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# Resveratrol, in its natural combination in whole grape, for health promotion and disease management

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## Abstract

The grape antioxidant resveratrol has been a topic of intense research for the past three decades. Resveratrol and other grape ingredients, as well as whole-grape products, have shown considerable promise in health promotion and disease management. Phytochemically, whole grape represents a natural combination of resveratrol and other phytonutrients, as it contains several catechins, anthocyanins, polyphenols, and flavonols. Thus, the whole grape products or specific combinations of grape constituents provide us with the possibility of synergistic interactions leading to improved efficacy. Recent research has suggested that whole-grape products may help in maintaining heart health and protect against aging, aging-associated diseases, neurodegeneration, and some cancers. Based on the available recent literature, the grape or whole-grape products seem to be safer choices for better health and disease prevention. However, for advanced disease conditions, individual grape ingredients (such as resveratrol) or combinations of multiple ingredients together with existing therapies appear to be better approaches. Further clinical studies are needed to understand the benefits of grapes and their products in the prevention and management of specific diseases.

### Keywords

resveratrol; grape; clinical trials

## Introduction

The dramatic increase in average life expectancy in the 21st century is associated with a greater risk for chronic diseases, especially among the older population. This has also spurred an interest among the human population in searching for a healthy, and possibly “disease-defying,” quality of life. Lifestyle changes that have the potential to make a significant impact towards a healthy life encompass multiple measures, including increasing physical activity, improving healthy dietary habits, stopping smoking, and limiting alcohol

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intake. A diet rich in antioxidants, vitamins, minerals, and other key nutrients that benefit the body can play an important role towards a healthy lifestyle, with less risk of chronic health problems. Resveratrol (trans-3,5,4′-trihydroxystilbene) is an antioxidant that is found in a variety of dietary botanicals including red grapes and been shown to afford health promotion in several chronic conditions such as aging, heart diseases, and cancers.[1–3] Although resveratrol-containing herbal formulations have been in use for health-promoting effects since ancient times, this antioxidant started receiving major attention in the 1990s. In the early 1990s, resveratrol was linked to the so-called *French paradox* (the observation that the French population possesses a lower risk of coronary heart disease despite consuming a diet rich in saturated fats), and the presence of resveratrol in red wine was established.[4–6] In 1997, in a landmark study from John Pezzuto's group, resveratrol was shown to afford skin cancer chemopreventive effects in the classical model of 7,12-dimethylbenz(a)anthracene (DMBA)–initiated and 12-*O*-tetradecanoylphorbol-13-acetate (TPA)–promoted murine skin carcinogenesis.[7] In this study, resveratrol was found to (1) act as an antioxidant and antimutagen, (2) induce phase II drug-metabolizing enzymes (anti-initiation activity), (3) mediate anti-inflammatory effects, (4) inhibit cyclooxygenase and hydroperoxidase functions (antipromotion activity), and (5) induce human promyelocytic leukemia cell differentiation (antiprogression activity). In 2003, resveratrol further received enormous attention from the general public, the media and the scientific world when a groundbreaking study from David Sinclair's group reported that resveratrol mimics calorie restriction, increases DNA stability, and extends the life span of budding yeast by 70%.[8] Specifically, they found that resveratrol lowers the Michaelis constant of SIRT1 for acetylated substrate as well as for $NAD^+$ and increases cell survival by stimulating SIRT1-dependent p53 deacetylation.[8] These studies and a plethora of other important studies published in the last three decades suggested that resveratrol and resveratrol-containing products could be useful in health promotion and possibly for the management of several disease conditions. Recently, we advocated the idea that resveratrol may be more useful when given in combination with other agents (reviewed in Ref. 9). We believe that resveratrol in combination with other factors within its natural matrix may be advantageous in disease prevention. Based on emerging evidence, the whole-foods concept could be a better approach owing to the possible synergistic interactions between different component ingredients within a food. Indeed, grapes contain numerous compounds with health-promoting properties.

