

# A Concise Review: Antioxidant Effects and Bioactive Constituents of Grape

## Üzümün Biyoaktif Bileşenleri ve Antioksidan Etkileriyle İlgili Kısa Bir Derleme

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### Abstract

Grape (*Vitis Vinifera*), one of the most widely consumed fruit worldwide, contain many bioactive constituents including flavonoids, polyphenols, anthocyanins and stilbene derivatives resveratrol. Scientific studies have shown that grape extracts especially grape seed and skin have biological and therapeutic effects such as antioxidative, anticarcinogenic, antimicrobial, antiviral, antiaging, antiinflammatory, antidiabetic activities as well as having cardioprotective, hepatoprotective and neuroprotective effects. These results confirm that grapes widely accepted as beneficial for human health to treat and prevent from diseases. This review focuses on the bioactive components and antioxidative effects of grape.

Key words: **Antioxidants; free radicals; Vitis Vinifera.**

### Özet

Bütün dünyada yaygın olarak en çok tüketilen meyvelerden biri olan üzüm (*Vitis Vinifera*), flavanoidler, polifenoller, antosiyaninler ve stilben derivesi rezveratrol gibi pekçok biyoaktif bileşeni içermektedir. Özellikle üzüm çekirdeği ve kabuğu gibi üzüm özütlerinin kardioprotektif, hepatoprotektif, nöroprotektif etkilerinin yanısıra antioksidan, antikarsinojenik, antimikrobiyal, antiviral, antiaging, antiinflamatuvar, antidiyabetik aktivitelerinin olduğu yapılan bilimsel çalışmalar ile gösterilmiştir. Bulgular hastalıklardan korunmada ve tedavide üzümün insan sağlığı için faydalı olduğunu doğrulamaktadır. Bu derlemede üzüm ve biyoaktif bileşenlerinin antioksidan etkilerine odaklanılmıştır.

Anahtar Kelimeler: **Antioksidanlar; Serbest Radikaller; Üzüm meyvesi.**

Submitted : October 22, 2009  
Accepted : October 26, 2009

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## Introduction

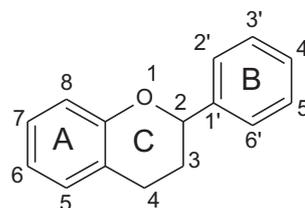
Resulting from increased production of free radicals, oxidative stress plays a key role in the pathogenesis of certain human diseases including atherosclerosis, ischemia and reperfusion injury of many organs, diabetes, neurodegenerative disorders, arthritis, gastrointestinal dysfunctions, AIDS, aging, tumor promotion and carcinogenesis (1–3). Biological oxidative stress of free radicals is controlled by endogenous antioxidants including the scavenger enzymes superoxide dismutase (SOD), glutathione peroxidase (GSH-Px) and catalase (CAT) and by exogenous dietary antioxidants vitamin E, C, carotenoids and flavonoids (4, 5). Briefly, antioxidants are potent scavengers of free radicals and serve as inhibitors of neoplastic processes.

The grape, having many established nutritional and medicinal properties for consumers, is a highly potent antioxidant and recognized for its wide spectrum of biological properties (6). Generally, the seeds and leaves of grapevine are used in herbal medicine and its fruits are consumed as a dietary supplement (7). In this review several scientific studies about antioxidant effects of grape and its bioactive constituents are described.

## Grape Composition

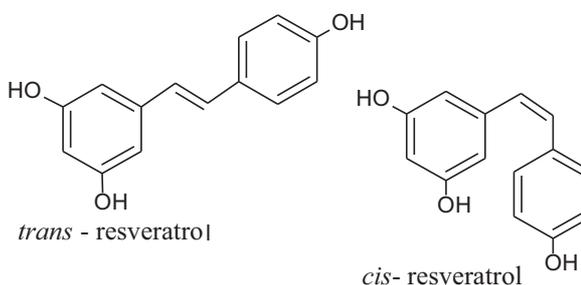
The principle components of grape are water, sugar and acids. It is a good source of water (81–87%), carbohydrates (12–18%), proteins (0.5–0.6%), and fat (0.3–0.4%). Additionally, the grape contains significant amounts of potassium (0.1–0.2%), vitamin C (0.01–0.02%), and vitamin A (0.001–0.0015%) and also has a little amount of calcium (0.01–0.02%) and phosphorus (0.08–0.01%) (8). Grapes are also a major source of other nutrients like boron (9), a possible substance for bone health. Nutritional analysis per serving with 100 g grape gives ~78 calories of energy, ~0.5 g of protein, ~19 g of carbohydrate, ~0.3 g of fat (3% calories from fat), ~0.18 mg of sodium, ~155 mg of potassium, 0.4 g of fiber, 13 mg of calcium, 9 mg of phosphorus, and 10 mg of vitamin C (8).

