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Review Article

# Why Consumption of Black Corinth Raisin (*Vitis vinifera* L.) is Continuously Recommended? A Review

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ABSTRACT

In traditional Iranian medicine as well as the hadiths of the Imams about nutrition, there are important points that are needed to be considered. Dietary recommendations for the consumption of Black Corinth Raisin (*Vitis vinifera* L.) in Islamic religious books and the low probability of distortion in such hadiths on the other hand, can have high scientific support to ensure the physiological health of individuals. Emphasis has been undertaken on continuous eating of the fruits/nuts in these books to prevent the forgetfulness, enhance the memory and happiness, and improve physical health. This review has investigated the published studies in details on properties of red/black grape regarding the mentioned issues.

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## Introduction

Grapes are fruits with high diversity in the world and each part of their constituents including skin, flesh, and seeds have specific compounds that can impact human health. Polyphenols are important compounds and the main ingredient in the composition of these fruits. Nowadays, these compounds are considered as golden factors used to prevent and even cure many diseases, based on the wide contents of free radicals and oxidants (1, 2). Anthocyanins and flavan-3-ols are the main polyphenols in the red and white grape, respectively; while white grapes contain less total polyphenols than the red ones. Grape skins and seeds are also a major dietary source of flavonoids, with significant amount of proanthocyanidins that are seen in the seeds (3). Dried form of grape (raisin) is a condition that can be kept for a relatively long time without any preservatives. This allows the fruit to be fed continuously throughout the year as a nutritional supplement. Due to frequent dietary recommendations in Hadiths for eating the grape, especially Black Corinth raisin (Zante Currant) to create physical and mental health, especially to prevent memory loss and enhance the happiness (4-6), we decided to review the some suggested beneficial properties of this type of grape.

**Table 1:** Ripe red grape berry and phenolic distribution patterns in several tissues.

| | Skin | Flesh | Seeds |
|---|---|---|---|
| Flavan-3-ols | Catechin, Epicatechin, Epigallocatechin, Proanthocyanidins | Catechin, Epicatechin, Epigallocatechin | Catechin, Epicatechin, Gallocatechin, Epigallocatechin, Catechin-3-*O*-Gallate, Proanthocyanidins |
| Anthocyanins | (Petunidin, Cyaniding, Peonidin, Malvidin, Delphinidin, Pelargonidin) | | |
| Stilbenes | Resveratrol, Viniferins | | Resveratrol, Viniferins |
| Flavonols | Quercetin, Kaempferol, Myricetin | | |
| Hydroxybenzoic acids | Gallic, Gentisic, Salicylic acid | | Gentisic, Salicylic acid |
| Hydroxycinnamic acids | *P*-Coumaric, Caffeic, Ferulic | *P*-Coumaric, Caffeic, Ferulic | *P*-Coumaric, Caffeic, Ferulic |

*Grape Composition*

A large variety of grapes are found in nature with relatively similar compounds such as anthocyanin in the skin of its berry (Table 1) and various color types (red-black) for nutrition and preparation of beverages. Sultana (Sultani) or Shahani type is one of these categories which is in reddish-black color (Seeded or seedless, Figure 1) and after drying, it is named "Maviz" (in Persian), *Zabibata hamra* (in Arabia), while Black Corinth raisin (*Vitis vinifera*) is called as Zante Currant (in Latin). Generally, phenolic compounds of the grape are divided into flavonoid compounds (flavonols, flavan-3-ols, anthocyanins, flavones and flavanones) and non-flavonoids (such as hydroxycinnamic acids, hydroxybenzoic acids, stilbenes and volatile phenols) (7, 8).

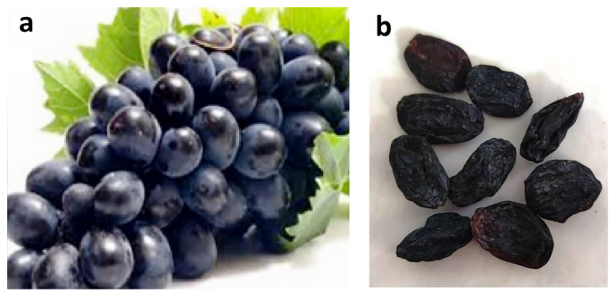


**Figure 1:** a) Ripe Shahani grape, b) dried form of Shahani grape (raisin).

*Grape and Memory Improvement*

Anthocyanins (of the Greek *anthos*=flower and *kianos*=blue) are polyphenols and a subgroup of flavonoids, which give these plants their distinctive colors. The other flavonoids are present in both the skin and the seeds of the grape. Chemotaxonomic parameter for the categorization of red *V. vinifera* varieties is proposed as the anthocyanin profile (9, 10). Many studies have been carried out about the protective effect of anthocyanins to impact the memory and learning impairment (11-13); while the compound in black rice can improve the memory and learning and can also diminish the amount of lipid peroxidation damage to the brain in cerebral-ischemic mice model (14).

