

# Overview Of Antioxidants: Emphasis On Raisins

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## Abstract

Antioxidants are components of foods and found in some supplements. They function to detoxify excessive free radical build-up, which results from normal metabolism and environmental stresses like air pollution. Most studies of dietary antioxidants showed beneficial effects in reducing the risk of chronic diseases like cardiovascular disease. In contrast, intervention studies using antioxidants from dietary supplements did not typically show these positive results; sometimes dietary supplement use increased disease risk. Herein is reviewed the definition of antioxidants, physiological actions, and selected studies of foods and supplements containing them. In addition, summarized are new studies on the antioxidative effects of raisins and cardiovascular disease risk reduction.

## INTRODUCTION

It seems ironic that after 60,000 years of evolution that in order to derive nutrient benefit from food and oxygenate the blood, the body must produce highly reactive, oxygen-based substances, which cause damage to every tissue in the body. Too many reactive oxygen species (ROS) puts the body under oxidative stress, which leads to premature death usually from an increased risk of chronic disease.<sup>1,2</sup> Environmental stresses (UV light radiation, cigarette smoke) also generate ROS, which, unlike those made by the body, can be avoided.

To avoid over-production of ROS, it is important to focus on strategies to reduce the harmful side effects caused by them. In extreme cases, some have resorted to caloric restriction, which results in less oxidative cell damage thereby delaying the age-dependent decline of some antioxidant defenses. Animal studies have shown that life span is extended with caloric restriction, but human data are lacking. Instead, most of the human nutritional literature on this topic relates to how dietary antioxidants from foods and supplements reduce oxidative stress and therefore reduce disease risk. The purpose of this review is to define ROS and antioxidants, and present selected antioxidant interventional studies showing their effects on health risks. Next, new information on raisins is presented. Raisins are rich sources of antioxidants, and new studies show how ingestion of small quantities each day may reduce cardiovascular disease (CVD) risk.

## DEFINITION OF TERMS

### OXIDANTS (REACTIVE OXYGEN SPECIES [ROS])

Compounds which cause oxidative damage are made endogenously, but also occur in the environment.<sup>2</sup> Endogenous oxidative compounds, formed from the by-product of metabolism include superoxide ( $O_2^-$ ), hydrogen peroxide ( $H_2O_2$ ), and hydroxyl radical ( $-OH$ ). A single oxygen is also reactive, and is produced as a result of respiratory bursts by neutrophils or lipid peroxidation.<sup>2</sup> Some common exogenous ROS include cigarette smoke, which contains oxides of nitrogen and iron generating ROS from peroxides. This is especially problematic for males with hemochromatosis disease.

All attempts should be made to avoid known sources of ROS. Obviously, giving up breathing or eating are not options, but avoiding unnecessary radiation, smoking, and possibly over-eating may reduce non-obligatory ROS production.

### ANTIOXIDANTS

An antioxidant is any substance that, when presented at low concentrations compared with that of an oxidizable substrate, significantly delays or inhibits oxidation of that substrate.<sup>1</sup> Antioxidant defenses can be made endogenously (enzymatic), or obtained from foods or dietary supplements (non-enzymatic). The diversity of the antioxidants matches that of ROS (pro-oxidants).

**Enzymes.** The body has several natural enzyme defense systems (e.g., superoxide dismutase catalase and glutathione peroxidase), which counteract the deleterious effect of ROS. Some enzyme systems operate throughout the body and some are tissue specific. For example, protein is protected by proteases; lipids by glutathione peroxidase, and DNA by a series of glycosylases.<sup>2</sup>

The half-life of major ROS varies greatly, underscoring the need for different types of defenses.<sup>1</sup> The hydroxyl radical does its oxidative damage at the site where it is produced. In contrast, some peroxy radicals are relatively stable; their half-lives are a few seconds. This gives them time to migrate from the site that they were first generated to transport an oxidative function to other parts of the body.

