

Grapes and Health: A Monograph



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*Grapes and Health*¹ is a comprehensive book that offers a thorough review of the current science linking the consumption of grapes to better health. A compilation and synthesis of peer-reviewed, grape-specific research, the recently published 235-page volume provides insight into the variety of ways in which grapes provide health benefits and demonstrates that the scope of impact is substantial. The book starts with the basics of grape biology then moves on to individual chapters written by subject experts who examine the state of research in the following key areas of health: heart health, inflammation, cancer, brain health, gastrointestinal health, joint health, bladder function, and eye health. *Grapes and Health* serves as an authoritative reference on the ways grapes are being shown to exert health benefits. Highlights of each chapter are outlined in the following pages.

For a full copy of the book, please contact healthresearch@grapesfromcalifornia.com.

Grape Anatomy and Physiology

There are approximately 8000 varieties of grapes in the world, differing in size, color, shape, flavor, etc. Biologically grapes are technically classified as a berry. The growth and maturation of the grape berry and/or seeds affect changes in sugars, acids, and phenolic compounds. Grapes are able to develop natural resistance to various types of plant disease by producing natural compounds such as resveratrol.

Grapes are comprised of water (between 75 – 85% of their weight), natural sugars (fructose and glucose); organic acids, simple phenolic compounds, and polyphenols including flavonoids such as proanthocyanins (tannins), anthocyanins, flavonols, and more. Grapes contain thousands of compounds that have been classified and likely thousands more as yet unidentified. The unique chemical composition of grapes provides many possible uses in nutritional and pharmaceutical applications.

Standardized Grape Powder for Basic and Clinical Research

In order to facilitate ongoing research into the potential health benefits of table grapes, a uniform and reproducible

source of grapes was needed for continuous, year-round scientific study. As a result, a standardized, freeze-dried powder made from a composite of fresh red, green, and black California grapes (seeded and seedless varieties) was created. The grape powder is provided to researchers studying the link between grapes and health. To make the powder, the grapes are frozen, ground with food-quality dry ice, freeze-dried, and blended using Good Manufacturing Practices for food products. The powder is processed and stored to preserve the integrity of the biologically-active compounds found in fresh grapes. As with fresh grapes, the powder is known to contain resveratrol, flavans (including catechin), flavonols (including quercetin), anthocyanins, and simple phenolics. The grape powder is incorporated into experimental diets – mixed into animal chow, or for human studies, stirred into water and consumed as a beverage. A placebo powder is also produced for use in human studies; it is formulated to closely match the freeze-dried grape powder in terms of dietary fiber, sugar profile, organic acid profile, as well as for sensory characteristics such as sweetness, tartness, mouthfeel, and viscosity. A select group of grape phytochemicals are measured periodically in each batch of grape powder including some phenols, anthocyanins, flavonols, and stilbenes.

¹ Pezzuto, J.M. (Ed.). (2016). *Grapes and Health*. Switzerland: Springer International Publishing. doi: 10.1007/978-3-319-28995-3

Grapes and Heart Health

Grape Polyphenols in the Prevention of Cardiovascular Disease

Consuming grapes is associated with a lower risk for heart disease, as indicated by an array of epidemiologic, clinical, and experimental studies. The heart health benefits of grapes are attributed to the bioactive compounds found in grapes, including simple phenols, simple phenolic acids, cinnamic acids, stilbenes including resveratrol, proanthocyanidins, anthocyanins, flavonoids, flavans, and carotenoids.

Individual grape polyphenols have been studied and shown to have multiple bioactivities, including antioxidant, lipid-lowering, and anti-inflammatory effects. These grape compounds are thought to act synergistically in the promotion of heart health and prevention of adverse cardiovascular activities.

In human studies, grapes and grape products have demonstrated an array of heart health benefits including promoting healthy blood vessels, healthy blood flow and pressure (endothelial health), healthy blood lipid levels, countering oxidative stress and inflammation, and reducing platelet aggregation/plaque formation, among others.