Grapes are rich in polyphenols (10) and polyphenolic substances in grape and products are usually divided into two groups: flavonoids and non-flavonoids. The flavonoids have a common core, the flavan nucleus, consisting of two benzene rings (A and B) linked by oxygen containing pyrane ring (C) (Figure 1).



**Figure 1.** Structure of flavonoid.

The most common flavonoids are (i) flavonols including kaempferol, quercetin and myricetin; (ii) flavan-3-ols including highly polymerized oligomers of monomeric (+)-catechins, (–)-epicatechins, (–)-epicatechin-3-O-gallate and dimeric, trimeric and tetrameric procyanidins and (iii) anthocyanins (11, 12, 13). The non-flavonoids, phenols with only one aromatic ring, are derivatives of hydroxycinnamic acid (caffeic acid, *p*-coumaric acid) and of hydroxybenzoic acid (gallic acid). Another class of non-flavonoids are stilbene and stilbene glycosides, with *trans*-resveratrol (*trans*-3,4',5-trihydroxystilbene) as its most well known representative (14). Their essential structure skeleton comprises two aromatic rings joined by a methylene bridge (Figure 2).

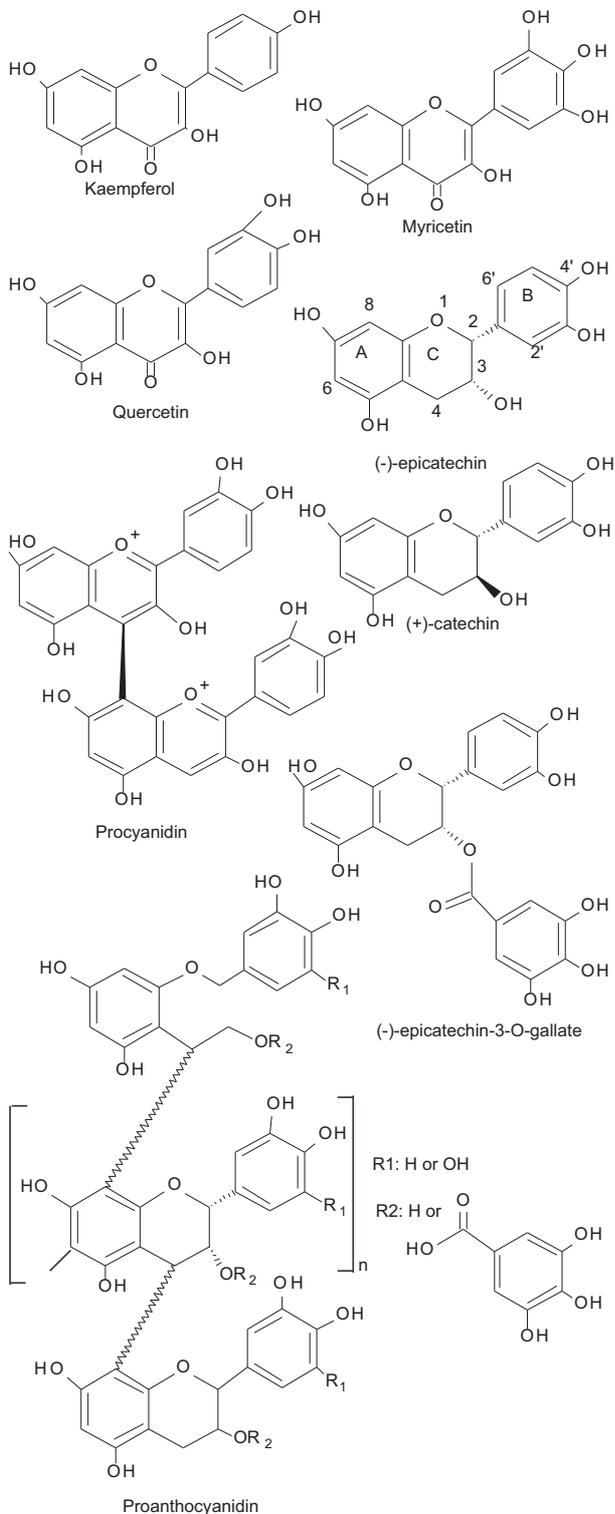


**Figure 2.** *Trans*-resveratrol and *cis*-resveratrol.

The total extractable phenolics in grape are present at only 10% or less in pulp, 60–70% in the seeds and 28–35% in the skin. The phenol content of seeds may range from 5% to 8% by weight (11, 15) and grape seeds are rich sources of proanthocyanidins (90%) (15). The chemical structures of some important biologically active grape derived constituents are given in Figure 3.

## Antioxidant Effects of Grape

Grape phenolics, including flavonoids and related polyphenols from grape, grape fruit and grape seeds have generated remarkable interest based on positive reports of their antioxidant properties and ability to serve as free radical scavengers. The specific mode of inhibition of oxidation is not clear, but they may act by scavenging



**Figure 3.** Chemical structures of some important biologically active compounds from grapes.

lipid alkoxyl and peroxy radicals by acting as chain-breaking antioxidants, e.g. as hydrogen donors and chelating metal ions, the appropriate structural features provided (16).