Although resveratrol has been identified in over 70 plant species, grape and grape products are obvious preferable dietary sources to avail the health-promoting effects of resveratrol. Phytochemical analysis of grape powder suggests that it contains several catechins, anthocyanins, polyphenols, and flavonols and therefore may represent a natural combination of resveratrol with other valuable phytonutrients. In this review, we discuss studies suggesting the health-promoting effects of whole grape and grape powder, which contain resveratrol as well as numerous other ingredients.

## Whole food concept: the whole may be greater than the simple sum of its parts

In recent years, naturally occurring compounds, especially antioxidants present in foods and beverages commonly consumed by the human population, have gained considerable attention as natural agents for potential human health benefits. Moreover, consumption of a polyphenol-rich diet has repeatedly been linked with decreased risk of human diseases, as well as protection against the development and progression of many chronic pathological conditions including cancers, metabolic diseases, and aging.[10] Investigators believe that the consumption of plant polyphenols in their natural matrix in whole foods may be a promising health-promoting approach, with implications for reducing risk for several diseases, as individuals can easily make smart choices to modify their dietary habits.

Interestingly, emerging scientific data suggest that the whole-food concept may be a better approach for health and disease prevention. These data make it appropriate to conclude that foods rich in antioxidants and bioactive compounds, mainly vegetables and fruits, may be capable of improving overall health and protecting against several diseases, such as heart diseases, metabolic disorders, aging, and cancer. It is possible that individual dietary factors in food may work additively or synergistically to yield a better response in preventing diseases. In 2008, Michael Pollan, an American author and journalist, wrote that everything he had learned about food and health could be summed up in the following seven words: “Eat food, not too much, mostly plants.”[11] Pollan’s conclusion is becoming increasingly well supported by scientific evidence. As described by Jacobs and colleagues, constituents delivered by foods taken straight from their biological milieu could possibly have different effects compared to those created through technological processing, such as in the case of supplements.[12]

## Grape and whole-grape products for better health

### Historical account and evidence from traditional medicine and epidemiological observations

Arguably, the grape crop *Vitis vinifera L.* is the most valuable fruit crop in the world. The archaeological record indicates that farming of the grape, *Vitis vinifera* subsp. *vinifera*, began approximately 8000 years ago from its wild progenitor, *Vitis vinifera* subsp. *sylvestris*.[13] *Vitis vinifera* is also known as wine grape, European grape, and grapevine. The three major uses for grapes are for dried fruit (raisins), wine, and fresh (table) grapes. Resveratrol is found in widely varying amounts among grape varieties, relatively higher in muscadine grapes (*V. rotundifolia*). Muscadine grapes are nearly immune to insects and diseases, and known to possess one of the highest antioxidant levels among fruits. Resveratrol is primarily found in grape skin, at a concentration of 50–100 μg/g.[14] Interestingly, UV irradiation and ozonization of grapes have been shown to increase the content of resveratrol endogenously in wine products and grape juice (reviewed in Ref. 15).

Remarkably, over 1600 compounds have been identified in grapes, including resveratrol, lycopene, quercetin, melatonin, and other potent antioxidants.[16] Many of these agents are associated with health-beneficial properties, and several of them have been shown to have

synergistic/additive effects. Thus, while the individual ingredients, such as resveratrol, have been shown to have limited *in vivo* bioavailability, the overall collective antioxidant content of whole grape is likely to be very high owing to the coexistence of catechins, procyanidins, flavonols, and anthocyanins. Further, there is a possibility that one specific individual ingredient of grape may enhance the bioavailability of others. For example, hepatic and duodenal sulphations are known to limit the bioavailability of resveratrol; however, quercetin (which coexists in red grapes, red wine, and other grape products) is known to inhibit *in vivo* sulfation of resveratrol.[17] Thus, it is possible that if quercetin and resveratrol are taken in combination, as in whole grape, grape juice, or grape powder, quercetin may increase the bioavailability of resveratrol by inhibiting its sulfation.

