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REVIEW

Review of the Pharmacological Effects of *Vitis vinifera* (Grape) and its Bioactive Compounds

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***Vitis vinifera*, known as the grapevine, is native to southern Europe and Western Asia. Grape seed and skin contain several active components including flavonoids, polyphenols, anthocyanins, proanthocyanidins, procyanidines, and the stilbene derivative resveratrol. Grape seed extract in particular has been reported to possess a broad spectrum of pharmacological and therapeutic effects such as antioxidative, anti-inflammatory, and antimicrobial activities, as well as having cardioprotective, hepatoprotective, and neuroprotective effects. Thus, the present review attempts to give a short overview on the pharmacological, toxicological, and clinical studies of grape and its active components. Copyright © 2009 John Wiley & Sons, Ltd.**

Keywords: Vitis vinifera; grape seed; flavonoids; proanthocyanidins; resveratrol; quercetin.

INTRODUCTION

The grapevine (*Vitis vinifera*) is indigenous to southern Europe and Western Asia and is cultivated today in all temperature regions of the world. Parts of this plant are known by several trade names throughout the world: Grape seed extract, grape seed, activin, and others (Gruenwald *et al.*, 2004). The seeds and the leaves of the grapevine are used in herbal medicine and its fruits are utilized as a dietary supplement (Sweethman, 2007). In this review, several pharmacological and clinical studies of the *Vitis vinifera* fruit, commonly known as grape and its active components are described.

Active constituents

Flavonoids. Grape seeds contain flavonoids (4–5%), including kaempferol-3-O-glucosides, quercetin-3-O-glucosides, quercetin and myricetin (Gruenwald *et al.*, 2004) (Fig. 1).

Polyphenols. Grapes are rich in polyphenols and 60–70% of grape polyphenols are found in grape seeds. The grape seed polyphenols are flavan-3-ol derivatives. The major compounds are (+)-catechins, (−)-epicatechin, (−)-epicatechin-3-O-gallate, procyanidins dimers (B1-B5), procyanidin C1, and procyanidin B5-3′-gallate (Escribano-Baiton *et al.*, 1992; Zhao *et al.*, 1999) (Fig. 2).

Grape seeds contain procyanidins or proanthocyanidins (mostly hexamers) (Escribano-Baiton *et al.*, 1992) (Fig. 3).

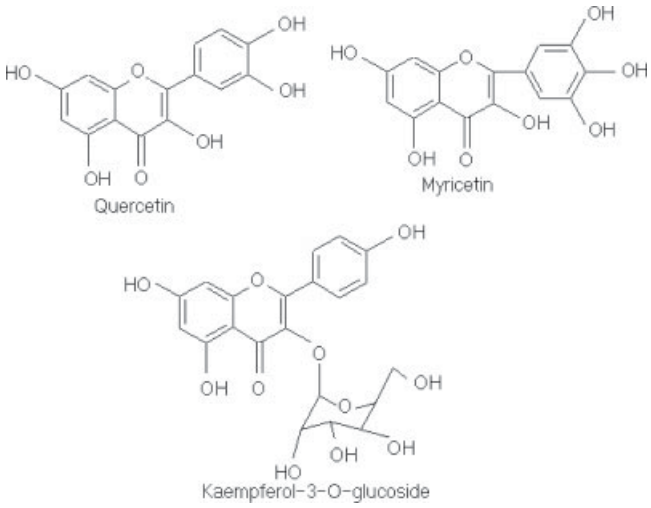

Figure 1. Chemical structure of some flavonoids found in grape.

All of the acylated procyandins of grape seeds are esters of gallic acid (Fuleki and Ricardo da Silva, 1997); however, monomers of (+)-catechin, (−)-epicatechin, and (−)-epicatechin-3-O-gallate, 14 dimeric, 11 trimeric, and one tetrameric procyanidin have also been reported (Gabetta *et al.*, 2000).

Anthocyanins. The anthocyanins that have been reported for *V. Vinifera* include 3-glucosides, 3-acetylglucosides, 3-coumaroylglucosides, 3-caffeoylglucosides, 3,5-diglucosides, 3-acetyl-5-diglucosides, 3-coumaroyl-5-diglucosides, and 3-caffeoyl-5-diglucosides of cyanidin, delphinidin, peonidin, petunidin, and malvidin (Wang *et al.*, 2003).