The antioxidant activity of grape seed polyphenols is superior to other well-known antioxidants, such as vitamin C, vitamin E and  $\beta$ -carotene. Some clinical studies have confirmed that grape seed procyanidins and proanthocyanidins are 20 times more potent than vitamin C and 50 times more potent than vitamin E as antioxidant (17).

Free radicals generated during oxidative stress have many cellular targets, but one of the primary targets is cellular lipids. Lipid peroxidation of polyunsaturated fatty acid (PUFA) results in formation of alkoxyl and peroxy radicals (primary products) that are highly reactive and relatively short-lived. Secondary products of lipid peroxidation include numerous aldehydes, including malondialdehyde (18). Cardiovascular diseases are associated with modifications in fatty acid metabolism and excessive lipid peroxidation of LDL. These oxidation products are also implicated in the formation of thromboxane, which leads first to enhance platelet aggregation, then to artery blockage, and finally to thrombosis (19). The accumulation of lipid oxidation products from LDL can be attributed to the low levels of plasma antioxidants. Grape seed polyphenols reduce the risk of heart disease by inhibiting the oxidation of LDL. A study by Bouhamidi et al (20) shown that PUFA peroxidation was inhibited by low concentrations of grape seed proanthocyanidins (2mg/1). Short-term ingestion of purple grape juice decreased LDL susceptibility to oxidation in coronary artery disease patients (21) and in hypercholesteremic human subjects supplemented with grape seed proanthocyanidin extract (22, 23).

Procyanidin supplementation in rat and rabbit reduced ischemia/reperfusion damage in the heart and this was associated with an increase in plasma antioxidant activity (24). Another study demonstrated that oral administration of grape skin extract significantly reduced systolic, mean, and diastolic arterial pressure in a hypertensive rat model (25).

Procyanidin B4, catechin, and gallic acid at low concentrations (10  $\mu$ mol/1, 25  $\mu$ mol/1) were reported to be good cellular preventive agents against DNA oxidative damage. However, these compounds may induce cellular DNA damage at higher concentrations (150  $\mu$ mol/1) (26).

Similarly, grape seed demonstrated significant protective ability against oxidative damage in leukocytes (27).