In addition, grapes are known to have a low glycemic index, ranging between 43 and 53, which allows a slow and steady release of glucose.[18] Grapes also possess low glycemic load, indicating good quality and less carbohydrate.[18] Healthier blood sugar levels and insulin chemistry have now been associated with the intake of whole-grape products and individual phytonutrients found in grapes. Several studies have shown that individuals who consume a diet with a low glycemic index over many years are at a significantly lower risk for developing metabolic and age-related diseases. Therefore, daily consumption of whole-grape products may be very useful to promote better health.

Grapes have been associated with human health for many centuries. Grapes contains up to 300 mg of polyphenols per 100 grams of fresh weight. Typically, a glass of red wine contains approximately 100 mg of polyphenolic antioxidants. Ayurvedic medicine, a 5000-year-old system of traditional medicine that originated on the Indian subcontinent, uses grapes in a variety of ways for health benefits. For example, drakshasava, a traditional Ayurvedic well-being tonic, is made from partially fermented grapes. In Ayurvedic medicine, drakshasava is touted to have beneficial effects against a variety of health imbalances including lethargy, weakness, heat exhaustion, and cardiac disease.[19,20] In 1999, Paul and colleagues performed high-performance liquid chromatography (HPLC) analysis of this age-old formulation, demonstrating the presence of polyphenols including resveratrol and pterostilbene, which existed in at concentrations of 1.296 mg/L and 6.86 mg/L respectively.[21]

In the modern era, between 1925 and 1930, a grape diet was popularized for its anticancer effect by Johanna Brandt, a South African dietitian. Brandt claimed to have used this grape diet to cure herself of stomach cancer. In 1927, she immigrated to the United States, subsequently opened the Harmony Healing Centre in New York City, and began to promote the grape diet. She wrote a book titled *Grape Cure* that was first published in 1928 and was republished several times throughout the 20th century, with a 2011 edition being the latest one.[22] Because of a lack of scientific evidence, Brandt and some of her followers, who promoted the grape diet as a cure for cancer, became the targets of criticism as well as some legal action.

In the last two decades of the 20th century, the concept of the French paradox started gaining popularity. The phrase “French Paradox” was first used in 1986, in the newsletter of the International Organization of Vine and Wine, and was then used by George Riley

Kernodle of the University of Arkansas in 1989. In the 1990s, Serge Renaud, a scientist from Bordeaux University, used the phrase in several publications to describe the low occurrence of heart disease within the French population despite the consumption of a high-fat diet.[23,24] This was later correlated with the presence of resveratrol in the skin of red grapes.[4–6]

## Evidence from *in vivo* studies

A number of studies have been performed with whole grapes or specific constituent of grapes to ascertain their health-beneficial effects. Some of these studies are described below.

Choi *et al*. demonstrated that grape pomace (grape seed extract and grape peel powder) supplementation activated the antioxidant enzyme system and prevented hypercholesterolemia in diet-induced hypercholesterolemic rabbits.[25] Nayak and colleagues showed wound-healing properties of grape-skin powder (100 mg/kg/day, tropical treatment) using an excision wound model in rats.[26] Rho and Kim demonstrated that grape intakes, especially grape pomace, (1) inhibited age-related or chemically induced increase of lipid peroxidation and DNA damage, and (2) promoted liver and red blood cell antioxidant enzyme activities.[27]

In another study, employing SENCAR (SENsitive to CARcinogenesis) mice treated with DMBA as a complete carcinogen, Hanausek and Spears demonstrated significant inhibition of skin tumorigenesis by grape powder.[28] In this study, the number of skin papillomas was reduced from 7.8 per mouse in the control group to 0.7 per mouse in the treatment group after 12 weeks of treatment with 1% dietary grape powder. The authors found that simultaneous dietary supplementation with grape powder and topical treatment with resveratrol reduced DMBA-induced epidermal hyperplasia, proliferation, inflammation, and the hydroxylation of 2′-deoxyguanosine, suggesting impressive effects of combined topical and dietary treatments with grape-derived antioxidants against skin cancer.[28]