Stilbene derivatives. trans-Resveratrol (trans-3,5,40-trihydroxystilbene) has also been reported in grapes (Fig. 4) (Iriti and Faoro, 2006).

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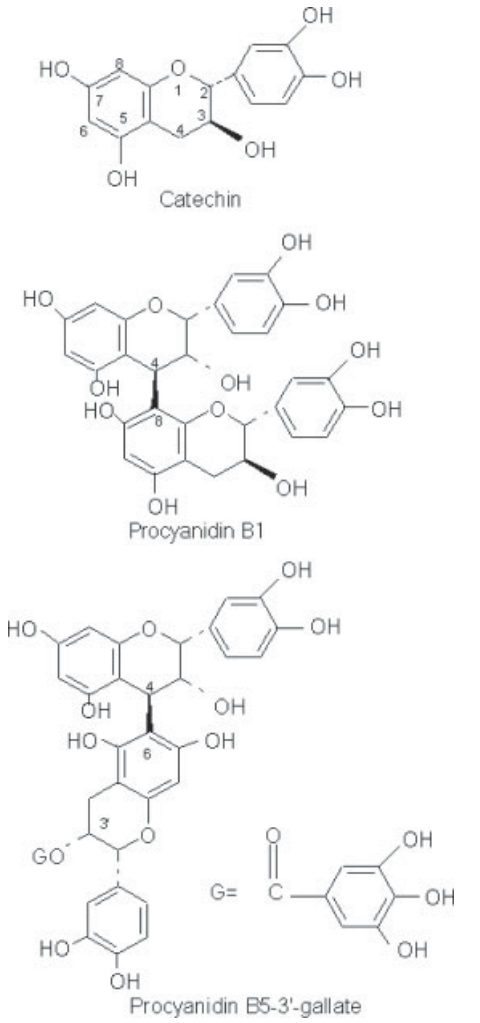

Figure 2. Chemical structures of some of polyphenols in grape seeds extract.

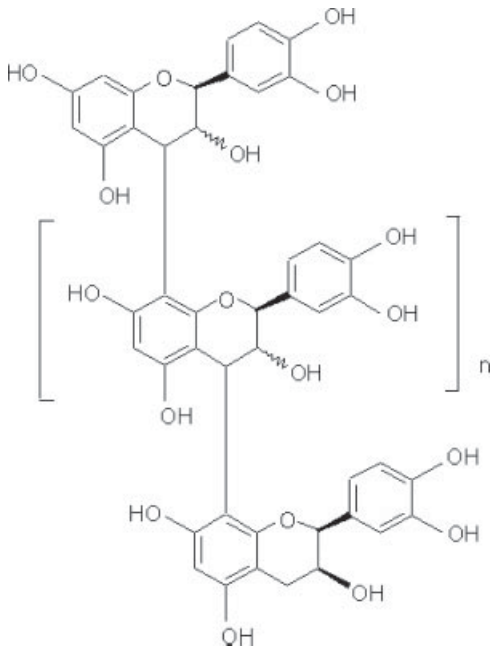

Figure 3. Chemical structure of proanthocyanidin.

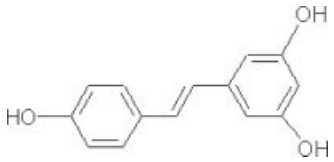

Figure 4. Chemical structure of trans-resveratrol.

Pharmacological studies

Antioxidant effects. Grape seed extract has antioxidant and free radical scavenging activity (Jayaprakasha *et al.*, 2003; Caillet *et al.*, 2006). The sparing/recycling effect of procyanidins from *V. vinifera* seeds on alpha-tocopherol was established in phosphatidylcholine liposomes and red blood cells (Facino *et al.*, 1998). Procyanidines, in addition to scavenging free radicals, strongly and non-competitively inhibit xanthine oxidase activity, the enzyme which triggers the oxy-radical cascade (Facino *et al.*, 1994).

In one study, polyunsaturated fatty acid peroxidation was inhibited by low concentrations of grape seed proanthocyanidins (2 mg/l) (Bouhamidi *et al.*, 1998).