Grapes and Atherosclerosis

There is a solid base of evidence that grape polyphenols exert protective effects against atherosclerosis.

Atherosclerosis – also known as hardening and narrowing of the arteries – is a specific, complex condition that is considered the main cause of heart disease. Healthy arteries are lined by a thin layer of cells called the endothelium that keeps the arteries smooth and blood flowing. The vascular function of the endothelium is regulated by the release of compounds which can constrict and dilate the blood vessels, and nitric oxide plays a central role. In cardiovascular disease, nitric oxide production is impaired. The vasodilation of the endothelium is also affected by diet, and antioxidants have been shown to beneficially impact vascular function.

However, the endothelium can be damaged by high blood pressure, smoking, or high cholesterol. When “bad” cholesterol, or LDL, crosses the damaged endothelium, it goes into the wall of the artery and starts to build up



over time and become oxidized. This accumulation of LDL cholesterol leads to the formation of plaque, which in turn leads to the narrowing of the arteries, stiffness, and the impairment of blood flow that are hallmarks of atherosclerosis. Atherosclerosis is associated with oxidative stress and inflammation.

Numerous studies provide evidence that shows that grape polyphenols help protect against atherosclerosis and that they do this in multiple ways. Grape polyphenols have been shown to exert beneficial effects on the cell-signaling pathways and metabolic routes that counter oxidative stress, inflammation, and dyslipidemias implicated in the development of atherosclerosis.

Specifically, grape polyphenols have been shown to:

- promote healthy endothelial function (improved vasorelaxation, lower blood pressure, and increased production of nitric oxide);
- modulate lipid profiles;
- decrease LDL oxidation and platelet aggregation; and
- exert anti-inflammatory activities



Some of the human studies have looked at the effects of consuming whole grapes in the form of a freeze-dried whole grape powder:

- In one pilot study, young healthy male subjects (mean age 24 years) consuming the equivalent of 1.25 cups of fresh grapes significantly improved blood flow within three hours of consumption; when grapes were consumed twice daily for 3 weeks, blood flow and antioxidant capacity were even further improved. Furthermore, researchers also found that consuming grapes with a single high fat meal offset the damaging impact to blood flow observed following a high fat meal without grapes.
- In another study, patients with metabolic syndrome consumed either the equivalent of 2 cups of fresh grapes or a placebo for 30 days followed by a 3-week washout period where neither placebo nor grape powder was taken, and then the alternate treatment for 30 days. For each subject, grape consumption resulted in improved blood flow (greater vasodilation), significant decreases in blood pressure, and decreases in an inflammatory marker.
- In a study of pre- and post-menopausal women, consuming either the equivalent of 1.5 cups of grapes per day or a placebo for four weeks, followed by a 3-week washout period and then the alternate treatment, showed distinct benefits with grape consumption. Specifically, supplementation with grapes lowered plasma triglycerides, LDL cholesterol, oxidative stress, and concentration of proinflammatory marker TNF α .

Additional human studies have looked at the impact of other grape products – from grape juice to grape polyphenols to dealcoholized wine – on different groups, including healthy subjects, obese but otherwise healthy subjects, hemodialysis patients, mildly hypercholesterolemic patients, subjects on statin treatment and at high risk for cardiovascular disease, and more. In most all of the cases

consuming the grape product positively influenced key markers of heart disease.

A wide range of animal studies further support the beneficial impact of grape consumption on decreasing atherosclerosis and provide insight into the mechanisms of how they do this. Findings have included observation of: lower concentration of cholesterol in the aorta and lower concentrations of plasma triglycerides; reduced markers of oxidative stress; increased serum antioxidant capacity; reduced cell uptake of oxidized LDL cholesterol and decreased oxidation of LDL in general; reduced blood pressure; reduction in atherosclerotic lesions; reduced heart enlargement and diastolic dysfunction; and more.

