

# Grapes and Health: Research That Matters



For the past several decades, there has been a steady increase in research studies investigating the relationship between consuming grapes and the resulting effects on human health, especially heart health. These studies have been sponsored by a number of respected institutions, manufacturers, and the California Table Grape Commission, an agricultural commodity group funded by California's grape growers.

Interest in the relationship between grapes and heart health can be traced back to earlier research on the Mediterranean Diet, which looked into the role of grapes and grape products and the relatively low percentage of cardiac disease in those regions where these items were consumed on a regular basis. Today, the research emphasis is on the overall impact of consuming grapes as a whole food, as well as the actions of the polyphenols found in grapes and how this relates to the heart and other aspects of health.

The heart-health-grape-consumption connection results are compelling and positive. A comprehensive literature review of studies investigating the health benefits associated with grapes<sup>1</sup> — including the fruit itself, grape juice, dealcoholized wine and other non-alcoholic grape products — outlines the “well-established health effects of grapes on cardiovascular risk.” Specifically grapes have been shown to improve endothelial function, reduce LDL oxidation, slow the progression of atherosclerosis, and reduce oxidative stress.<sup>2</sup>

Emerging research continues to explore the potential connections between eating grapes and promoting healthy eyes, bone and joint health, as well as healthy cells in other parts of the body, including the brain, breast, and bladder. The possible link between grape consumption and the allaying of metabolic syndrome is another exciting area of research.

Highlights of the research are outlined below and in the pages that follow. The studies and presentations include a mix of cell, animal and human subjects.

## **Grape Consumption and Heart Health: The Promising Results**

Numerous studies on grapes and grape products suggest that grapes contribute to heart health. The benefits observed are typically attributed to the polyphenols present in grapes, which work through a variety of actions. Specifically, grape polyphenols display antioxidant

activities, as well as the ability to influence cell communications that mediate important biological processes in the body, such as the ability to enhance the production of nitric oxide. In cardiovascular disease, nitric oxide production is severely impaired, thus the ability to increase it is very beneficial. Grapes have also shown anti-inflammatory properties; inflammation of the lining of the arteries is a known contributor to atherosclerosis.

The studies below provide an illustration of the multi-faceted ways through which grapes appear to beneficially impact heart health.

In a pilot human study conducted at Ohio State University<sup>3</sup>, healthy male subjects that consumed the equivalent of 1 ¼ cups of grapes per day improved brachial artery flow within 3 hours of consumption. When consumed twice daily for three weeks, blood flow and antioxidant capacity were further improved. Additionally, researchers observed that consuming grapes with a high fat meal prevented the 50% reduction in blood flow that was seen with the high fat meal alone.

A parallel, crossover study at the University of Connecticut<sup>4</sup> compared the effects of both pre- and post-menopausal women consuming grapes (freeze-dried whole grape powder made from a mix of red, green and black grapes) or a placebo for four weeks, followed by a washout period of three weeks, and then consumption of the alternate treatment for four weeks. The researchers observed a significant decrease in triglycerides, LDL cholesterol, inflammatory markers and overall oxidative stress.

In a parallel, placebo-controlled, crossover study of male subjects with metabolic syndrome, also conducted at the University of Connecticut, consuming grapes resulted in significant decreases in blood pressure, improved blood flow (greater vasodilation) and decreases in a compound associated with inflammation.<sup>5</sup> This study suggests potential for grapes to help reduce risk factors for heart disease in a population that is already at higher risk.

In a laboratory study of atherosclerosis development in mice,<sup>6</sup> adding grapes to the diet helped prevent the accumulation of harmful oxidized cholesterol and significantly reduced the size of the atherosclerotic

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lesion area. The grape-enriched diet reduced oxidative stress, increased serum antioxidant capacity, and reduced the oxidation of LDL cholesterol and its uptake by cells. These processes can help reduce the accumulation of cholesterol in the cells and inhibit atherosclerosis.

A series of laboratory studies coming out of the University of Michigan consistently demonstrated that grapes lowered blood pressure, signs of heart failure and heart damage that are typically associated with a high salt diet.<sup>78</sup> In one study, rats consumed one of five diets: a low salt control; a high salt control; a low salt + grape diet; a high salt + grapes diet; or a high salt diet with a mild blood pressure medication. The results: grapes significantly lowered blood pressure; improved cardiac function; reduced cardiac hypertrophy, fibrosis and oxidative damage; and reduced cardiac malonaldehyde (MDA) formation, which is a marker of oxidative stress. Additionally, grapes were shown to increase cardiac glutathione, an antioxidant tripeptide, reflecting improved antioxidant defense. The blood pressure medication did not provide the same benefits as the grapes: while the drug lowered blood pressure, it did not confer the additional protection of the heart that was observed in the grape-fed group. Another study from this research group looked at the impact of grape intake on animals with hypertension-associated diastolic dysfunction, where stiff ventricles cannot fill back up with blood properly. Once again the grape-enriched diet protected the heart tissue and these benefits were attributed to both cell-signaling and antioxidant activities of compounds found in grapes.<sup>9</sup>

Additional laboratory studies on grapes and heart health have demonstrated grape protection against oxidative injury to the heart,<sup>10,11</sup> as evidenced by improved post-ischemic ventricular recovery (aortic flow, blood pressure, reduced incidence of myocardial infarction) and reduced markers of oxidative stress.