**Non-enzymes.** Dietary antioxidants mainly come from fruits and vegetables, but many are found in supplements.<sup>2</sup> The most commonly studied antioxidants are vitamins A, beta-carotene, C, and E. These are deemed essential for life and have government recommendations for daily intake. However, fruits and vegetables have other components, which also have antioxidant activity, but these are not considered essential and do not have known requirements. These include compounds such as phenolic acids, and its subgroup, flavonoids (including flavones, isoflavones, flavonones, anthocyanins, catechins, and isocatechins).<sup>3</sup> Other components include carotenoids, other than beta-carotene, and sulfur-containing compounds.<sup>4</sup>

Individuals who consume higher intakes of fruits and vegetables (i.e., five or more servings per day) consistently have reduced risk of cancer and other chronic diseases.<sup>2,3</sup> The following is a summary of the conditions favorably affected by high antioxidant intake from foods:

**Cancer:** Those with the lowest 25 percentile for intake of antioxidants have double the risk of cancer in the lungs, head and neck, stomach, pancreas, bladder, and cervix. Lesser affected areas are breast (30% risk reduction), ovary/endometrium, and prostate.<sup>2</sup>

**Heart-related diseases including stroke, ischemic heart disease, and metabolic syndrome:** High fruit and vegetable intake was related to 30% lower risk.<sup>5</sup> Risk of elevated blood pressure was reduced by 40% with high intakes of plant-based foods (grains, fruits, vegetables) coupled with a low-meat intake.<sup>6</sup>

**Diabetes:** Higher levels in the blood of beta-carotene were

associated with less insulin resistance, and a lower risk of type 2 diabetes and cardiovascular disease (CVD).<sup>7</sup>

**Cataracts:** Eating fewer than 3.5 servings of fruits and vegetables increased the risk of cortical cataracts five times, and posterior subcapsular cataracts 13 times.<sup>8</sup>

**Age-related macular degeneration:** High intakes of lutein and zeaxanthin reduced risk.<sup>9</sup>

**Obesity.** Increasing intake of foods with low-energy densities (mainly fruits and vegetables) resulted in weight loss and controlled hunger.<sup>10,11</sup>

Depending upon age and caloric requirements, government recommendations for fruit and vegetable intake (at least five per day) are met by only 10% of the population.<sup>12</sup> Even more troubling is that there is some evidence that even eating the recommended amount may not be enough to offer full antioxidant protection.<sup>4</sup> Significant DNA oxidation occurred when eight to ten servings a day of fruits and vegetable were consumed from nine different plant families. In contrast, when the same number of fruit and vegetable servings were consumed, but selected from a greater biological diversity (18 different plant families), DNA oxidation was reduced. Both diets (9 and 18 different plant families) offered protection against lipid peroxidation, suggesting that eight to ten servings of fruits and vegetables may be adequate for that function. This study demonstrated the need to consume more than five servings a day of fruits and vegetables, and that eating many different types was advantageous.

In contrast to antioxidant studies using foods, antioxidant from dietary supplements produced mixed results (Table 1). Supplemental vitamin D had the most promising results in reducing cancer risk, and for other nutrients (e.g., vitamin C), cataract risk reduction was demonstrated.<sup>8,21</sup> Supplemental antioxidants for the most part had no effect on some forms of cancer (prostate and oral lesions) and cardiovascular disease.<sup>13-18</sup> In addition, no benefit was seen for improving cognitive function with vitamin E, or for reducing the incidence of the common cold with vitamin C.<sup>19,20</sup>

Some intervention studies using antioxidant dietary supplements showed adverse side effects.<sup>16,22,23</sup> Smokers seemed particularly susceptible to increased risk of cancer from beta-carotene from supplements.<sup>16</sup> Trace elements like selenium are prone to problems, because it is easy to overdose on them.<sup>22</sup> One company inadvertently added 200

times the labeled concentration of selenium to its tablets, which resulted in 201 reported adverse events. Moreover, supplemental antioxidants (vitamin C and E) taken during physical activity were shown to interfere with normal physiological responses.<sup>23</sup> Exercise creates ROS, which leads to favorable changes in gene responses that improve insulin sensitivity. Use of exogenous antioxidants blocks the naturally occurring beneficial effects of exercise-induced ROS.