In summary, epidemiological data, human studies, and animal and cell studies collectively document a protective role for grape polyphenols against atherosclerosis.

Grapes and Inflammation

Controlling inflammation is critical to good health and the prevention of a wide range of health problems, including arthritis, atherosclerosis, type 2 diabetes, cancer and more. Diet plays a crucial role in the regulation of inflammation, and grapes can positively impact both inflammation and oxidative stress, as demonstrated in clinical, animal, and cell studies.

Inflammation is directly linked to oxidative stress throughout the body. Oxidative stress occurs when there is an imbalance between the production of free radicals and the body's ability to counteract them. While the body has inherent defenses against oxidative stress, such as enzyme activities or direct scavenging and neutralizing of the free radicals, sometimes they are not enough and foods that promote antioxidant activity, such as grapes, can help limit oxidative damage.

Grape polyphenols appear to help stop chronic inflammation by reducing oxidative stress and by preventing the activation of critical pathways that cause inflammation. For example:

In a study of hypertensive rats, consuming a grape-enriched diet increased the concentration of naturally occurring antioxidant proteins, including cardiac glutathione, while also reducing the activities of a protein complex [nuclear factor kappa beta or NF-KB] that controls the activity of inflammatory genes. Other animal and cell studies also suggest that grape polyphenols are able to inhibit inflammatory NF-KB target pathways and other inflammation mediators. Grapes and grape-derived components (grape juice, grape seed extract, etc.) have also been shown to lower markers of inflammation in important organs, including the colon, liver, and kidneys.

Grapes and their constituents have also been shown to impact broader systemic diseases linked to inflammation such as obesity, metabolic syndrome, cardiovascular disease, type 2 diabetes, and heart failure. Some examples include:

- In a human study looking at the effects of grape consumption on inflammation and oxidation in metabolic syndrome, consuming grapes decreased markers of inflammation in those subjects with normal levels of blood lipids. Grape consumption also resulted in significant decreases in blood pressure and improved blood flow.
- In a clinical study of adolescents with metabolic syndrome, consuming grape juice for a month led to significant improvements in blood flow and a reduction in two key inflammatory markers.

- An animal study tested the effects of adding grapes to a typical, high-fat American diet. Obesity-prone rats consuming a grape-enriched diet showed a significant reduction in key markers of inflammation (C-Reactive Protein, TNF- α , and IL-6) as well as a decrease in liver, kidney, and abdominal fat weight.
- Another animal study looked at the impact of a grape-enriched diet on hypertension-associated heart failure, by feeding salt-sensitive rats one of five diets: low salt (LS); low salt + grape (LSG); high salt (HS); high salt + grape (HSG) or high salt + vasodilator drug hydralazine (HSH.) Adding grapes to a high-salt diet lowered blood pressure and improved heart function; reduced systemic inflammation and oxidative damage; reduced structural problems in the heart muscle (hypertrophy and fibrosis) and increased the presence of glutathione, a naturally occurring antioxidant, in the heart. The high-salt diet plus the drug hydralazine reduced blood pressure but did not provide any of the other benefits observed with grape intake. The low-salt grape diet reduced cardiac oxidative damage and increased glutathione.

Numerous other studies looking at the impact of grape components on inflammation related to obesity or high-fat diets further support these beneficial findings regarding grapes and inflammation. Grapes and grape products have been shown to exert anti-inflammatory effects in diverse tissues which is very promising for a range of chronic diseases and deserves further attention in preclinical and clinical investigations.

Current scientific evidence suggests that antioxidant activity observed with the consumption of certain foods is likely achieved through cell signaling mechanisms that activate gene activity versus direct scavenging actions. It has been suggested that the beneficial effects observed with grapes may primarily affect gene expression and molecular interactions and be mediated by very small quantities of polyphenolic compounds. Because of this, using traditional serum biomarkers to show efficacy to assess physiologic response to grapes may underestimate the true physiologic impact of grape intake.