In a study from the University of Connecticut, a grape-enriched diet decreased plasma triglycerides, VLDL cholesterol and cholesterol accumulation in the aorta of guinea pigs.<sup>12</sup> The decrease in cholesterol accumulation was attributed to significantly decreased activity of a liver enzyme, cholesterol acyl transferase (ACAT), which is thought to play a role in lipoprotein metabolism and composition, thereby altering the deposition of cholesterol in the aorta.

These studies indicate the many ways in which grapes may confer protection to support heart health. Additionally, there are numerous studies on grape products — including grape juice and de-alcoholized wine — that further reinforce the findings that support grapes and heart health benefits.<sup>13</sup>

## Noteworthy Emerging Study Areas

Beyond the established effects of grapes on cardiovascular health,<sup>14</sup> the scientific community has also been looking at the potential beneficial impact of grape consumption on age-related and chronic degenerative diseases. Research has been undertaken on the relationship between grapes and eye, joint, brain, bladder, and liver health, as well as diabetes and certain cancers. Additional research is currently underway in these areas as well as others, to further explore the role that grapes may play in helping to optimize health and to uncover just how they may deliver these benefits.

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## EYE HEALTH

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Age-related macular degeneration is a debilitating condition affecting millions of elderly people worldwide. In a study conducted at Fordham University,<sup>15</sup> a grape-enriched diet prevented blindness in mice prone to developing retinal damage in old age by protecting the retina from oxidative damage. Grapes were found to be significantly more protective than lutein, which was also studied. The results also demonstrated that consumption of grapes, starting at an early age, protected vision in old age.

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## DIABETES

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A new area of study that shows promise is that of grapes and diabetes. Grapes are a low glycemic fruit, and an accepted fruit within a balanced diabetic diet. But grapes may offer more potential benefits in this area. A laboratory study of mice conducted by the USDA Agricultural Research Services looked at the impact of grape consumption on Type I diabetes,<sup>16</sup> which is characterized by autoimmune inflammation and destruction of insulin-producing beta cells in the pancreas. The grape-enriched diet protected against the destruction of the insulin-producing cells in the pancreas, and reduced levels of an inflammatory protein, TNF-alpha, in spleen cells. Additionally, the grapes increased the antioxidant capacity of the blood. Overall, grapes significantly reduced the incidence of diabetes: while 71% of control mice became diabetic, only 33% of the grape-fed mice developed the disease. Other studies on grapes and diabetes have used grape extracts or isolated grape compounds. These studies demonstrated beneficial impacts, including decreased hyperglycemia, increased insulin sensitivity, and decreased oxidation in the pancreas, among others.<sup>17</sup> More human studies that look at consumption of the whole fruit will be important to further explore potential benefits for diabetics.

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## BRAIN HEALTH

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The preservation of cognitive ability and brain function is another emerging area of grape research, with intriguing results. In a laboratory study done at the University of Missouri, grapes were shown to protect neurons from oxidative damage and cell death as well as inflammation.<sup>18</sup> Preliminary research looking at the effect of a diet with or without grapes on aging mice, found that the grape-enriched diet was able to dramatically increase the expression of critical target genes that block the Alzheimer's pathway and decrease inflammation in the brain.<sup>19</sup> Additionally, a human study of older adults with memory decline showed that consumption of grape juice helped improve verbal and spatial memory function.<sup>20</sup>

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# Grape Polyphenols: Protecting the Health and Function of Cells

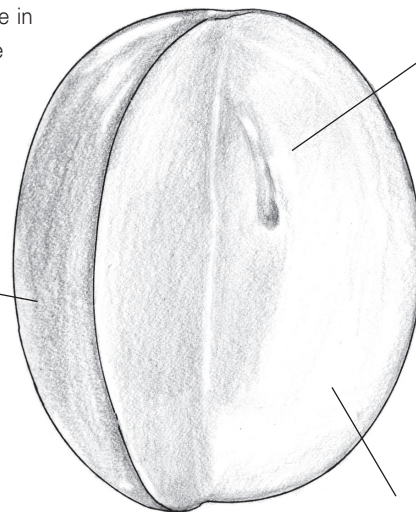
Grapes contain over 1600<sup>24</sup> natural compounds, but of these, the phytonutrient “family” of polyphenols has been the most widely studied. Polyphenols are found in every part of the grape: the skin, the flesh, and the seeds. They are found in grapes of all colors – red, green and black. Resveratrol, perhaps one of the most widely studied individual grape compounds, is a type of polyphenol known as a stilbene. Flavonoids are another group of polyphenols and are also well-known components of grapes. Anthocyanins are a type of flavonoid that provide the vibrant color in red and black grapes. Green grapes do not contain anthocyanins, but they do contain other flavonoids.