Other studies have confirmed that grape seed proanthocyanidin extract (GSPE) (50 mg/l) provided protection against free radicals in *in vitro* free radical scavenging assay and this effect was better than vitamins C and E (Bagchi *et al.*, 2000). Moreover, GSPE (100 mg/kg), compared to other antioxidants, provided significant protection against 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced oxidative damage (Bagchi *et al.*, 1998).

In addition, procyanidin B4, catechin, and gallic acid at low concentrations (10 μmol/l, 25 μmol/l) were reported to be good cellular preventive agents against DNA oxidative damage. However, these compounds may induce cellular DNA damage at higher concentrations (150 μmol/l) (Fan and Lou, 2004). Similarly, GSPE demonstrated significant protective ability against oxidative damage in rat leukocytes (Morin *et al.*, 2008).

Recently, co-administration of grape seed extract (75 mg/kg) and *Marjoram volatile* oil (0.16 ml/kg) prevented oxidative damages and resulted in a reduction of the hazardous effects of ethanol toxicity on male fertility, liver, and brain tissues. In this study, rats received ethyl alcohol (10 ml/kg body weight, 25% v/v), daily orally by gavage for 10 weeks (El-Ashmawy *et al.*, 2007). Also, pretreatment with resveratrol (10 μmol) prevented ethanol-induced disruption of embryonic development in blastocysts and ESC-B5 embryonic stem cells (Huang *et al.*, 2007). Resveratrol has also shown protective effects against ischemia reperfusion in the skeletal muscles of rat due to its potent antioxidant properties (Elmali *et al.*, 2007).

Cardioprotective effects. Oral consumption of standardized grape extract (100 and 200 mg/kg) provided significant cardioprotection by improving post-ischemic ventricular recovery and reducing the amount of myocardial infarction in rats (Cui *et al.*, 2002). In an *ex vivo* experiment using rat aortic rings, ExGrape seeds (7 μg/ml) induced 77% endothelium-dependent relaxation, whereas ExGrape total and grape seed extract (30 μ/ml) induced 84 and 72%, respectively (Auger *et al.*, 2004). Dietary grape seed tannins (2% monomers

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or 2% polymers, 3 or 9 weeks) have a pronounced antihypercholesterolemic effect resulting from enhanced reverse cholesterol transport and also by reduced intestinal cholesterol absorption and increased bile acid excretion in rats (Tebib *et al.*, 1994).

Procyanidin supplementation in rat and rabbit reduced ischemia/reperfusion damage in the heart and this was associated with an increase in plasma antioxidant activity (Berti *et al.*, 2003). Also, it was able to prevent a peroxynitrite attack to vascular cells by layering on the surface of coronary endothelial cells, and enhancing endothelial NO-synthase-mediated relaxation in human internal mammary aortic rings (Aldini *et al.*, 2003). On the other hand, it was shown that the modest vascular relaxations observed with catechin and epicatechin are not endothelium-dependent, but rather the relaxing effects of procyanidin from grape seed and anthocyanins were both related to the integrity of the endothelium and the synthesis and release of nitric oxide (NO) (Mendesa *et al.*, 2003). Polyphenolic compounds of grape seed extracts caused an endothelium dependent relaxation of blood vessels. It was suggested that the endothelium dependent relaxation evoked by the grape seed extract was mediated by activation of the AKT/PI3 kinase signaling pathway through a redox-sensitive mechanism resulting in the phosphorylation of eNOS rabbit aortic rings (Edirisinghe *et al.*, 2007).

Similarly, proanthocyanidins-rich extract of grape seed had cardioprotective effects against reperfusion-induced injury in isolated rat hearts (Pataki *et al.*, 2002). The ability to reduce or remove, directly or indirectly, free radicals in myocardium that is reperfused after ischemia has been suggested as a possible mechanism (Sato *et al.*, 1999). However, the ability to block the antideath signal through the inhibition of the proapoptotic transcription factor and gene, JNK-1 and c-Jun has been discussed as another possible mechanism (Sato *et al.*, 2001). Quercetin (50–100 μmol/l) and catechin (10–20 μmol/l) synergistically inhibited platelet adhesion to collagen and collagen-induced platelet aggregation (Pignatelli *et al.*, 2000). Also, resveratrol-inhibited platelet aggregation (10–1000 μmol/l) and (4 mg/kg.d) respectively both *in vitro* and *in vivo* (Wang *et al.*, 2002).