Allam and colleagues reported that grape powder treatment for 3 weeks prevented L-buthionine-(*S,R*)-sulfoximine (BSO) induced oxidative stress, anxiety-like behavior, learning-memory impairment, and high blood pressure in rats.[29] They also suggested the possible involvement of brain ERK-1/2, GLO-1, GSR-1, CAMK-IV, CREB, and BDNF levels in these processes. This study was further replicated in ovariectomized Wistar rats, with similar results.[30]

Stress is one of the major contributing factors for the onset of several diseases. Using the single-prolonged stress (SPS) model (2 h restraint, 20 min forced swimming, 15 min rest, and 1–2 min diethyl ether exposure), Naimesh Solanki and colleagues investigated whether grape powder prevents SPS-induced behavioral and memory impairment in rats.[31] The authors found that grape powder (5 g/L grape powder in tap water for 3 weeks) prevented SPS-induced increase in plasma corticosterone levels, reversed behavioral deficits (anxiety- and depression-like behaviors), improved memory, and protected BDNF levels from degradation in the amygdala of SPS rats. In addition, grape powder significantly enhanced acetylated histone 3 and histone deacetylase 5 in the amygdala and hippocampus of SPS rats, suggesting an involvement of epigenetic regulation of BDNF.[31]

Grapes and resveratrol have been linked closely with heart health. Seymour *et al*. have reported a reduction of heart failure pathogenesis with the administration of grape powder–enriched diets in Dahl-Salt sensitive rats, a model of salt-sensitive hypertension and diastolic dysfunction.[32] In this study, grape powder (3.0% per weight; for 18 weeks) administration (1) lowered blood pressure, (2) improved cardiac function, (3) reduced systemic inflammation, cardiac hypertrophy, fibrosis, and oxidative damage, and (4) increased cardiac glutathione.[32] In addition, grape feeding enhanced cardiac peroxisome proliferator-activating receptor (PPARα and PPARγ) DNA-binding activity but reduced NF-kB DNA-binding activity, reduced cardiac TNFα and TGF-β protein expression, increased IκB-α expression, and reduced cardiac fibrosis, suggesting cardioprotective properties of grape powder.[33] The findings of these studies support the efficacy of grape-enriched diets against hypertension-associated cardiac pathology, specifically for older patients, as salt-sensitive hypertension is common in the aged population. Similarly, Thandapilly *et al*. reported that grape powder treatment significantly reduced blood pressure, improved arterial relaxation, increased vascular compliance, and attenuated cardiac hypertrophy in spontaneously hypertensive rats,[34] suggesting a pharmacological options to combat hypertension.

Approximately 90% of the vision loss associated with age-related macular degeneration occurs as the consequence of choroidal neovascularization (CNV). Kanavi and colleagues have shown that sustained delivery of resveratrol or a defined grape powder inhibited new blood vessel formation in a mouse model of CNV.[35] The authors argued that the antiangiogenic effects of these compounds are comparable to those obtained with ranibizumab or bevacizumab, which are recombinant monoclonal antibodies used to blocks angiogenesis in human patients.[35]

Metabolic syndrome is a disorder of energy utilization and storage and is clinically diagnosed when three of the five following conditions are present: abdominal obesity, higher blood pressure, elevated fasting plasma glucose, excessive serum triglycerides, and decrease in high-density cholesterol (HDL) levels. Metabolic syndrome further imposes a risk for the occurrence of cardiovascular disease and diabetes. Chuang and colleagues demonstrated that 3% grape powder–supplemented high-fat diets for obese mice acutely improve glucose tolerance and decrease markers of inflammation without affecting body fat.[36] Zunino *et al.* demonstrated that dietary interventions with grape powder inhibited the development of type I diabetes in non-obese diabetic mice and enhanced diabetes-free survival of the mice.[37] Further, grape powder intervention reduced or delayed the infiltration of immune cells into the islets and, thus, resulted in prolongation of beta cells in the islets of Langerhans.[37] Fuhrman *et al.* found that grape powder reduced the progression of atherosclerotic lesions in apolipoprotein E–deficient (E0) mice, which was suggested to be due to an increase in serum antioxidant capacity and reduction in serum oxidative stress, macrophage uptake of oxidized low-density lipoprotein (LDL), and macrophage-mediated oxidation of LDL.[38]

