Can resveratrol fight obesity?

Resveratrol induces brown-like adipocyte formation in white fat through activation of AMP-activated protein kinase (AMPK) α1

Introduction

Resveratrol, an antioxidant commonly found in red wine, was supposed to be the breakout supplement of our time. Many media outlets have praised its anti-cancer, anti-aging, and anti-heart disease properties. The anti-aging claims drew the most attention, as resveratrol seemed to act as a "calorie restriction mimetic" and was theorized to slow aging and reduce the risk of age-related diseases. While there have been many promising animal studies, these miraculous benefits have not panned out in human trials.

In ERD #2, we reviewed the ergogenic effects of resveratrol in the context of high-intensity interval training and found that it was unlikely to increase performance and may even impair training adaptations. Even though most positive health outcomes seen in the animal models don't usually manifest in humans, there remains a chance that resveratrol supplementation could moderately improve metabolic markers for insulin sensitivity and cardiovascular health.

The article reviewed here continues to expand our knowledge of how resveratrol operates, inching us closer toward a potentially practical use for the supplement. The study under review examined the effect of resveratrol supplementation on what is known as beige or 'brown-like' adipose tissue. The human body contains three distinct types of adipose tissue: white, brown, and beige fat. The basic characteristics of these are described in the sidebar.

Brown adipose tissue (BAT) is a relative newcomer to the obesity management scene, with seminal papers only coming out in the late 2000s. BAT has the ability to increase thermogenesis (body heat production) via its high concentration of mitochondria. These mitochondria have the unique ability to oxidize substrates like fat at a high rate all while producing low amounts of ATP by interacting with a protein called UCP1. Because BAT is so metabolically active, it can possibly help to

Know your fat

There are three predominant types of fat in your body.

White Adipose Tissue (WAT) - This is the kind of fat your doctor warns you about. It can be damaging to both health and self-image once it accumulates around your midsection. White fat's role as an endocrine organ is increasingly being researched, as hormones like leptin and adiponectin play critical roles in metabolic health.

Brown Adipose Tissue (BAT) - Considered a 'healthy' fat in the body, it is a very metabolically active and highly thermogenic tissue. Though it is found in significant quantities in infants, adults tend to have very small deposits. It is thought that stimulating brown fat growth in adults could help fight weight gain. The more brown fat you have, the less likely you are to develop metabolic dysfunction.

Beige Adipose Tissue - This kind of fat can be described as the child of white and brown fat. It is found within white fat but displays many of the beneficial qualities of brown fat. White fat contains stromal vascular cells that help to shift the structure and function of the white fat cell to that of a brown fat cell. The amount of brown and beige fat tissue one has inversely correlates with body-mass index.

fight weight gain and aid in weight loss. Beige fat is very similar to BAT but is located within the subcutaneous white fat tissue, whereas BAT resides in specific deposits around the scapula and along the spine. Theoretically, if we are able to stimulate the growth of beige fat in white fat, it could be an important factor in reducing the harmful effects of adiposity and improve metabolic markers. The researchers conducting this study sought to find out how well resveratrol stimulates the growth of beige adipose tissue in mice.

The many promised health benefits of resveratrol have not amounted to much when tested in humans. However, the study under review extends the line of research looking at the weight management properties of resveratrol in mice. This supplement may increase the amount of 'healthy' beige adipose tissue, which is very metabolically active.

Who and what was studied?

This study was a randomized controlled trial assessing the role of resveratrol in the formation of beige adipose tissue within WAT and the underlying mechanisms of this process. Specifically, researchers looked into the role of the enzyme AMP-activated protein kinase (AMPK) and its ability to interact with resveratrol to bring about body weight changes.

The experiment was done on 12 adult female mice, who were randomized into two groups: a control group fed a high-fat diet (45% of total calories) and an intervention group fed the same high-fat diet where all food contained 0.1% resveratrol. Basal metabolic rate (BMR) and respiratory exchange ratio (RER) were evaluated at baseline and after the trial's completion. RER is a measure that allows us to determine if the body is predominantly burning fat, carbohydrates, or a mix of both for energy. Tissue samples were taken at the end of the experiment to measure activity levels of genes related to the formation of brown adipose tissue.