Evidences revealed that anthocyanins, flavanols and/or flavanones possess the highest impact on the cognitive procedures, so that the flavonols can have a remarkable effect in blocking oxidant-induced neuronal injury by modulating PI3 kinase/Akt and mitogen-activated protein kinase signaling (15, 16). This suggests the ability of fruits to affect cognition that seems to be related to the flavonoid content in protecting neurons from damages induced by neuroinflammation and neurotoxins, a potential to improve cerebrovascular blood flow and to activate synaptic signaling. This protection seems to be related to the interaction of these compounds and their metabolites with cellular signaling cascades in central nervous system (CNS) and peripheral nervous system (PNS), with inhibiting the apoptosis, which started by toxins and finally enhancing the survival of neural cells. Morphological changes are achieved through interaction of the flavonoids with neuronal signaling, as a result of cognitive alterations associated with long term intake of fruit flavonoids (17).

Varadinova *et al.* revealed that anthocyanins improve learning and memory in ovariectomized rat model with estrogen deficit. They showed that anthocyanins from red grapes exhibited learning- and memory-boosting effects in an estrogen deficit condition (11). In another study by Yong-Na Zhao *et al.* (18) on resveratrol (3,4',5-trihydroxy-trans-stilbene) (RSV), as a natural non-flavonoid polyphenol antioxidant extracted from red grapes, they demonstrated another subject improved learning and memory in 8-9 month-old mice through microRNA cAMP-response-element-binding-brain-derived neurotrophic factor (CREB-BDNF) pathway. Asha Devi *et al.* reported the possibility of using the grape seed polyphenolic extract (GSPE) in reducing oxidative stress-related lipofuscinogenesis with age in the hippocampus (19). They demonstrated that GSPE supplementation can improve reduction of blood glucose and cognitive ability in the middle-aged rats. Given that aging is followed by oxidative stress-related protein and lipid oxidations which lead to the increase of lipofuscinogenesis in the neurons of hippocampus; therefore, decline memory ability and learning. In a study on immature rats with traumatic brain injury, the neuroprotective effect of RSV was investigated. It increased cortex/hippocampus dependent memory and decreased anxiety of animals subjected to blunt head trauma (18).

### *Antidepressant Effects of Grape*

In an animal model of depression study by Laura *et al.*, they showed that RSV has antidepressant-like effect probably through activation of hippocampal brain-derived neurotrophic factor (BDNF) (20). Results of one study showed an increase in biogenic amines in the hippocampus and the cortex due to the treatment of higher doses of RSV in mice (21). :It was shown that RSV can reduce depressive-like symptoms induced by stress in rats (22) . In another animal model study by Rania et al. a high intake of RSV by depression induced- rats, with reserpine, antidepressant-like results were illustrated in comparison with fluoxetine (23). This study revealed that the induced decrease of the dopamine, serotonin, and norepinephrine levels, increased to the normal range after the administration of trans-RSV. A recent research also indicated that trans-RSV can inhibit monoamine oxidase (MAO) activity (21).

Due to the role of inflammation in the creation of depression, anti-inflammatory compounds may be useful in this field. It has been proven that RSV can have anti-inflammatory effects (24-26). This property can be related to the RSV effects including inhibition of production of nuclear factor kB (NF-kB), histamines, proteases and cytokines by microglial, mast cells, neutrophils and macrophages (27-29). In a study by Solanki *et al.*, they reported that antioxidant rich grape powder (GP) prevents single prolonged stress (SPS)-induced behavioral, as an excellent rodent model of posttraumatic stress disorder which mimics clinical symptoms such as depression, anxiety, cognitive and memory impairment in Male Sprague Dawley rats and also increase the plasma corticosterone level (30). Moreover, BDNF levels significantly decreased in amygdala of SPS rats, but not in GP-SPS rats when compared to the controls.

### *Grape and Alzheimer Disease*

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by progressive impairments in memory and cognition. One of the important risk factors for the start and progression of declined cognition in AD is aggregation of soluble extracellular high molecular weight (HMW) oligomeric amyloid β species in the brain (31, 32). Therefore, the inhibition of this accumulation might result in ameliorated cognitive function in the disease. Marambaud *et al.* reported that RSV could reduce amyloid β by elevating its intracellular degradation *in vitro* (33). Wang *et al.* found that a naturally derived GSPE can significantly prevent amyloid β accumulation into HMW oligomers *in vitro*. Orally administration of GSPE to Tg2576 mice was shown to decline HMW soluble oligomeric amyloid β coincidentally with attenuated AD-type cognitive deterioration in the brain (34).