Grapes and Cancer

The consumption of grapes and grape compounds holds promise for both cancer prevention and treatment, as suggested by both human and laboratory studies.

Individual grape compounds such as resveratrol, quercetin, and proanthocyanidins have been shown to act at the cellular level, promoting tumor cell death and inhibiting proliferation of cancer cells through cell signaling, suppressing inflammatory responses, and hindering the spread of blood vessels that can support tumor growth.

Resveratrol is the best studied of the individual grape compounds and has been shown to significantly inhibit the growth of tumors in multiple rodent cancer models and for different types of tumors but primarily colon, breast, and skin. It should be noted that in the case of breast cancer, the possible phytoestrogen effects of resveratrol may neutralize its cancer inhibitory activity in certain circumstances. In a human study of colorectal cancer, supplementation with resveratrol for 10 – 21 days increased cell death in colorectal cancer metastases in the liver.

Human studies have also investigated the impact of whole grapes on cancer with promising results:

- A pilot study of colon cancer patients examined the impact of consuming the equivalent of 2 1/2 cups of grapes per day or resveratrol on normal, healthy colon tissue and on colon tumors, before and after two weeks of grape consumption. Study results showed that in healthy colon tissue, grape consumption inhibited target genes responsible for promoting tumor growth, suggesting that consumption of grapes may be beneficial in the prevention of colon cancer. The whole grape powder elicited a greater effect than the resveratrol alone, suggesting that synergy exists among the many phytochemicals present in grapes.
- Another study involved the consumption of 1/3 – 1 pound of fresh grapes per day to the diet of healthy volunteers for two weeks. At the end of that time, colon tissue biopsies were examined, showing a reduction in mucosal proliferation rate and a decrease in the target genes responsible for promoting tumor growth, similar to the previous study with grape powder. These beneficial effects were most likely to be seen in subjects over the age of 50 and on a high arginine diet, two groups that are at increased risk for colon cancer.

Grapes and Gastrointestinal Health: Implications with Intestinal and Systemic Diseases

Understanding the role of the intestinal microbiome – essentially the collection of bacteria in our intestines - and how it affects health and wellness, is a growing area of scientific research. Intestinal bacteria have been linked to a wide range of health issues, from digestive problems, to diabetes and obesity, to immune health, to inflammation, and more. The diversity of the bacteria in the intestine determines how healthy the microbiome is, as well as the proportion of “good” to “bad” bacteria.

Not surprisingly, diet is a crucial driver of intestinal bacteria, and there is much interest in how specific foods influence the microbiome. Grapes and grape polyphenols appear to influence intestinal bacteria, with subsequent metabolic consequences.



The anti-inflammatory, antioxidant, and antimicrobial properties of the nutrients and phytochemicals found in grapes potentially influence intestinal and systemic health. In some cases they may positively affect absorption, as when grape polyphenols promote antioxidant activity that protects other nutrients from oxidative damage, essentially preserving their efficacy.

Dietary polyphenols that do not get absorbed in the upper GI tract will come into contact with microbes in the intestine, and such interactions may favorably influence microbial growth. The impact of the microbes on the polyphenols may transform the polyphenols to enhance their absorption into other organs and tissues.

Research suggests that certain grape polyphenols may act in the following ways to positively impact intestinal health:

- Acting as prebiotic agents that alter intestinal microbial populations for improved health status in the host
- Acting as antimicrobial agents to help decrease the growth and adherence of disease causing bacteria
- Altering bile acid metabolites or neutralizing pro-oxidants that damage DNA and proteins
- Reducing populations of gut microbes that produce pro-oxidants
- Modulating inflammation by activating certain anti-inflammatory pathways, and deactivating pro-inflammatory pathways

More research is needed to determine the ways in which whole grape consumption may advance intestinal health, and whether those benefits are associated with improved systemic health.