To determine the role of resveratrol on AMPK in terms of inducing the browning of white fat, a separate experiment was conducted using WAT samples from two mice strains (wild-type and AMPK knockout). Many of the promising health advantages seen in previous resveratrol studies have been partially attributed to its interactions with AMPK, as this enzyme plays a large role in energy metabolism and homeostasis (some functions of AMPK are shown in Figure 1).

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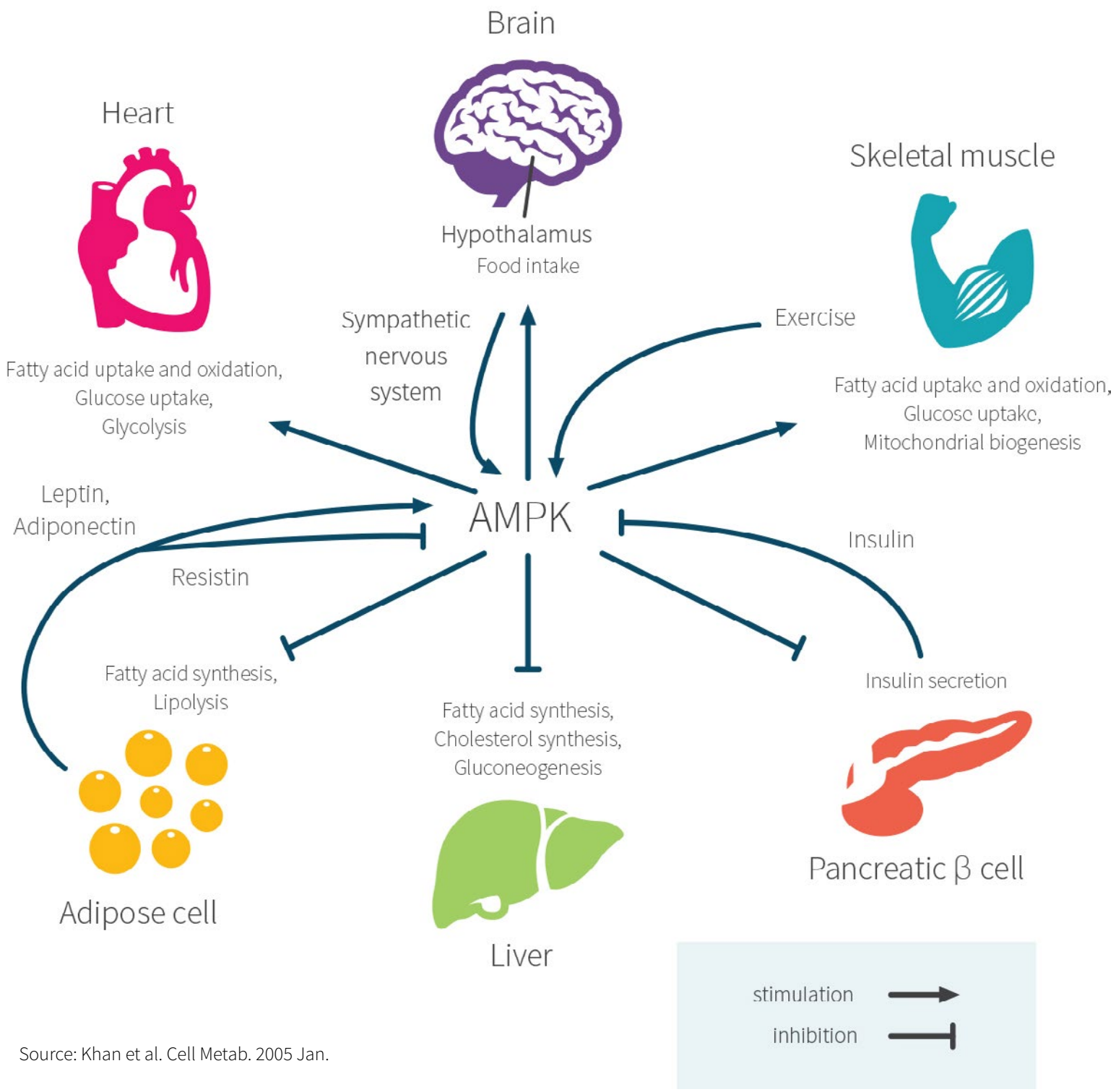
Figure 1: AMPK's role in energy metabolism



Source: Khan et al. Cell Metab. 2005 Jan.