Hepatoprotective effects. It has been shown that pre-exposure of grape seed extract (3 or 7 days, 100 mg/kg, p.o.), followed by hepatotoxic doses of acetaminophen (400 and 500 mg/kg, i.p.) significantly attenuated acetaminophen-induced hepatic DNA damage, apoptotic and necrotic cell death of liver cells, and counteracted the influence of acetaminophen-induced changes in bcl-XL expression in mice (Ray *et al.*, 1999). In one study, grape seed extract (50 mg/kg a day orally for 28 days) protected the liver from oxidative damage following bile duct ligation in rats (Dulundu *et al.*, 2007). Also, in another study, administrations of grape seed extract at a dose of 50 mg/kg/day orally for 15 days before ischemia/reperfusion injury and repeated before the reperfusion period, reduced hepatic ischemia/reperfusion injury in rats (Sehirli *et al.*, 2008).

Anticarcinogenic effects. Topical application of a polyphenolic fraction isolated from grape seeds or commercial grape seeds resulted in highly effective protection against phorbol ester-induced tumor promotion in chemical carcinogen-initiated mouse skin (Bomser *et al.*, 1999; Zhao *et al.*, 1999). This effect may be largely due to the significant antioxidant activity of the procyanidins.

In recent studies, mixed polyphenolic fractions on a toyopearl matrix (TP-2, TP-4, and TP-6) from grape cell culture acted as potent catalytic inhibitors in a human DNA topoisomerase II assay for cancer chemoprevention. Treatments that combined anthocyanin-rich fractions (TP-2; 0.5 or 2.0 μg of dried material/ml), fractions containing catechins, procyanidin dimers, and flavanones (TP-4; 0.25 μg of dried material/ml), and/or fractions enriched with procyanidin oligomers and polymers (TP-6; 0.15 or 0.5 μg of dried material/ml) showed additive effects toward catalytic inhibition of the enzyme (Jo *et al.*, 2005, 2006a). TP-6, a procyanidin-rich fraction, and its subfractions were selectively cytotoxic to cancerous cell lines tested (maximal toxicity = 67.2%; ED (50) = 50.5 μM) (Jo *et al.*, 2006b).

The anticarcinogenic effects of compounds and extracts isolated from grape are summarized in Table 1.

The red grape skin polyphenolic extract (25 μg/ml) also prevented and inhibited angiogenesis in the Matrigel model by decreasing the basal motility of endothelial and cancer cells, and reversing the chemotactic effect of sphingosine-1-phosphate (S1P) and vascular endothelial growth factor (VEGF) (Barthomeuf *et al.*, 2006).

Antimicrobial and antiviral effects. Antimicrobial activity has been reported in several components of grapes including gallic acid (Panizzi *et al.*, 2002), hydroxycinnamic acids (Wen *et al.*, 2003), flavanols (Rauha *et al.*, 2000), flavonols (Mori *et al.*, 1987), trans-resveratrol (Docherty *et al.*, 2001), and tannins (Jayaprakasha *et al.*, 2003). Moreover, antilisterial activity has been reported for grape seed extract (1%) (Ahn *et al.*, 2004). The seed and skin of Ribier grapes extracts decreased L. monocytogenes numbers from 10^6–10^7 CFU/ml to no detectable colonies within 10 min (Rhodes *et al.*, 2006).

CNS effects. 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 brain injury in neonatal rat (Feng *et al.*, 2005). Grape seed extract (60 mg/kg) also showed neuroprotective effects on neuronal injury induced by transient forebrain ischemia in gerbil achieved by inhibiting DNA damage in the gerbil hippocampus (Hwang *et al.*, 2004). Furthermore, the extract (100 mg/kg, 30 days) could inhibit the accumulation of age-related oxidative DNA damage in the spinal cord and in various brain regions (Balu *et al.*, 2006). The administration of grape seed extract (100 mg/kg, 30 days) to aged rats increased memory performance and reduced reactive oxygen species production, which may be related to enhancement of the antioxidant status in the central nervous system (Balu *et al.*, 2005).

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. Changes in the cholinergic system, however, indicated an increase in the ACh concentration with a moderate reduction in AChE activity, further suggesting that proanthocyanidin may have a potent role in enhancing cognition in older rats (Devi *et al.*, 2006).