Grapes and the Brain

Brain health is critical to both mental and physical functioning and ultimately quality of life. How to prevent the loss of brain function and to restore it after injury has been the subject of much research. Since losses in brain function can involve multiple targets, finding treatments that work in several ways and that can impact a variety of targets is optimal. Grapes are a potential solution, having been shown to work in a variety of ways, in a wide range of studies.

Cognition

Grapes, and products made from grapes, including grape juice and grape seed extract have been shown to beneficially impact brain function in animal and human studies. The majority of studies on grape products and brain function thus far have investigated learning and memory effects, but a few have addressed other behaviors such as anxiety.

Stress, hypertension, aging, including menopause, and dementia are known contributors to cognitive difficulties. Findings from animal studies in these areas have shown that:

- Adding grapes to the diet reduced the negative impact of oxidative stress on anxiety and memory. Without grapes, oxidative stress directly increased anxiety and impaired cognitive function.
- A grape-enriched diet reduced multiple symptoms of post-traumatic stress disorder including anxiety, depression and memory loss.
- Adding grapes to the diet reduced blood pressure, decreased anxiety and improved short-term memory in an animal model of menopause. Grape seed extract has shown benefits to learning and memory in a model of menopause.
- A grape-enriched diet reduced serum markers of stress and promoted memory retention and recovery.
- In a model of memory loss, grape seed extract reduced serum markers of stress and helped promote memory retention and hasten memory recovery.

Two human studies looked at grape juice and age-related cognitive decline.

- In the first, older adults (avg. 78 years) with early memory decline but not dementia who consumed grape juice showed beneficial effects on cognitive function related to normal aging.
- In a follow-up study, older adults (avg. 76 years) with mild cognitive impairment who consumed grape juice learned new information at the same level as those on placebo, but they were better able to selectively retrieve previously presented material. Additionally, brain scans for grape consumers showed significant increases in brain activity in certain regions, which is associated with increased neuronal activity.

Stroke

Ischemic stroke occurs when the blood supply to the brain is disrupted, often by an artery blockage or blood clot, and deprives the brain of oxygen. Immediate nerve cell death is followed by an inflammatory response leading to secondary tissue damage after blood flow is restored.

- Consuming a grape-enriched diet protected neurons and helped reduce inflammation against ischemic damage in an animal model of ischemic stroke.

Alzheimer's Disease

Alzheimer's disease is the most common type of dementia. It is characterized by the presence of plaques in the brain containing amyloid beta peptide and intracellular neurofibrillary tangles containing tau. Alzheimer's disease results in a progressive loss of cognitive ability and eventually daily function activities. Grapes have been studied in several animal models of Alzheimer's and have shown beneficial effects:

- Grape seed extract helped improve learning and memory, and reduced levels of amyloid beta in the brain in two studies.
- A combination of grape seed extract, resveratrol and concentrated grape juice helped with learning and memory and in reducing amyloid beta. However, neither resveratrol nor grape juice alone had any effects on these parameters in this study.
- In another study, grape seed extract reduced the levels of amyloid beta peptides and amyloid plaque, and also greatly reduced damaging microglial activation, which is linked to loss of nerve cell function.

Potential Mechanisms of Action

There appear to be multiple ways by which grapes may exert protective actions in the brain including:

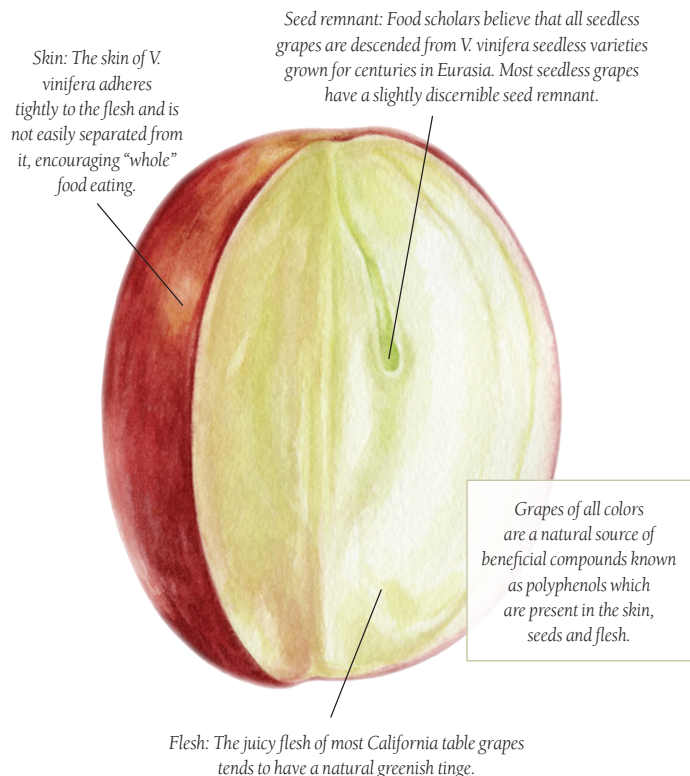
- Inhibiting or reducing oxidative stress in the brain
- Helping to maintain levels of a key brain chemical involved in promoting memory (brain-derived neurotrophic factor or BDNF)
- Promoting healthy blood flow and pressure which benefits brain health

- Inhibiting protein aggregation that could result in inappropriate or excessive protein accumulation.
- Maintaining active neurotransmitter signaling
- Exerting anti-inflammatory effects

Research strongly supports the idea that grapes and grape products can improve brain function and specifically learning and memory in animals exposed to stress, aging, and disease. Grapes appear to work through multiple mechanisms and further research in this area will be very important.

Grapes and Joint Health

Osteoarthritis (OA) is a chronic disease, usually age-related, where there is degeneration of joint cartilage and the underlying bone that typically causes pain and stiffness, especially in the hip, knee, and thumb joints. Inflammation is directly responsible for much of the structural degeneration and clinical symptoms, such as pain and swelling, seen in OA. Unlike many other chronic diseases, there is no reliable biomarker or clinical measure for diagnosing OA. Prevention of joint damage is thus a critical component of OA therapies and one that may be enhanced with grape intake.



There is evidence that dietary polyphenols provide benefits for both osteoarthritis and rheumatoid or other forms of inflammatory arthritis. Several mechanisms may be responsible for the benefits observed, including preserving cartilage cells; inhibiting inflammatory pathways; influencing antioxidant pathway signaling, and/or activating estrogen receptors.

Human studies on grapes and arthritis are limited, but promising.

- A sixteen week clinical study investigated the benefits of grape consumption on inflammation and osteoarthritis outcomes. 72 men and women with knee osteoarthritis (OA) were assigned to consume either the equivalent of 1.5 cups of grapes, or a placebo.

The study results showed that both men and women consuming the grape-enriched diet had a significant decrease in self-reported pain related to activity and an overall decrease in total knee symptoms, although this beneficial effect was more pronounced in females. Additionally, age-related differences were observed related to activity: grape-consuming subjects under 64 years of age reported a 70% increase in “very hard” activity, while those receiving the placebo reported a significant *decrease* in very hard activity. Participants over 65 years reported a decline in moderate to hard activities whether consuming grapes or the placebo.

The impact of grape consumption on cartilage metabolism was also studied, with evidence of increased cartilage metabolism observed in the grape-consuming men; they had higher levels of an important cartilage growth factor (IGF-1) compared to those on placebo. This protective effect was not observed in the females.

The researchers noted that no difference in range of motion was observed for either the grape group or the placebo group. The serum marker for inflammation (IL1-β) measured was increased in both placebo and grape groups, although much less of an increase was observed in the grape group suggesting some modulating influence of the grape polyphenols.

- In another study, nine females with knee osteoarthritis added grape seed extract, some vitamins, and the amino acid L-lysine to their diet for 5 weeks. After 3 - 4 weeks, all subjects reported either significant pain relief (4) or being pain-free.