This RCT was conducted on mice. One group was fed resveratrol along with their high-fat diet. BMR and RER were measured. Fat samples were analyzed to determine the mechanism through which resveratrol could promote brown fat growth.

What were the findings?

When tested in vitro (in a petri dish), resveratrol exerted a dose-dependent effect on forming beige fat cells from stromal vascular cells (SVC) found in WAT. SVCs are the stem cells of white adipose tissue that allow them to shift the structure of WAT into beige fat. The authors' measurements from the in vivo samples showed that, within the resveratrol group, activity of two genetic markers associated with adiposity were suppressed while the expression of genes specific to brown adipocytes, such as uncoupling protein 1 (UCP1), were elevated. Resveratrol also increased the mRNA expression of PGC-1α, a primary player in mitochondrial formation, 3.3-fold over the control group.

It appears that AMPK does play a critical role in the resveratrol-mediated browning of WAT, specifically AMPKα1, which is a subunit of AMPK that's likely to

play an important role in metabolic health and obesity. In the samples from mice lacking AMPK, no effect was observed when WAT SVC's were exposed to the supplement. On the other hand, the wild-type mice where AMPK was left intact experienced a higher rate of AMPKα phosphorylation (1.3-fold). Protein levels of SIRT1, another regulator of mitochondrial creation, were 1.5-fold higher within the wild-type mouse samples as well.

The most intriguing results of the study were the body weight reductions and increased lipid oxidation seen in the resveratrol group. The average weight gain in the intervention group was 2.99 grams, while the control group gained 5.91 grams. Other improvements seen in the resveratrol group were smaller individual adipocytes, decreased insulin levels, and lower triglyceride concentrations. The data indicated that the reduction in body weight and triglyceride levels was due to the increased lipid oxidation brought about by the new beige fat tissue. These finding were further supported by the corresponding decreases seen in RER and increased BMR. While all mice in the study were allowed to eat freely, the authors noted no apparent differences in average weekly food intake between the two groups.

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Resveratrol promotes the growth of beige adipocytes in WAT in a dose-dependent manner through AMPKα1. The increased beige fat tissue allowed the resveratrol-fed mice to increase BMR and lower RER, preventing weight gain and improving metabolic markers.

What does the study really tell us?

Previous research has shown AMPK is a main player in bringing about the positive effects of resveratrol. The current study has echoed these findings by showing AMPK to be central in the resveratrol-induced browning of WAT. The test results revealed that the activation of AMPKα1 promoted the upregulation of genes tied to brown adipocyte tissue formation. These genes act to promote the growth of beige fat tissue within the white adipose tissue itself, a finding that had not been observed in previous research.

It is likely that resveratrol can act to shrink adipocyte size in WAT, as this effect has now been demonstrated in both animal and preliminary human trials. This is a very interesting outcome as it is one of the few effects from animal trials that have translated into statistically significant effects in humans. More research will need

to be conducted to see if the fat cell shrinking abilities of resveratrol are relevant in clinical settings.

Based on the established mechanisms of action, there does remain a chance that resveratrol could be used as a long-term therapy in weight management or for attenuating symptoms of metabolic syndrome. Further long-term trials in humans using varying doses with larger sample sizes would be needed to answer these questions.