Thus it seems prudent to eat a diet which is rich in fruits and vegetables, and to include a great variety. Use of multivitamins is still condoned by some, but use of single, or groups of antioxidants, may not be beneficial, and in some cases, harmful.

### RAISINS

#### ANTIOXIDANT COMPOSITION

Several laboratories have evaluated the antioxidant compounds in raisins (Hall C. Multi-functional food additive from raisins. Personal communication, 2006; Cisneros-Zellallos L. Phenolic content, antioxidant activity, and antimicrobial properties of raisins in food systems. Personal communication, 2001; Miller DD. Iron bioavailability and antioxidant activity of raisins and raisin products. Personal communication, 2003).<sup>24,25</sup> Their major group of antioxidants is polyphenols (Hall C, personal communication, 2006) (Table 2). In addition to the ability to scavenge active ROS, polyphenols can inhibit nitrosation and chelate metals (Hall C, personal communication, 2006).

Blueberries, which are rich in antioxidants, have similar amounts of polyphenols to raisins (Hall C, personal communication, 2006). The average phenolic content of blueberries was  $548.55 \pm 89.317$  mg/100 g compared to  $514.39 \pm 32.921$  mg/100 g for raisins. The range for phenols in raisins was between  $477.3 \pm 103.2$  mg/100g for Thompson, up to  $799.4 \pm 44.1$  mg/100g for golden raisins. Sub-groups of these phenols differed between blueberries and raisins. Anthocyanins are almost none existent in raisins (< 2 mg/100g), whereas they are high in blueberries  $89.22 \pm$  mg/100g.

Another laboratory analyzed the polyphenolic composition of raisins, looking at the different compositions among types of raisins and frozen grapes.<sup>24</sup> Golden raisins contained the highest concentration of trans-caftaric and trans-coutaric acids, compared to sun-dried raisins, dipped raisins, and frozen grapes. The quercetin glycosides A and B

concentrations did not differ significantly for the three types of raisins (ranging from 42 mg/kg to 78 mg/kg). In contrast to sun-dried and dipped raisins, Golden raisins had significantly less kaempferol B (7.6 mg/kg vs. 23.7 mg/kg for sun-dried and 29.5 mg/kg for dipped raisins). Resveratrol was not detected in any sample of raisins, suggesting that during ripening it is lost.

Vitamin C, a potent antioxidant, content is not the same as blueberries or within different types of raisins (Hall C, personal communication, 2006). On average, blueberries have 1,323 µg/g of vitamin C compared to 446 µg/g for raisins. Golden raisins have the highest concentration (1,509 µg/g) of vitamin C among commonly consumed raisins – Thompson, Zante, and Dipped – each of which have about 460 µg/g.

The oxygen radical absorbance capacity (ORAC) is often used as an indication of anti-oxidative capacity. Compared to fresh grapes, sun-dried and golden raisins have higher ORAC values.<sup>25</sup> Green grapes had an average ORAC value of  $10.8 \pm 0.49$  µmole TE/g, while the value for sun-dried raisin was  $37.4 \pm 3.7$  µmole TE/g and for golden raisin is  $104.5 \pm 8.7$  µmole TE/g). Thus, the drying process for making raisins seems to preserve and concentrate the anti-oxidant capacity over fresh grapes.

#### CLINICAL STUDIES

It is well known that consuming a high intake of polyphenols, like those found in tea, onions, apples, and raisins, reduces the risk of CVD.<sup>26</sup> One specific group of polyphenols, flavonoids, was shown to reduce the risk of stroke by 20% when consumed in high amounts from the diet. Most of the work specific to raisins has focused on CVD. Increasing fruit intake by just one serving a day may reduce this risk of CVD by 7%.<sup>27</sup> Raisins, like other fruits and vegetables, are beneficial because:

The dietary fiber content leads to lowering plasma LDL-cholesterol and improvements in insulin sensitivity

The antioxidant composition reduces inflammation

Specifically, raisins contain fiber and a significant amount of polyphenols. Fiber this thought to interfere with enterohepatic circulation of bile, increasing bile acid excretion. The depletion of hepatic cholesterol then results from an increase in bile acid synthesis to replace losses. This triggers a subsequent increase in expression of hepatic LDL receptor, thereby reducing LDL-cholesterol in the plasma.<sup>28</sup>

The polyphenols in raisins not only act as antioxidants, but also interfere with cholesterol absorption by decreasing hepatic cholesterol concentrations. The polyphenols from raisins can also decrease serum triglyceride concentrations (a marker of CVD risk) by reducing apo E. These substances reduced superoxide, thereby decreasing its interaction with nitric oxide to improve vaso-relaxation and blood pressure.