Grape seed extract (50 mg/kg) reduced the incidence of free-radical-induced lipid peroxidation in the central nervous system of aged rats and reduced hypoxic ischemic injury in neonatal rat brain (28). In another study, the extract (100 mg/kg, 30 days) was able to inhibit the accumulation of age related oxidative DNA damage in the spinal cord and in various brain regions (29). The administration of grape seed extract (100 mg/kg, 30 days) to aged rats increased memory performance and reduced reactive oxygen species (ROS) production, which may be related to enhancement of the antioxidant status in the central nervous system (30). Proanthocyanidin intake (75 mg/kg, 9 weeks) was effective at up-regulating the antioxidant defense mechanism by attenuating lipid peroxidation and protein oxidation in the adult rat brain (31).

The administration of grape seed extract, which contains 38.5% procyanidins, prevented the progression of cataract formation by their antioxidative action in hereditary cataractous rats (32).

In recent years there is an increasing evidence of the cancer chemopreventive properties of antioxidants such as catechins and procyanidins (33). Although antioxidants may play a role in the primary prevention of cancer in part by reducing the oxidative modification of DNA (34), the same action might be expected to be counter productive against radiation therapy and chemotherapeutic agents that act solely via the production of ROS and induction of apoptosis (35). Chemotherapeutic agents including the anthracyclines, most alkylating agents, platinum-coordination complexes, epipodophyllotoxins, and camptothecins are known to generate a high level of oxidative stress in biological systems (36). Preclinical studies involving the use of in vitro systems and animal models support the contention that the administration of antioxidants during cancer chemotherapy affects antineoplastic efficacy or the development of side effects. Oxidative stress induced by low levels of hydrogen peroxide has been shown to elevate the LD<sub>50</sub> of several types of antineoplastic agents and to block drug-induced apoptosis in neoplastic cells, causing cells to undergo necrosis instead of apoptosis (37,38). These effects of hydrogen peroxide are prevented by the addition of certain antioxidants. The reduced cytotoxicity of anticancer agents in the presence of hydrogen peroxide, an effect that might

also occur during chemotherapy-induced oxidative stress, may result from the effects of the cellular products generated by ROS. In addition, several studies (39, 40) have provided evidence that antioxidants can decrease the adverse effects of radiation therapy. Similarly, in our studies grape seed proanthocyanidins resulted in highly effective protection against methotrexate and radiotherapy induced injury by increasing antioxidant enzyme activities in rat liver tissues (41, 42).

Recently, pretreatment of resveratrol (10 mg/kg/day p.o.), mostly found in grape seed and skin, prevented oxidative damages and resulted in a reduction of the hazardous effects of ionizing radiation (800 cGy whole-body) on rat liver and ileum tissues (43). Resveratrol reduces the generation of H<sub>2</sub>O<sub>2</sub> and normalizes the levels of oxidized glutathione reductase and myeloperoxidase (MPO) activities. By normalization of the ROS levels, resveratrol limits the oxidative stress, which inhibits nitric oxide (NO) synthesis by NO synthase necessary for vasorelaxation. Furthermore, resveratrol inhibits vasoconstrictor endothelin-1 surproduction and cytosolic phospholipase A<sub>2</sub> activity stimulated by oxidative stress(44). Resveratrol has shown protective effects against ischemia reperfusion in the skeletal muscles of rat due to its potent antioxidant properties (45). Also pretreatment with resveratrol (10 µmol/l) prevented ethanol -induced disruption of embryonic growing in blastocytes and ESC-B5 embryonic stem cells (46). Interestingly low doses of resveratrol can sensitize to low doses of cytotoxic drugs and so provide an innovative strategy to enhance the efficacy of anticancer therapy in various human cancers (47). By these properties, resveratrol seems to be a good candidate in chemopreventive and chemotherapeutic strategies.

### **Conclusions**

Epidemiological evidence links high antioxidant status with low risk of degenerative disease including tumor promotion and cancer in humans. Research studies have shown that the consumption of grapes and its bioactive constituents have positive effects on human health. Nowadays because of grape seed as a safe, novel, highly potent and bioavailable free radical scavenger and antioxidant, interest of researchers has focused on grape seed proanthocyanidins. In the light of these results we can say that grape seeds and their active components should be studied in more detail for development as agents to assist in the treatment of different health problems including cancer.

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