In an another similar animal model study, researchers exhibited that long-term feeding of grape seed extract (GSE) diet was well tolerated without behavioral abnormality, changes in body weight, food consumption, and liver function or fatality (35). The amyloid β levels in the serum and brain of the mice fed with GSE decreased by 44% and 33%, respectively, when compared with the control group. GSPEs are able to inhibit amyloid β aggregation, reduce its production and protect against an *in vitro* neurotoxicity. Microgliosis and amyloid plaques also reduced by 70% and 49%, respectively, in the brain of mice with AD fed with GSE.

The other particular mark of AD and some neurodegenerative diseases is accumulation of microtubule-associated protein tau into insoluble intracellular neurofibrillary tangles. Abnormal hyperphosphorylation of tau in AD and its aberrant phosphorylation are neuropathic agents of the diseases (36-38). Therefore, anti-phosphorylation and anti-aggregation can be the main pathways for tau-based therapy. In a study by Wang *et al.*, they observed that the assembly of tau peptides into neurotoxic aggregates could be potently interfered by the selected GSPE (39). They identified that development of AD type tau related neuropathy was attenuated by intake of GSPE via TMHT mice. It was shown that taupathy can be improved by GSPE via two probably mechanisms of (i) attenuating extracellular signal-regulated kinases 1 and 2 (ERK1/2) mediated phosphorylation of tau at Thr181 and Ser396/400/404, and (ii) interfering with tau fibrillization (40).

### *Red Grape and Its Phytochemicals Roles/Effects in the Prevention of Diabetes*

High production/exposure to the reactive oxygen species (ROS) and the decrease in antioxidant capacity are the major issues in impaired hemostasis in diabetes mellitus (41). The results of a study revealed that oral administration of 50 and 100 mg kg−1 (body weight of adult male Wistar rats) of natural grape seed proanthocyanidins (GSP), as potent free radical scavengers for 72 h could remarkably enhance the pancreatic glutathione levels and protect the increase in lipid peroxidation. Also, it caused significant decrease in the hyperglycemia induced by alloxan (42). Oral administration of GSE (100 mg/kg/day) decreased the levels of carbonylated proteins and lipid peroxides and enhanced the antioxidant activity in hepatic tissue and plasma in rats treated with GSE in comparison with the diabetic control rats. These results suggested that the GSE improved the antioxidant defense against ROS produced under hyperglycemic states; therefore, protected the hepatic tissue and was associated with decreased glucose concentrations in diabetic rats (43). Postprandial hyperglycemia is one of primary anti-diabetic targets; hence the inhibition of alpha-glucosidase, the key enzyme for oligosaccharide digestion and further glucose absorption, can be effective in treatment of the state (44). In an animal study by Hogan *et al.* on male 6-week old C57BLKS/6NCr mice, the oral administration of the grape pomace extract (400 mg/kg body weight) significantly prevented the postprandial hyperglycemia by 35% in diabetic animals after starch challenge (45). They also revealed that the anti-postprandial hyperglycemic and antioxidant activities, especially in red grape pomace (Cabernet Franc, RGPE) in comparison with white type (Chardonnay, WGPE), suggested a potential to employ grape pomace in management of diabetes. Van Dam RM and Colleagues demonstrated that intake of flavan-3-ols and anthocyanidins may reduce the risk of type 2 diabetes (T2DM) (46). Also, same results were achieved in another study in terms of anthocyanins effects on prevention of T red grape and its phytochemicals roles in prevention of T2DM development (47). In addition, a meta-analysis by Liu *et al.* suggesting that the consumption of total flavonoids is associated with a lower risk for diabetes (48). Therefore, the polyphenolic compounds found in abundance in grape composition, especially red-black ones can be used as a diet to prevent diabetes.

### *Grape and Cardiovascular Health*

One of the leading causes of death in emerging economies, as well as in many economically developed nations, is cardiovascular diseases (CVDs). Given that nitric oxide is an important factor which is used by endothelium of blood vessels to signal the surrounding smooth muscle to relax and for vasodilation; dietary compounds can stimulate the production of this factor and can be a turning point in prevention of CVDs. Some *in vivo* studies demonstrated that grape polyphenols, especially in red ones, can influence on endothelial nitric oxide production and potentially improve the vascular function (3, 49). In a clinical trial, the intake of grape juice led to a significant decrease in systolic and diastolic blood pressure which happened in hypertensive or coronary artery disease subjects (50). Development of CVDs due to the increase in the plasma low-density lipoprotein cholesterol (LDL-c) has been well established (51). Oxidation of these lipoproteins is a critical stage in development of atherosclerosis, while an increasing serum antioxidant capacity can be protective. Endothelial cells are stimulated by oxidized LDLs and produce the chemokines to exert chemotactic functions for monocytes as shown in Figure 2. Oxidized LDLs is trapped by monocytes/macrophages through scavenger receptors, and they finally are converted