Grape products have been studied for bone health as well. Hohman and Weaver have investigated the long-term benefits of a grape-enriched diet (25% freeze-dried grape powder) on bone in ovariectomized rats for 8 weeks.[39] Sprague-Dawley rats fed a grape-enriched diet had 44% greater net bone calcium retention, 3% greater cortical thickness, and 11% greater breaking strength than rats fed a control diet. This study suggested that a grape-

enriched diet bestows benefits to bone health and calcium metabolism, which may be highly beneficial in the postmenopausal state.

Reperfusion injuries play a crucial part in the brain's ischemic cascade, which is involved in stroke and brain trauma, as well as in brain failure following reversal of cardiac arrest. Wang and colleagues have shown protection by grape powder supplementation against neuronal damage due to global cerebral ischemia induced in the Mongolian gerbil via occlusion of the common carotid arteries, a model known to cause delayed neuronal death in the hippocampal CA1 area. This study suggested the efficacy of grape powder for protection against stroke and neurodegenerative damage.[40] In another study, using rabbits as a model, Lin and colleagues also found that dietary administration of grape powder provide significant protection against the hypoxic effects of ischemia and ischemia/reperfusion (I/R).[41]

From all these studies, it is clear that whole grape may be beneficial for several health-related issues.

## Evidence from clinical trials

Because of promising experimental data on the health-promoting effects of resveratrol and whole grape, a number of human clinical trials were conducted in the recent past. Some of these studies are discussed below.

In a recent study, Nguyen and colleagues evaluated the effects of either a low dose of plant-derived resveratrol formulation or a resveratrol-containing freeze-dried grape powder on Wnt signaling in colon cancer patients.[42] This study demonstrated significant inhibition in Wnt target gene expression in normal colonic mucosa, with no change in the cancer tissue.[42] The Wnt signaling pathway plays a critical role in many biological processes and its deregulation is known to occur in colon cancer. In this study, tissue biopsies were obtained from cancer tissue and normal colonic mucosa in same patients, before and after exposure to resveratrol/grape powder, and analyzed using a Wnt pathway–specific microarray and quantitative reverse transcriptase polymerase chain reaction (qRT-PCR) assays. The highest effect on Wnt target gene expression was realized following supplementation of 80 g of grape powder per day.[42]

The antioxidant potential of grapes and grape juice has been studied in several human trials, which have largely yielded positive results. Prior and colleagues have reported that consumption of standardized grape powder increases plasma antioxidant capacity.[43] In this study, blood samples were obtained before and 1, 2, and 4 h after a meal or meal plus freeze-dried grape powder (74.2 ± 13.9 g), for antioxidant analysis measured as oxygen radical absorbance capacity. The mixed grape meal produced an increase in the area under the curve (AUC) for hydrophilic antioxidant capacity.[43] In another study, Janiques and colleagues evaluated the effects of grape powder supplementation on inflammatory and antioxidant biomarkers in non-diabetic hemodialysis (HD) patients.[44] In this study, the patients receiving grape powder displayed an increase in GSH-Px activity and did not exhibit increased C-reactive protein levels, as seen in placebo group, suggesting that grape powder

could play a crucial role as an antioxidant and anti-inflammatory agent in non-diabetic HD patients.[44]

