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Resveratrol: Beneficial For Your Patients?

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Currently resveratrol is probably the most actively researched phytochemical worldwide and many favorable properties have been demonstrated in pharmacological models. A PubMed search in June 2011 retrieved more than 4,000 articles on resveratrol. It demonstrates an amazing array of favorable pharmacological activities including antioxidant, cardioprotective, antidiabetic, anticancer, antiviral, neuroprotective, antiplatelet, anti-inflammatory and modulation of fat metabolism. Resveratrol inhibits cancer development at all the three known phases of chemical carcinogenesis, namely initiation, promotion and progression. The development of other chronic diseases might also be reduced by resveratrol, based on the many lab studies. These diseases include cardiovascular disease, dementia, type 2 diabetes and osteoarthritis. In addition to its indirect effects on the aging process via SIRT1, this one simple molecule has the potential to directly prevent most of the chronic diseases associated with aging.

However, the relative lack of clinical research raises questions about the effective and safe human dose, especially for health maintenance. A landmark animal experiment and subsequent discussions over dosage, together with three recent human trials, provide some insights into the appropriate human dosage of resveratrol.

The important pharmacological study was published in the eminent journal Nature in 2006. Rather than giving resveratrol to normal mice to see if it simulated calorie restriction, the effect of resveratrol on a high calorie diet was studied. Middle-aged (one-year-old) male mice on a high calorie diet were given resveratrol and compared to untreated mice on the same diet or a standard diet. The administered doses of resveratrol were either 5.2 or 22.4 mg/kg/day for 6 months, but only results for the higher dose were reported.

The mice receiving the high-calorie diet (HCD) become overweight, whether they were receiving resveratrol or not. However, a clear survival benefit from resveratrol was evident: survival rates for mice on the HCD plus resveratrol were the same as those for the mice on the standard diet (SD). Although resveratrol increased survival, it was also important to understand if quality of life was maintained. This was determined by the rotarod test, which measures balance and coordination. Surprisingly, the resveratrol-fed mice on the HCD steadily improved their motor skills as they aged, to the point where they were indistinguishable from the SD group. Resveratrol also corrected the following parameters in the overfed mice to levels similar to those observed in the SD mice: plasma insulin, fasting glucose, plasma albumin, plasma amylase, liver weight, aortic elastic lamina morphology and mitochondria levels in liver tissue. Furthermore, resveratrol opposed the effects of the HCD on 144 out of 153 significantly altered metabolic pathways.

These dramatic results provoked worldwide attention and the observation that with resveratrol "you can eat your cake and not have it". However, they also led to considerable discussion as to whether the amount of resveratrol given to the mice was realistically achievable in humans. Many media sources at the time stressed that the doses used could be interpreted to mean several hundred or even thousands of litres of wine per day in human equivalent doses (HEDs). A 2007 paper pointed out that this was a serious misinterpretation of the results, leading to unnecessary

scepticism of this important research.4 It reflected a general ignorance of the scientific community and public regarding appropriate methods of dosage extrapolation between animal species, which should be based on surface area rather than body weight.4 In other words, the HED for a 130 lb (60 kg) human adult from a mouse dose of 22.4 mg/kg is not 60 times 22.4 mg (1344 mg), but instead works out at just 109 mg. While not reasonably achievable through the consumption of wine (which typically contains 2 to 3 mg resveratrol per litre), this dose of resveratrol is readily reached by the use of an extract of the herb Polygonum cuspidatum (giant knotweed).

Information about the appropriate human dose of resveratrol comes also from recent clinical trials. Nineteen overweight/obese men or post-menopausal women (BMI 25-35 kg/m2) with untreated borderline hypertension consumed three different single doses of resveratrol (30, 90 or 270 mg) or a placebo at weekly intervals in a double blind, randomized, crossover comparison. One hour after the resveratrol consumption, its level in plasma and its impact on flow-mediated dilatation (FMD) of the brachial artery were assessed. Impaired FMD is associated with several cardiovascular risk factors, including hypertension and obesity. With increasing doses of resveratrol, there were proportional increases in plasma resveratrol concentrations. FMD was significantly increased by all doses of resveratrol compared to placebo ($p < 0.05$), but the higher doses had only a marginally greater impact than the 30 mg dose.

Two groups (10 in each) of normal-weight healthy participants were randomized to placebo or a Polygonum cuspidatum extract containing 40 mg/day resveratrol for 6 weeks. In mononuclear cells taken from participants after 6 weeks, the extract had induced significant antioxidant and anti-inflammatory effects ($p < 0.05$). Also, it significantly reduced plasma concentrations of TNF-alpha (tumor necrosis factor-alpha), IL-6 (interleukin-6) and C-reactive protein ($p < 0.05$).

In a third study, 19 patients with type 2 diabetes received just 10 mg/day of resveratrol for 4 weeks in a double blind, placebo-controlled, randomized clinical trial. By the end of the trial, resveratrol had significantly decreased insulin resistance (homeostasis model of assessment for insulin resistance, HOMA-IR) compared with placebo ($p = 0.044$). The time to maximum plasma glucose after a test meal was also significantly delayed by resveratrol ($p = 0.03$ versus placebo). Mechanistic investigations suggested the improvement in HOMA-IR might be due to a resveratrol-induced decrease in oxidative stress leading to more efficient insulin signalling, rather than enhanced pancreatic beta-cell function.

Based on these studies, an effective long-term human dose for resveratrol probably ranges from 10 to 120 mg/day. While higher doses up to 200 mg/day could be considered where the need exists, doses beyond this limit might not only be unnecessary, they could also prove to be unsafe with prolonged usage. There are still many uncertainties in the resveratrol research and it would be wise to exercise caution at this stage. A daily dose of resveratrol of 100 mg from Polygonum cuspidatum is certainly within the realms of the traditional doses used for Chinese herbs.

One of the issues with resveratrol is that it is rapidly metabolized and has limited bioavailability as such. However, resveratrol metabolites (mainly phase II conjugates) might also be bioactive, or act as a reservoir of resveratrol at target tissues. One study found that to maximize plasma resveratrol levels it should be taken with a standard breakfast and not with a high fat meal.

Make sure to talk to your patients about what dosage of resveratrol is right for them.

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