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Table 1. Some cytotoxic and antiproliferative effects of grape and its different components

Compound	Method	Effects
Grape seed	Human prostate carcinoma cells	Modulation of mitogenic signaling and cell-cycle regulators, induction of G1 arrest, cell-growth inhibition, apoptotic death (10-100 μg/ml) (Agarwal *et al.*, 2000a)
	MDA-MB468 human breast	Inhibited constitutive activation of MAPK (25,50,75 μg/ml) (Agarwal *et al.*, 2000b)
Purple grape juice	DMBA-induced rat mammary tumorigenesis	Inhibited the initiation stage of tumorigenesis and DMBA-DNA adduct formation (346 and 692 mg/dl) (Jung *et al.*, 2006)
Catechin	In the Min/+ mouse, colon cancer cell lines (DLD-1, HT-29 and rodent NIH3T3 cells)	Inhibited intestinal tumor formation and suppress FAK (125 μmol) (Weyant *et al.*, 2001)
GSPE	AOM-treated rat	Inhibited ACF formation and ODC activity in the distal third of the colon, (0.1-1.0% w/w) (Singletary *et al.*, 2001)
	Colon cancer cells (CaCo2 cells)	Inactivated the PI3-kinase/PKB pathway and induced apoptosis (10–100 μg/ml) (Engelbrecht *et al.*, 2007)
	Human AML 14.3D10 cells	Induced apoptosis (50 μg/ml) (Hong and Yi-Min, 2006)
	UVB-induced photocarcinogenesis in mice	Induced IL12, modulated MAPK and NF-kappaB signaling pathways, reduced oxidative damage and tissue fat content (0.5% w/w) (Mittal *et al.*, 2003; Sharma *et al.*, 2007)
	UVB-induced photocarcinogenesis in NHEK	Inhibited UVB-induced H_2O_2, lipid peroxidation, protein oxidation, DNA damage(30 μg/ml) (Mantena and Katiyar, 2006)
	Human epidermoid carcinoma A431 cells	Induced apoptosis of A431 cells which was associated primarily with the caspase-3-dependent pathway, inhibited the expression of COX-2, iNOS, PCNA, cyclin D1 (20-80 μg/ml) (Meeran and Katiyar, 2008)
	Athymic nude mice	Reduced the growth of A431-xenografts in mice, inhibited mRNA expression of PCNA, cyclin D1 and of NF-kappaB activity (50,100 mg/kg) (Meeran and Katiya., 2008)
	Yoshida AH-130 ascites hepatoma in rat	Decreased the tumor cell content (15, 30 μmol) (Carbo *et al.*, 1999)
Resveratrol	KBrO3- treated rat	Prevented the oxidative DNA damage induced in the kidney (16 mg/kg) (Cadenas and Barja, 1999)
	Human histiocytic lymphoma U937 cells	Antiproliferation effect, arrested the S phase (3-60 μmol) (Park *et al.*, 2001)
	Human colon cancer cells	Antiproliferation effect, inhibited ODC expression (25 μmol) (Schneider *et al.*, 2000)
	Human epidermoid carcinoma A431 cells	Inhibited cell growth, arrested G1-phase, induced apoptosis (1-50 μmol) (Ahmad *et al.*, 2001)
	Human prostate cancer cells	Changed gene expression in the androgen axis and cell cycle regulation (75, 150 μmol) (Jones *et al.*, 2005)
	PMA-treated human mammary and oral epithelial cells	Inhibited induction of COX-2 mRNA and protein with IC_{50} (32.2 μmol) (Subbaramaiah *et al.*, 1998)
	TPA-stimulated mouse skin	Inhibited COX-2 expression may be via blocking the activation of MAPKs and AP-1 (1 μmol) (Kundu *et al.*, 2006), down regulated the activation of NF-kappaB subsequently in macrophages (30 μmol) (Tsai *et al.*, 1999)
Quercetin	Leukemia cell lines U937	Arrested G2/M phase (20 μmol) (Lee *et al.*, 2006)
	Human colon carcinoma cell lines HT29, Cao-2	Induced cytotoxic effect on active proliferating cells, decreased of total cellular ATP (15-120 μmol) (Agullo *et al.*, 1994)
	Colon carcinoma cell lines HCT-116, HT29 and the mammary adenocarcinoma cell line MCF-7	Inhibited proliferation (50 μmol) (van der Woulde *et al.*, 2003)
	Human Colon cancer cells Caco-2	Down-regulated expression of cell cycle genes, unregulated down-regulated cell proliferation, induced cell cycle arrest, expression of several tumor suppressor genes (5, 50 μmol) (van Erk *et al.*, 2005)
	Human colorectal cell line Caco-2	Inhibited cell differentiation (40-80 μmol) (Dihal *et al.*, 2006)
	Colon-adenocarcinoma cell line CO115	Induced cell-cycle arrest by modulation of cell-cycle-related and apoptosis genes (100 μmol) (Murtaza *et al.*, 2006)
	Human breast cancer cell line MDA-MB468	Arrested G2-M phase, inhibited mutated p53 protein with IC_{50} (7 μg/ml) (Avila *et al.*, 1994)
	Prostate cancer cell line PC-3, DU-145	Inhibited the expression of specific oncogenes, genes controlling G1, S, G2, and M phases of the cell cycle, up-regulated the expression of several tumor suppressor genes genes (25, 50 μmol) (Nair *et al.*, 2004)
	Prostate cancer cells PC-3	Altering the expression of cell cycle regulators and apoptotic proteins (50-100 μmol) (Vijayababu *et al.*, 2005)