Herrington and colleagues evaluated the effect of muscadine grape seed supplementation on endothelial function and cardiovascular risk factors in subjects with increased cardiovascular risk.[45] In this double-blind, randomized crossover trial, there was no evidence that 4 weeks of daily supplementation with muscadine grape seed improved endothelial function measured by brachial flow-mediated dilatation (FMD). However, there was clear evidence that this supplement produced an increase in resting brachial diameter. This increase in resting diameter was not accompanied by a reduction in blood pressure or changes in other plasma markers of cardiovascular risk, including plasma lipids and C-reactive protein.[45] The findings of no effect on FMD was unexpected, in light of the antioxidant and other properties of the muscadine seed polyphenolics. It is possible that the whole muscadine grape could have better efficacy than seed-alone polyphenolics. Interestingly, in another study, Vaisman and Niv also examined blood pressure, FMD, and oxidative stress in subjects with prehypertension and mild hypertension. This study found that red grape cell powder consumption was associated with an improvement of FMD, endothelial function, diastolic blood pressure, and oxidative stress, without any adverse effects.[46]

In a recent study, Zunino and colleagues assessed the effects of dietary grapes on blood lipid profiles, plasma inflammatory marker concentrations, and immune cell function in a randomized, double-blind crossover study in 24 obese human subjects.[47] This study suggested that dietary grapes may induce beneficial alterations in potentially atherogenic lipid sub-fractions associated with an increased risk of obesity-related disease, such as cardiovascular diseases.[47] In this study, dietary grape powder supplementation (46 g grape powder in 240 mL of water, two times per day for 3 weeks, representing four servings of grapes/day) was found to (1) reduce plasma concentrations of large LDL cholesterol and large LDL particles, and (2) increase production of IL-1β and IL-6 in supernatants from lipopolysaccharide-activated peripheral blood mononuclear cells (PBMCs).[47]

In another study, Barona *et al.* evaluated the effects of grape consumption on inflammation and oxidation in metabolic syndrome–affected men: 11 men with high triglycerides and low HDL and 13 men with no dyslipidemia.[48] Grape consumption showed favorable responses by increasing IL-10 and adiponectin, two anti-inflammatory cytokines, in non-dyslipidemic subjects. In addition, iNOS expression was higher in PBMCs from non-dyslipidemic individuals.[48] Why grape consumption did not provide benefits to men with dyslipidemia may be the subject of future research. In a separate study, Barona *et al*. also demonstrated that daily consumption of grape powder for 30 days significantly potentiated vasorelaxation, decreased circulating cell adhesion molecules, and reduced blood pressure, resulting in improved vascular function in men with metabolic syndrome.[49] In another recent study, Zern and colleagues found that grape powder supplementation (36 g daily for 4 weeks) resulted in an improvement in plasma lipids, inflammatory cytokines, and oxidative stress in 24 pre- and 20 postmenopausal women, suggesting possible beneficial effects for coronary heart disease in women.[50]

Although all of the studies described above showed promising health-beneficial effects of whole-grape products, in a few studies grape powder was not found to be ineffective for specific marker or disease conditions. For example, Allen *et al*. recently investigated the role of freeze-dried grapes (94 g/day for 6 weeks) as a potential aromatase inhibitor by testing of plasma hormone levels in 18 postmenopausal women, and found no change in plasma hormone levels.[51] Aromatase inhibitors are potentially considered for the treatment of breast and ovarian cancers in postmenopausal women as well as for gynecomastia, a condition where male breasts overdevelop.

## Safety of grape products: whole grape versus supplements and proprietary products

Grapes are one of the 20 most frequently consumed raw fruits. Generally, there are no or extremely limited safety issues regarding the consumption of raw fruit. Similarly, the safety issues are always minimal in whole-food products. Many studies have been conducted with grape-derived ingredients in regard to several health claims, antioxidant activity, and so forth; and they have been found to be safe. However, caution must be taken with supplements, as the products are often altered during manufacturing. Similarly, one must be careful regarding the use and consumption of proprietary products. For example, a proprietary formulation of resveratrol, SRT501 (synthesized by Sirtris), has been studied in several healthy and disease populations, and shown to be safe. However, when supplemented at a daily dose of 5 g, alone or in combination with bortezomib, SRT501 exhibited renal toxicity in multiple myeloma patients;[52] this was later suggested to be specifically attributable to the disease condition. Detailed safety analysis for grape products for subjects with specific conditions must be performed, especially for higher doses.