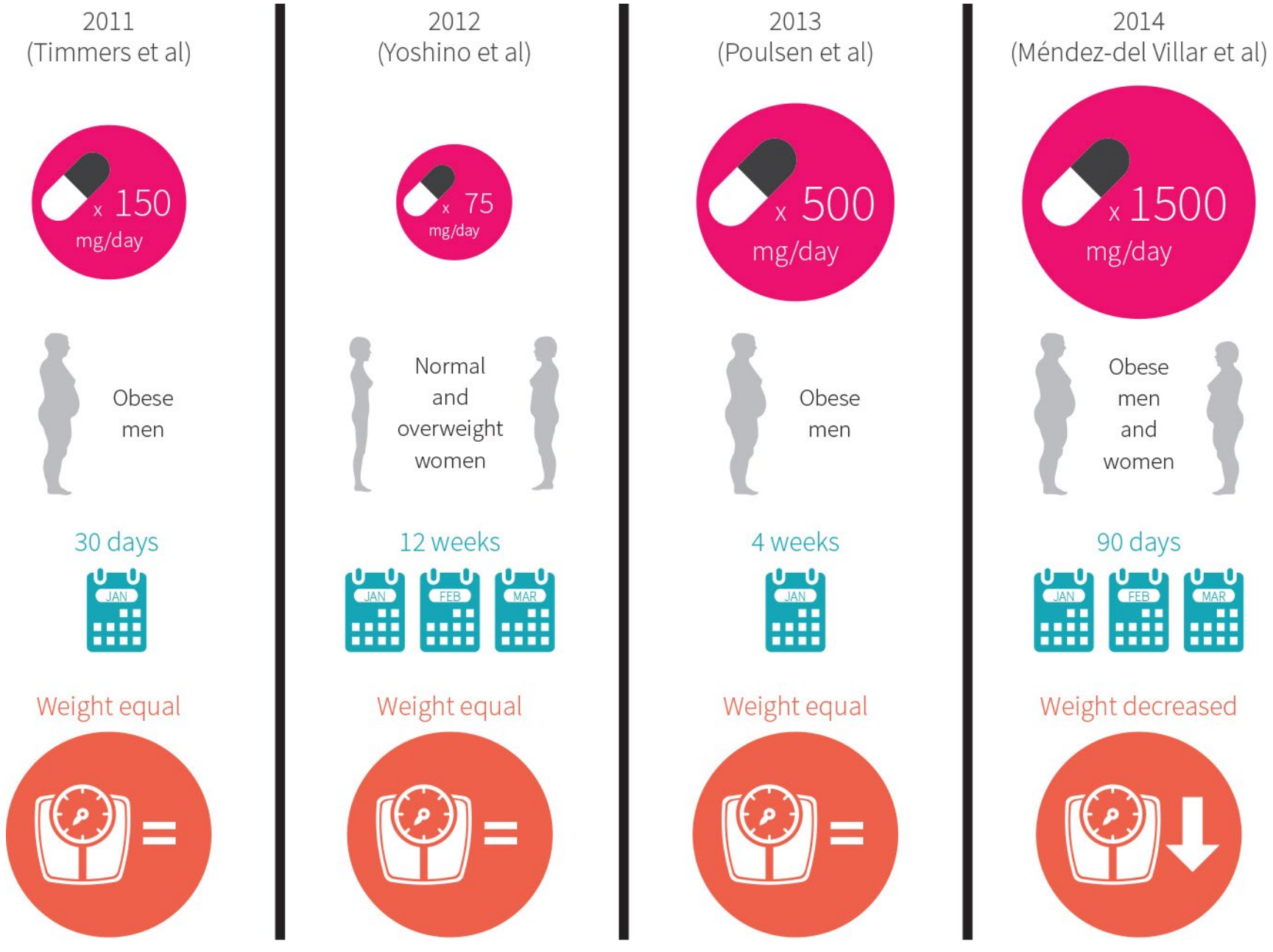
There is a possibility that low doses of resveratrol could improve some metabolic markers if taken in the long-term. Lengthier RCTs are needed to confirm this hypothesis.