- In animal models of osteoarthritis, resveratrol and grape seed extract have shown a protective effect on cartilage. Even more research has been done in animal models of inflammatory arthritis where there is more severe inflammation, oxidative stress and physical impairment than osteoarthritis. These study results also show a reduction in joint inflammation and damage, with evidence of antioxidative and anti-inflammatory effects by the grape compounds.
- Most cell studies on grapes and arthritis have examined the beneficial impact of resveratrol, which has been shown to inhibit inflammation and cartilage cell death. However a recent study looked at the effects of grapes on human cartilage cell integrity and markers of cartilage health, using whole grape extract with a variety of grape polyphenols. The cells were first treated with the grape polyphenols, then stimulated with an inflammatory agent. The results showed an increase in cartilage cell proliferation and a significant decrease in a marker for cartilage degradation, suggesting a possible protective effect of grapes on cartilage cells.

Grapes and Urinary Bladder Function

Urinary bladder outlet obstruction is a common medical problem. More than 80% of males older than 50 years of age have varying degrees of bladder outlet obstruction as a result of an enlarged prostate gland (benign prostatic hyperplasia or BPH.) The prostate is the only organ that continues to grow throughout life and in doing so, gradually compresses the urethra causing the bladder to weaken. The result: increased frequency of urination, increased urgency and poor urine flow.

A number of studies have been conducted in this area, using an animal model that correlates well with humans. Researchers have found that partial bladder outlet obstruction results in elevations of free radicals – both reactive oxygen species (ROS) and reactive nitrogen species (RNS) - that stimulate the oxidation and nitration of proteins within the bladder. These changes disrupt normal cellular function and cause damage of the nerves, synapses and smooth muscle cells in the bladder wall.

A series of studies investigated the impact of adding grapes to the diet on bladder function in the presence of partial bladder outlet obstruction. The findings showed that the progression from a healthy bladder to a severe obstructive bladder is significantly reduced in both severity and advancement by consuming grapes.

Specifically, the studies showed that grapes provided an antioxidant effect that helped to prevent and delay the damaging effects of oxygen deprivation (ischemia) and free radicals on cells that result from a partial obstruction to the bladder. Grape consumption helped maintain membrane and mitochondrial function in the cells, and reduce and reverse bladder damage caused by a partial outlet obstruction. The beneficial effects were attributed to the combination of multiple active components in grapes.

Grapes and Vision

Increased oxidative stress is associated with many eye diseases, including the progression of Age-Related Macular Degeneration (AMD), which is the leading cause of blindness in the elderly. The retina is extremely vulnerable to oxidative damage. The incidence of cataracts and glaucoma is also linked to oxidative stress, and diabetic retinopathy, while initially caused by uncontrolled high blood sugar over time, is exacerbated by oxidative stress as well.

Grapes contain a variety of natural phytochemicals that promote antioxidant and anti-inflammatory activity. These include polyphenols, including resveratrol and quercetin, as well some carotenoids, including lutein and zeaxanthin. Research studies have investigated whether increased intake of grapes or grape compounds may be effective in maintaining eye health and preventing or delaying the progression of eye disease. Although there are no human studies to date, several laboratory studies have been published that directly tested the effects of grapes on eye health. The findings are promising.

- *Of relevance to aging of the human retina and age-related macular degeneration:* The effects of grape consumption were tested in a mouse model of age-related blindness and AMD. Mice lacking a gene that clears lipofuscin (a mix of metabolic waste) from the retina exhibit increasing

dysfunction of the photoreceptor cells due to oxidative damage, and loss of vision. However, supplementing their diet with grapes throughout adulthood prevented the accumulation of lipofuscin, oxidative damage and vision loss. Consuming grapes in early and middle adulthood protected vision throughout old age, while starting to consume grapes in late adulthood did not stop vision loss.