Abbreviations: Mitogen-activated protein kinases (MAPK); 7, 12-dimethylbenz[a]anthracene (DMBA); Focal adhesion kinase activation (FAK); Grape seed proanthocyanidin extract (GSPE); Azoxymethane (AOM); Colonic aberrant crypt foci (ACF); Ornithine decarboxylase (ODC); Acute myeloid leukemia (AML); Hydrogen peroxide (H2O2); Normal human epidermal keratinocytes (NHEK); Cyclooxygenase-2 (COX-2); Inducible nitric oxide synthase (iNOS); Phorbol ester (PMA); Tumor promoter 12-O-tetradecanoylphorbol-13-acetate (TPA); Activator protein-1 (AP-1).

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Dermatological studies

The combination GSPE containing 5000 ppm resveratrol could accelerate wound contraction and healing in mice. The application of topical GSPE facilitates oxidant-induced vascular endothelial growth factor (VEGF) expression in keratinocytes by modulating pathways that are common to both H_2O_2 as well as TNF-a signaling (Khanna *et al.*, 2002).

Antidiabetic effects. GSPE has been reported to be effective in treating diabetic nephropathy, though little is known about the functional protein changes. After GSPE therapy in diabetic rats, only nine kidney proteins were found to return to normal levels. It was shown that these proteins are involved in oxidative stress, glycosylation damage, and amino acid metabolism (Li *et al.*, 2008). GPSE (250 mg/kg body weight/d) also ameliorated glycation-associated cardiac damage in diabetic rats (Cheng *et al.*, 2007).

Other effects. Administration of grape seed extract, which contains 38.5% procyanidins, to hereditary cataractous rats (ICR/f rats) prevented the progression of cataract formation by their antioxidative action (Yamakoshi *et al.*, 2002).

Studies by Gunjima *et al.* (2004) on rat mandibles in the growth phase suggested that supplementation of the diet with GSPE could increase bone quality and bone strength of the mandibles.

The protective effects of a vinifera grape skin extract (200 mg/kg/day) were shown against the deleterious effects of experimental preeclampsia in rats, a condition where reduced nitric oxide production and increases in oxidative stress are present. It seems that an endothelium-dependent vasodilator effect and an antioxidant action play an important role in mediating the effects of GSE in experimental preeclampsia (De Moura *et al.*, 2007).

Clinical Studies

Cardioprotective effects. Ingestion of purple grape juice (7.7 ± 1.2 ml/kg/day) for 14 days in 15 adults with angiographically documented coronary artery disease (CAD) improved flow-mediated vasodilation (FMD) and reduced LDL oxidation susceptibility (Stein *et al.*, 1999). Similarly, ingestion of 4–8 ml/kg/day of purple grape juice for 4 weeks in patients with coronary heart disease improved FMD of the brachial artery (Chou *et al.*, 2001). Consumption of purple grape juice (7 ml/kg/day) for 14 days in 20 healthy subjects could inhibit platelet aggregation, reduce superoxide release, and increase platelet-derived NO production. Moreover, *in vitro* incubation of platelets with purple grape juice has shown similar results (Freedman *et al.*, 2001). In addition, administration of purple grape juice (500 ml/day) from 14 days to 16 to hypercholesterolemic individuals without other risk factors improved FMD (Coimbra *et al.*, 2005).