Healthy males (n=15) consumed 42-grams of raisins per day (129 kcal; one commercial snack size of golden, and on a separate occasion, sun-dried), or the same amount of fresh grapes.<sup>25</sup> Subjects did not experience a change in LDL-oxidation over four weeks. However, the serum ORAC value while consuming raisins and grapes tended to increase. The study was not likely adequately powered to capture the full benefit on CVD risk for consuming raisins long-term. However, short-term serum ORAC analysis (2 hours) was made after grape and raisin consumption, eaten along with a high-glycemic index (GI) food (bagels).<sup>25</sup> Although ORAC values decreased after ingestion of the high-GI food, the decline was smaller when combined with grapes or raisins. This may provide support for fruit consumption like raisins to blunt pro-oxidant side effects of a high-GI diet.

In a subsequent study, others<sup>28</sup> showed a CVD risk reduction for raisins alone, or when combined with walking. Healthy subjects (n=34) were randomized to raisins (one cup per day; about 690 kcal), walking (increasing over normal exercise pattern by 10, 20, and 30 minutes every other week over the six-week study), or both. All three interventions significantly decreased total- and LDL-cholesterol concentrations (9.4% and 13.7%, respectively) and systolic blood pressure, thereby reducing CVD risk. Blood pressure changes could have been a result of the polyphenols in raisins. The scavenging of ROS by these compounds results in inhibition of NAD(P)H oxidase, and subsequent decreases in superoxide production. This leads to a lowering of nitric oxide (NO) degradation by preventing interaction of superoxide with NO. The polyphenol effect on lowering superoxide may also induce vaso-relaxation and reduce blood pressure. These changes lead to improved endothelial function, which is important to promote vasodilation, and decrease platelet aggregation and adhesion of monocytes to endothelium. The inflammatory marker, tumor necrosis factor (TNF)-alpha was reduced with the raisins-only group, and sICAM-1 was significantly lower in all groups. The reduction in ICAM-1 was likely a result of reduced NF- $\kappa$ B activation, which would likely decrease other inflammatory markers and adhesion molecules. A decrease in TNF-alpha

could have contributed to the decrease in sICAM-1 as well. These changes potentially prevented progression of CVD disease. Thus, simple dietary modifications (eating raisins) and walking a little longer each day had beneficial effects on reducing CVD risk.

Subjects ingesting raisins (90 g/day [270 kcal] for 14 days) had a significant reduced IL-6 response to a high-fat, 900-kcal meal challenge of a low-flavonoid-controlled diet.<sup>29</sup> However, other inflammatory markers (e.g., ICAM, C-reactive protein) did not change during this study. These subjects were overweight and obese, which may have influenced the results. More work is needed to determine the exact amount of raisins necessary to reduce inflammation. It is possible that those who are overweight or obese may require more raisins than those who are not.

Polyphenols from raisins were shown to affect CVD risk according to an antioxidant capacity measurement. Keen et al. (Keen CL. The effect of raisins on antioxidant capacity and cholesterol concentrations in human subjects. Personal Communication) measured changes in the antioxidant capacity of the blood and CVD risk factors in response to consuming 2, 3.5, and 5.5 ounces a day of raisins (172, 301, and 473 kcal, respectively) by healthy subjects (n=28). Although the fasting phenolic blood content did not change in any group, one of the antioxidant capacity tests (FRAP) increased with 5.5-ounce serving of raisins. Most important was that all three amounts of raisins significantly reduced the plasma oxidized LDL-cholesterol content. This a strong marker of CVD risk, because 94% of subjects with high circulating oxidized LDL-cholesterol have CVD. On the other hand, raisin consumption appeared to have no effect on platelet aggregation, another risk factor of CVD. Thus, raisins seem to exert their cardio-protective effect from antioxidants by protecting LDL-cholesterol from oxidation.