## Conclusions

Onset of any disease is not an abrupt transition; instead, multi-step processes are known to be involved in disease pathogenesis. Grape polyphenols seem to work effectively at different stages of the progression of several diseases. However, for the prevention of diseases, the dietary grape seems to be the best-case scenario. In addition, whole grape seems to be more advantageous, owing to the possibility of synergistic interactions among multiple ingredients leading to enhanced bioactivity and bioavailability. As detailed in Tables 1 and 2, studies conducted with whole-grape products have largely yielded beneficial results and suggested that they can modulate a number of factors that are associated with several health benefits. The famous quote of Hippocrates, the renowned Greek physician, “Let food be thy medicine,” seems to be valid, as the whole-grape products increasingly show promising results in the management of several disease conditions. However, for advanced disease conditions, individual grape ingredients (such as resveratrol) or the combination of multiple ingredients together with existing therapies appears to be a better approach.

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## Table 1

*In vivo* studies to assess the effect of grape powder in different diseases

| Grape formulation and dosages | Model system | Outcome of the study | References |
|---|---|---|---|
| Grape powder (1, 2, or 5%) in AIN-93G diets beginning 2nd week before the first dose of DMBA for up to 12 weeks | SENCAR mice treated with DMBA (N = 30/group) | Grape powder was found to exert antitumor effects against DMBA-induced skin tumorigenesis, which was associated with reduced levels of 8-OH-dG (oxidative DNA damage), Ha-ras mutations (antitumor initiation potential), and COX-2 expression (antitumor promotion potential). | 28 |
| Grape powder (15 g/L) in tap water for 3 weeks | Sprague-Dawley rats (N = 10/group) | Grape powder attenuated L-buthionine-(*S*,*R*)-sulfoximine–induced anxiety-like behavior, memory impairment, and high blood pressure. | 29 |
| Grape powder (15 g/L) in tap water for 3 weeks | Ovariectomized Wistar rats (N = 10/group) | Grape powder treatment improved anxiety-like behavior and learning memory function, restored systolic and diastolic blood pressure, and reduced the level of oxidative stress. | 30 |
| Grape powder (15 g/L) in tap water for 3 weeks followed by SPS. | Male Sprague Dawley rats (N = 10/group) | Grape powder prevented SPS-induced behavioral, cognitive, and biochemical impairments in rats. | 31 |
| Grape powder (3.0% wt/wt) in AIN-76A diet for 18 weeks | Male Dahl-Rapp salt-sensitive rats (N = 12/group) | Grape powder–enriched diets reduced hypertension-associated cardiac pathology and diastolic dysfunction. | 32 |
| Grape powder (600 mg/day by gavage for 10 weeks | Male SHR and Wistar-Kyoto rats (N = 8/group) | Grape powder reduced blood pressure, improved vascular function and compliance, and attenuated cardiac hypertrophy in spontaneously hypertensive rats (SHR). | 34 |
| Grape powder (20 mg/mL) in drinking water for 24 days | Female C57BL/6J (N = 5/group) | Grape powder reduced the extent of choroidal neovascularization (CNV). | 35 |
| Grape powder (3.0%) in high-fat diet for 18 weeks | C57BL/6J obese mice (N = 10/group) | Grape powder improved glucose tolerance at 5 weeks and decreased markers of inflammation in serum and adipose tissue at 18 weeks. | 36 |
| Grape powder (1.0%) in NIH-31 diet for ~ 20 weeks | Non-obese diabetic mice (N = 15/group) | Grape powder inhibited the onset and pathogenesis of autoimmune diabetes. | 37 |
| Grape powder (30 mg) daily for 10 weeks | Apolipoprotein E–deficient (E0) mice (N = 10/group) | Grape powder attenuated atherosclerosis development and reduced macrophage atherogenicity. | 38 |
| AIN93M diet with 25% freeze-dried grape powder or control diet for 8 weeks. | Ovariectomized Sprague-Dawley rats (N = 22/group) | Grape powder was suggested to improve calcium utilization and suppress bone turnover, resulting in improvements in bone quality | 39 |
| Grape powder (5 or 50 g/kg diet) for 2 months | Mongolian gerbils (N = 11/group) | Grape powder protected against neuronal damage due to cerebral ischemia. | 40 |
| Treated by gavage with 10 mL suspension of grape powder (40 mg/mL) | Male New Zealand White rabbits (N = 4/group) | Grape powder was found to protect the bladder from ischemia/reperfusion (I/R), which is a causal factor in obstructive bladder dysfunction. | 41 |