- *Of relevance to neovascular AMD:* In neovascular AMD, abnormal blood vessels grow underneath the retina, and can leak fluid and blood which may lead to swelling and damage of the macula. In an animal model of neovascular AMD, grape supplementation provided throughout the day significantly reduced the severity of abnormal vessel growth, in a manner comparable to resveratrol. Changing the treatment to just once a day eliminated this beneficial effect, suggesting that continuous low dose supplementation may supply the phytonutrients more efficiently than periodic high doses.
- *Of relevance to ocular inflammation:* In an animal model of ocular inflammation, pretreatment with grape polyphenols (muscadine grape extract) prevented the activation of inflammatory proteins and retinal tissue damage. A supporting study using human RPE cells showed that grape polyphenols prevented chemically induced cellular stress as well as an increase in inflammatory response.

Grape polyphenols quercetin and resveratrol have been studied individually for their effect on eye disease. Quercetin has been shown to exhibit potent antioxidant properties when applied to ocular cells. Resveratrol has been shown to beneficially impact oxidative stress, neovascularization, inflammatory processes, and cellular death in a variety of eye diseases and dysfunction. These studies support the possibility that grape consumption may benefit eye health.

Newly Published Study Results Generated Post Printing

Since *Grapes and Health* was printed, additional research into the health benefits of grapes has been completed and published:

- Most recently a new study on brain health showed that a grape-enriched diet helped protect against metabolic

brain decline in Alzheimer's-related areas of the brain.² Specifically, in a pilot study of people with early memory decline, consuming grapes preserved healthy metabolic activity in regions of the brain associated with early Alzheimer's disease, where metabolic decline takes hold. Subjects who didn't consume grapes exhibited significant metabolic decline in these critical regions. Additionally, those consuming the grape-enriched diet showed beneficial changes in regional brain metabolism that correlated to improvements in cognition and working memory performance.

- A new study on eye health - using an animal model of macular degeneration - showed that a grape-enriched diet preserved retinal function in multiple ways, from countering oxidative stress, to lowering inflammatory proteins and increasing protective proteins in the retina.³
- A third recently published study showed that daily intake of whole grape powder reduced the progression of kidney disease in obese diabetic rats.⁴ The renal protection of the grape-enriched diet was associated with an increase in antioxidant activity within the kidneys.

Conclusions

The evidence that grapes contribute to heart health is well-established, including the protective effects of grape polyphenols against the development of atherosclerosis. Heart-healthy grapes may play a role in healthy aging as presented in the *Grapes and Health* chapters that cover an intriguing and broad range of relevant health issues. These include the role of grapes in modulating inflammation; influencing microbial growth and metabolism in the gut; protecting cell health to help maintain healthy colon tissue and help defend against cancer; and supporting healthy brain function and eye health through antioxidant actions that help protect the structure and function of these critical organs.

As detailed in *Grapes and Health* and in the steady stream of research results since, current scientific evidence suggests that grapes exert these benefits in a myriad of ways, and on a wide variety of systems that are beneficial to health. Research is ongoing in these and other important areas of health to continue to define the intriguing health-promoting potential of grapes.

² Lee, J.K., Torosyan, N., and Silverman, D.H. (2017). Examining the impact of grape consumption on brain metabolism and cognitive function in patients with mild decline in cognition: A double-blinded placebo controlled pilot study. *Experimental Gerontology*, 87 (Pt A):121-128.

³ Patel, A.K., Davis, A., Rodriguez, M.E., Agron, S., & Hackam, A.S. (2016). Protective effects of a grape supplemented diet in a mouse model of retinal degeneration. *Nutrition*, 32: 384-390.

⁴ Almomen, S.M.K., Guan, Q., Liang, P., Yang, K., Sidiqi, A.M., Leven, A., & Du, C. (2017). Daily intake of grape powder prevents the progression of kidney disease in obese type 2 diabetic ZSF1 rats. *Nutrients*, 9, 345.





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