The big picture

The numerous health-promoting claims of resveratrol have, to date, not been substantiated by human trials. Weight loss trials using resveratrol are summarized in Figure 2. It is easy to latch onto and promote a supplement as a 'cure-all' for many of the complex chronic illnesses that ail the general public. As humans, we have a tendency to gravitate towards simple solutions for health problems we face, which may be one reason resveratrol has received so much attention. In fact, resveratrol may be one of the most heavily studied polyphenols, as a search for journal articles containing 'resveratrol' in the title yields over 4,500 academic papers on the subject.

Animal studies, like the one examined in this article, are

Figure 2: Human trials of resveratrol's effect on weight loss



often used as a 'proof of concept' to determine potential mechanisms of action before beginning human testing. As with previous animal research, the present trial elucidates promising mechanisms that may or may not translate into significant health benefits for humans. To date, only two studies in humans have looked at the effects of resveratrol on adipose tissue morphology and energy metabolism. Both lasted just 30 days and were conducted on 11 obese participants. These trials had participants taking resveratrol at a dose of 150 mg per day. While improvements were seen in insulin sensitivity, blood pressure, and adipose cell diameters, the overall effect on metabolic rate and weight loss was insignificant.

At the moment it would be prudent to ingest resveratrol from sources that contain high amounts of phenolic compounds, like grapes, berries, and peanuts. While red wine does contain small amounts of resveratrol (with levels ranging widely between wine types, as seen in Figure 3), it appears that the total sum of all the compounds found in red wine play a synergistic role in imparting health benefits to people who drink it in moderation (one to two drinks a day). Megadosing red wine to attain high resveratrol levels is obviously not a great idea, and supplementing with isolated resveratrol may not as beneficial for overall health as eating resveratrol-containing foods.

Resveratrol is a contender for the Most Studied Supplement title. For now, get your daily dose of polyphenols from food and the occasional glass of red wine.

Frequently asked questions

Is there any other reason to take a resveratrol supplement?

Some evidence suggests a low dose supplement of resveratrol at five to 10 mg a day could improve insulin sensitivity and heart health. However, these improvements have only been demonstrated in short-term studies. As with most areas of resveratrol research, long-term human data is not yet available. There do not appear to be any substantial health gains to resveratrol supplementation for healthy people, aside from the antioxidant properties this polyphenol provides.

What about red wine?

It is true that red wines contain a small amount of resveratrol in addition to other polyphenols. Moderate consumption of red wine has been linked with metabolic improvements such as decreased risk for cardiovascular disease. In all likelihood, it is probably the combination of compounds in red wine that work together to promote

Figure 3: Average trans-resveratrol content of various red wines per 5-ounce glass

Source: Stervbo et al. Food Chem. 2007.

these changes rather than resveratrol alone. In fact, many cohort studies have associated low doses of any type of alcohol with moderate health benefits.

In ERD issue #3, we covered research showing that alcohol benefits for heart health may have a major genetic component. In other words, not everyone may be able to benefit equally from alcohol consumption, which further emphasizes that alcohol (and red wine) shouldn't necessarily be a go-to strategy for health improvement.

Was the dose of resveratrol the mice received relevant to humans?

Animal studies can sometimes produce positive results with a supplement when the animals have been administered a large dose that would be impractical or infeasible in humans. In this trial, the mice received a dose that would be equivalent to about one gram per day for humans. That is roughly double what the average healthy person would typically supplement with. The recommended range for otherwise healthy people is between 150-500 milligrams per day. While taking one gram of resveratrol a day is unlikely to produce any negative side effects, it is unlikely that any added benefits will be observed above a 500 milligram per day dose.

What should I know?

Based on the available evidence, significant weight management benefits of resveratrol supplementation are unlikely. However, there remains a possibility that long-term supplementation may yield improvements in markers of metabolic syndrome. The study under review provides us with a potential mechanism through which these effects could be seen. Namely, resveratrol can interact with AMPK, inducing beige adipose tissue formation. The evidence for this effect is still in the preliminary stages of research. ◆

The up-and-down rollercoaster of a given supplement's popularity is partially due to evolving research. Where will the resveratrol ride end up? Talk it over at the ERD Facebook forum.

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