DMBA, 7,12-dimethylbenz(a)anthracene; SPS, single-prolonged stress

## Table 2

Clinical trials to assess the effect of grape powder in different diseases

| Grape formulation and dosages | Model/disease condition | Outcome of the study | References |
|---|---|---|---|
| Grape powder (80 or 120 g/day) or resveratrol (20 or 80 mg/day) for 14 days | Colon cancer (N = 8) | Grape powder inhibited the expression of a panel of Wnt target genes in normal colonic mucosa. | 42 |
| Grape powder (74.2 g) was given on two occasions separated by 2 weeks | Oxidative stress (N = 8) | Consumption of grape powder with meal was found to increase the levels of hydrophilic antioxidant capacity. | 43 |
| Grape powder (500 mg of polyphenols/day) or placebo for 5 weeks. | Inflammatory and antioxidant markers in HD patients (N = 16) | Grape powder consumption increased the activity of GSH-Px and reduced the inflammation progression in hemodialysis (HD) patients. | 44 |
| Muscadine grape seed (1300 mg or placebo) daily for 4 weeks, with a 4 week washout. | Subjects with coronary disease or ≥ 1 cardiac risk factor (N = 50) | Muscadine grape seed supplementation increased baseline diameter (mm) without improved flow-mediated dilatation (FMD). | 45 |
| Red grape cell powder (RGC) (200 or 400 mg or placebo) daily for 12 weeks. | Subjects with prehypertension and mild hypertension (N = 50) | RGC consumption was associated with an improvement of FMD (indicating endothelial function), decrease in lipid peroxidation and diastolic blood pressure without any adverse effects. | 46 |
| Grape powder (46 g) or placebo two time a day for 3 weeks | Obese subjects with BMI = 30–45 $kg/m^2$) (N = 24) | Grape powder increased IL-1β and IL-6 production, and reduced plasma concentrations of large LDL and large LDL- cholesterol particles in obese humans. | 47 |
| Grape powder (46 g/day) for 4 weeks | Men with metabolic syndrome (N = 24) | Grape consumption displayed anti-oxidative markers and increased anti-inflammatory markers in the absence of the inflammatory milieu associated with dyslipidemias. | 48 |
| Grape powder (46 g/day) for 30 days | Men with metabolic syndrome (N = 24) | Grape supplementation improved vascular endothelial function and biomarkers of metabolic syndrome by increasing FMD, and decreasing systolic blood pressure and circulating inflammatory molecules. | 49 |
| Grape powder (36 g) or a placebo for 4 weeks | 24 pre- and 20 postmenopausal women | Grape supplementation demonstrated a cardioprotective effect in pre- and postmenopausal women by lowering oxidative stress and plasma lipid levels. | 50 |
| Grape powder (94 g/day) for 6 weeks | Postmenopausal women (N = 18) | No significant changes were noticed in plasma hormone levels. | 51 |