Spanish red grape juice is also rich in polyphenols; it has 640 mg/100 g, which is slightly higher than raisins.<sup>30</sup> Patients receiving hemodialysis, and normal volunteers, both experienced reduced concentration of oxidized LDL-cholesterol in response to drinking 100 mL of grape juice a day for two weeks. This strengthens the argument that phenols like those in raisins and grapes have an antioxidant capacity that significantly reduces CVD risk.

**Figure 1**

Table 1. Dietary supplementation and disease risk reduction

STUDY DESIGN	NUTRIENTS	OUTCOME
Cataract development (Jacques PF, 1991)	Vitamin C, E, and carotenoids	Reduced risk
Prostate cancer (Gaziano JM, 2009)	Vitamin E and C	No effect
Prostate cancer (Wright, 2007)	Vitamin E from supplements and foods	-No effect on risk from supplements  -Reduced risk (32%) of gamma-tocopherol from foods
Prostate cancer (Lippman, 2009)	Vitamin E and selenium, alone or combined	No effect on risk
Oral premalignant lesions (men) (Maserejian, 2006)	Vitamin C, A, E, and carotenoids	-No effect of vitamin A and C, or carotenoids  -Dietary vitamin C, but not from supplements, reduced risk  -Beta-carotene in current smokers increased risk
Cardiovascular disease (men) (Sesso, 2008)	Vitamin C and E	No effect on risk
Cardiovascular disease (women) (Cook, 2007)	Vitamin C and E, and beta-carotene	No effect
Cognitive function (women) (Kang, 2006)	Vitamin E	No effect
Common cold (Douglas, 2007)	Vitamin C	No effect
Cancer (Garland, 2006)	Vitamin D	Reduced risk of incidence and death for colon, breast, prostate, and ovarian cancers

**Figure 2**

Table 2. Polyphenol profile of freeze-dried raisin extract†

POLYPHENOLIC COMPOUNDS	CONCENTRATION IN ETHANOL EXTRACT (mg/kg)
Rutin	7.47 ± 0.36
Quinic acid	0.124
Quercetin-3-β-D-glucoside	32.7 ± 1.69
Kaempferol	290.04 ± 9.69
(+)-Catechin	47.10 ± 0.70
(-)-Epicatechin	7.61 ± 0.39
(-)-Epigallocatechin gallate	13.05 ± 0.83
trans-resveratrol	Not detectable
Protocatechuic acid	10.99 ± 0.36
Chlorogenic acid	4.65 ± 0.20
Gallic acid	8.51 ± 1.05
Ferulic acid	0.55 ± 0.03
Shikimic acid	18.82 ± 1.03

†Based on: Hall C, personal communication, 2006; Cisneros-Zellallos, personal communication; Miller DD, personal communication, 2003 and references 24 and 25

**SUMMARY**

Antioxidants are a necessary dietary component to scavenge oxygen free radicals, which arise endogenously from metabolism and oxygenation of tissues, and exogenously from environmental stresses like air pollution and smoking. The nutritional literature favors a role for obtaining antioxidants from the diet rather than dietary supplements to reduce disease risk caused by oxidative damage. Fruits and vegetables have the most concentrated antioxidant content of any foods, and regular intake of a wide variety of at least five servings a day is recommended. Most individuals consume just over one per day. What drives this low intake is unknown but may be related to poor flavor, rapid spoilage, and cost.<sup>31</sup> Raisins possess antioxidants, which have been shown in several clinical studies to mitigate common risks factors for CVD. Since raisins are sweet and don't spoil so can end up being less costly than other fruits and vegetables, they are a reasonable fruit to include regularly in the diet to increase antioxidant intake.

## CONFLICT OF INTEREST AND FUNDING DISCLOSURE

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