways! These included the well-known TCA (tri-carboxylic acid) cycle, glycolysis and sterol biosynthesis pathways. With the help of databases, the authors went on to compare the pathway changes common to a caloric-reduced diet *and* a resveratrol diet. Could this reveal those pathways common to the enhancement of health and longevity? Based on their results, the authors encourage further studies in this direction.

In conclusion, resveratrol was able to shift the physiology of mice consuming excess calories towards that of mice on a standard diet, improving their health, as indicated by *longer survival, better motor function, reduced diabetes, decreased organ pathology*, and *higher mitochondrial number.* The 27 authors end their article with the following quote: "Resveratrol - and molecules with similar properties- might be valuable tools in the search for key regulators of energy balance, health and longevity […] This study shows that a small molecule that can be administered orally at doses achievable in humans can safely reduce many of the negative consequences of excess caloric intake, with an overall improvement in health and survival". As we know, red wine is a source of resveratrol. In the next summary, we will look at levels of resveratrol in wines.

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