Polyphenols have been associated with numerous health benefits, but at their most basic level, they appear to protect the health and function of cells, which is critical to overall health. Polyphenols work in a variety of ways, including serving as antioxidants and enhancing cell communications, known as “signaling,” that affect important biological processes.

Numerous studies suggest that polyphenols contribute to heart health, with emerging evidence suggesting that they may also play a role in the prevention of age-related diseases. Research regarding grape polyphenols and cell signaling is ongoing, and study results will have broad implications for human health.



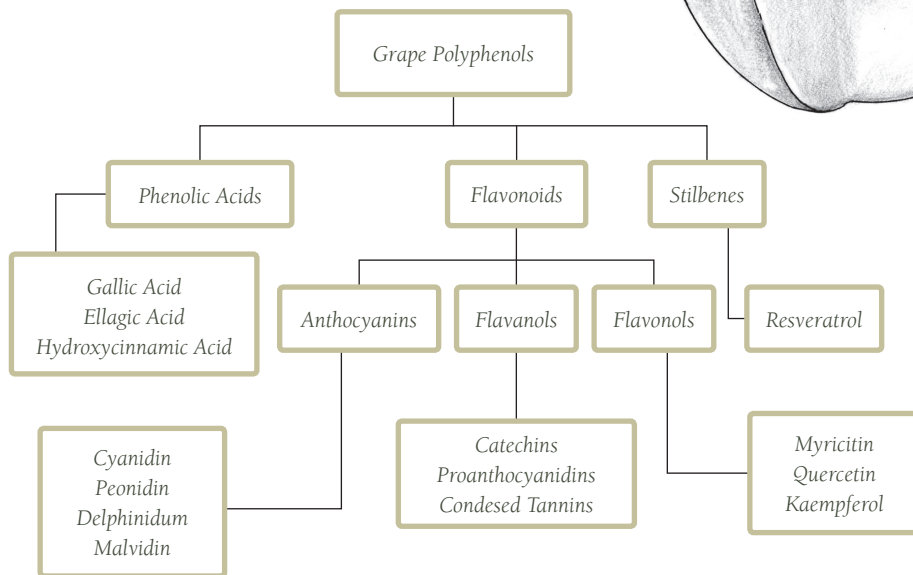
All California table grapes are of the European species *Vitis vinifera*, the same grape species most commonly used to make wine, as well.



*Skin:* The skin of *V. vinifera* adheres tightly to the flesh and is not easily separated from it, encouraging “whole” food eating.

*Seed remnant:* Food scholars believe that all seedless grapes are descended from *V. vinifera* seedless varieties grown for centuries in Eurasia. Most seedless grapes have a slightly discernible seed remnant.

*Flesh:* The juicy flesh of most California table grapes tend to have a natural greenish tinge.



Do both the skin and flesh of grapes confer cardioprotection? One study specifically addressed this question, and found no difference in benefit between the flesh and the skin, including free radical scavenging abilities.<sup>25</sup>

The grape polyphenol family tree has many branches, but is comprised of three main categories of compounds: phenolic acids, flavonoids and stilbenes. Within each of these groups are more “members”, some of which are depicted above.

## CANCER

The role of grapes in helping to protect against the development of cancer is an area of ongoing interest in the scientific community. There is promising preliminary work in the areas of breast, colon, and prostate cancer, particularly with cell and animal studies involving grapes, grape products and isolated grape compounds, such as resveratrol.<sup>21</sup> One study that demonstrates the potential of grapes in humans is a small study of colon cancer patients conducted at the University of California Irvine.<sup>22</sup> After subjects had consumed grapes for two weeks, samples of healthy and cancerous colon tissue were studied. While no benefits were observed in the cancerous tissue, in the healthy colon tissue, there was a 47% reduction in the composite expression of target genes responsible for promoting tumor growth in the colon, suggesting that grapes may be able to play a role in helping to maintain a healthy colon.

## JOINT HEALTH

Grapes are also being examined for their role in joint health. A preliminary study conducted at the John Hopkins University School of Medicine looked at an animal model of arthritis.<sup>23</sup> Four different treatments were studied: sugar water as the control; grapes; anti-inflammatory drug meloxicam; grapes plus meloxicam. The grape-enriched diet reduced the amount of pain from the arthritis, while the anti-inflammatory drug showed no impact on pain. However, the combined treatment of grapes plus meloxicam gave greater pain relief than either did on its own. More research is underway, including a human study on grapes and osteoarthritis.

## Integrity of the Research

The California Table Grape Commission established and implemented its own research grant program more than 10 years ago with oversight by advisors from the scientific community, including the National Cancer Institute. Each year, the program solicits investigator-initiated research proposals for grapes and health. The proposals are rigorously reviewed by a panel of scientific advisors, and recommendations made for funding. As a result of this program, numerous studies have been published in peer-reviewed journals, adding important data to the growing body of scientific evidence on grapes and health. In order to ensure solid, reproducible data, the commission sponsors the production of a freeze-dried powder made from a blend of red, green and black grapes. A grape powder placebo is also provided for human studies.



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