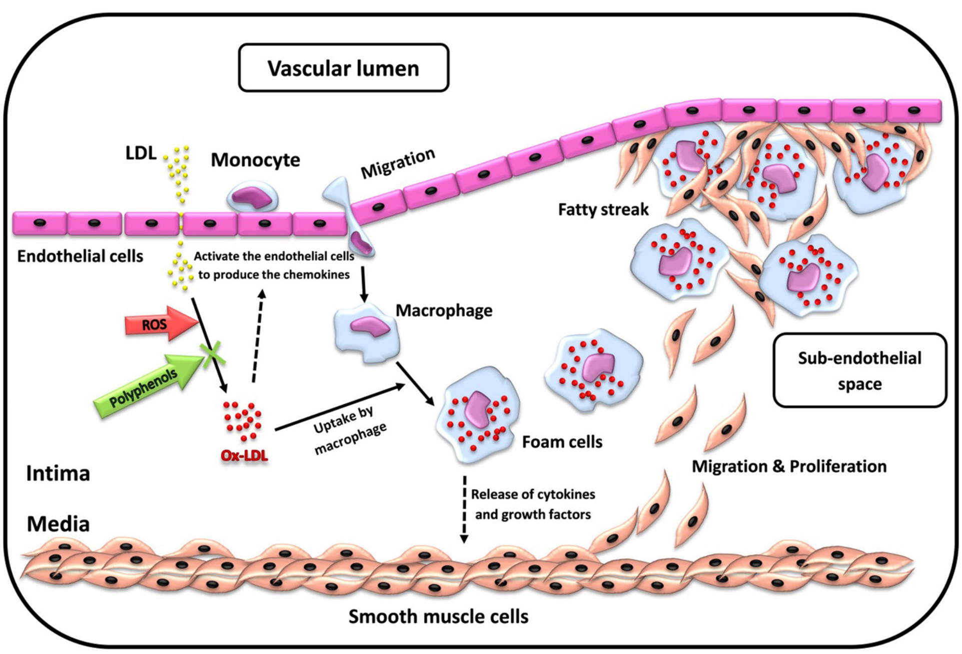


**Figure 2:** The effect of antioxidant behavior of polyphenols (in grapes especially red ones) in preventing atherosclerosis by inhibiting the oxidation of lipoproteins.

into foam cells (52). Accumulation of the foam cells in fatty streaks is a major trigger of atherosclerosis, which can be an indicator of atherosclerotic lesions in the aorta. Thus, this oxidation has been known as a major event in atherosclerosis; therefore, the risk of atherosclerosis can be reduced by consumption of dietary supplementation rich in polyphenols such as grape especially the red one (8).

### *Grape and Cancer*

Study results showed that the growth of estrogen receptor (ER)-positive MCF-7 cells can be inhibited by resveratrol, as a natural phytoalexin compound found in grapes, in a dose-dependent manner. This polyphenol antagonize the growth promoting effect of 17-β-estradiol (E2) at both the molecular and cellular levels (53). In a study by Engelbrecht *et al.*, the antiproliferative/chemopreventative properties of grape seed proanthocyanidin extract against CaCo2 colon cancer cell line were evaluated (54). Cell viability was inhibited, as well as apoptosis that increased significantly by the extract in colon cancer cells; but no significant toxic effect was noticed on normal colon cell line (NCM460). One of the main causes in increasing the apoptosis in this study was the decrease in protein kinase B (PKB) Ser473 phosphorylation and the attenuation of PI3-kinase (p110 and p85). The other effect of the extract was the suppression of the important phosphatidyl-inositide 3 (PI3)-kinase survival-related pathway. Grape skin polyphenols were able to inhibit the viability and migration in a dose-dependent manner in 4T1 mammary carcinoma cells. Blocking the PI3k/Akt and MAPK pathways was considered as the cause of inhibition of migration (55). In a study by Rashedi *et al.* (56) about quercetin as one of the flavonoids in grape skin on induced adenocarcinoma by dimethylhydrazine (DMH) in Wistar rats colons, quercetin could exert pro-apoptotic, anti-proliferative and anti-angiogenic effects with no toxic impact on healthy control tissues.

## Conclusion

In summary, the consumption of seeded grapes, especially the red/black and dried form, for long-term throughout the year, can be beneficial in terms of general health, in particular it can prevent the Amyloid-beta accumulation in the brain (in Alzheimer's disease), enhance the survival of neural cells to improve the memory, stimulate the apoptotic pathway as well as inhibition of proliferation in cancer cells. It also has an antioxidant behavior to prevent cardiovascular diseases as well as diabetes mellitus. By inhibiting the activity of monoamine oxidase, it increases plasma levels of the serotonin in the body and ultimately acts as an antidepressant.

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## Conflict of Interest

None declared.

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