Recently, it was shown that consumption of concentrated red grape juice (50 ml, twice a day, for two weeks) increased the antioxidant capacity of plasma, reduced the concentration of oxidized LDL and increased the concentration of cholesterol-standardized α-tocopherol in both healthy subjects and hemodialysis patients. Also, in hemodialysis patients, consumption of red grape juice resulted in a significant reduction in plasma monocyte chemoattractant protein 1, an inflammatory biomarker associated with cardiovascular disease risk (Castilla *et al.*, 2006). However, it was shown that consumption of purple grape juice did not result in additive antithrombotic effects for patients who were already on aspirin.

In healthy volunteers who consumed 300 mg of a proanthocyanidin-rich grape seed extract, the postprandial oxidative stress was minimized by decreasing the oxidants and increasing the antioxidant levels in plasma. Thus, the resistance to oxidative modification of LDL was increased (Natella *et al.*, 2002). The administration of red grape polyphenol extract (600 mg) to patients with coronary heart disease improved endothelial function. The extract of grapes contained 4.32 mg epicatechin, 2.72 mg catechin, 2.07 mg gallic acid, 0.9 mg trans-resveratrol, 0.47 mg rutin, 0.42 mg epsilon-viniferin, 0.28 mg, p-coumaric acid, 0.14 mg ferulic acid and 0.04 mg quercetin per gram. Flow-mediated dilatation was measured after fasting and 30, 60 and 120 min after the intake of the grape extract. Intake of the red grape polyphenol extract caused an increase in flow-mediated dilatation, peaking at 60 min, which was significantly higher than the baseline values ($P < 0.001$) and the corresponding values at 60 min after the intake of placebo ($P < 0.001$). There was no change in FMD values after the intake of placebo throughout the whole duration of the study (Lekakis *et al.*, 2005).

Also, in one double-blind study, the intake of 400 mg of flavanol-rich grape seed extract for 8 weeks yielded positive results for platelet function in postmenopausal women. Their data indicated a trend toward increased ADP-collagen-stimulated platelet closure time at week 8 (Shenoy *et al.*, 2007).

However, the grape juice (Lakewood Organic Juices, FL), which contained considerable amounts of fructose and glucose with exercise-enhanced adenine nucleotide degradation and lactic acid production which play an important role in the increase in plasma concentration of urate (Ohno *et al.*, 2008).

Drug Interaction. Proanthocyanidin from grape seeds 12.5 and 25 mg/l *in vitro* and 10 mg/kg *in vivo* enhanced the doxorubicin-induced antitumor effect and reversed drug resistance by increasing intracellular doxorubicin, Ca^{2+}, and Mg^{2+} concentrations, and reducing pH and mitochondrial membrane potential. In this study, experimental transplantation Sarcoma 180 (S180) and Hepatoma 22 (H22) was done in mice (Zhang *et al.*, 2005).

Also, grape juice impaired CYP2C9 activity *in vitro* (Greenblatt *et al.*, 2006). It was shown that grape seed extract has a synergic effect with amphotericin B against fungal infection in mice (Han, 2007).

Toxicity. Acute oral toxicity, dermal toxicity, dermal irritation, and eye irritation studies have been performed with GSPE. The LD50 of GSPE was found to be greater than 5000 mg/kg when administered once orally via gastric intubation to rats. The dose-dependent chronic effects of GSPE in mice were evaluated and it was found that GPSE did not cause any detrimental effects (Ray *et al.*, 2001). Furthermore, administration of the grape seed extract ActiVin to rats in the feed at levels

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of 0.5, 1.0, or 2.0% for 90 days did not induce any significant toxicological effects (Wren *et al.*, 2002). Similarly, it was reported that there was no observed adverse effect of the dietary concentration of grape seed extract or grape skin extract in rats (Bentivegna and Whitney, 2002).

CONCLUSION

In summary, *V. vinifera* and its bioactive compounds have several pharmacological activities such as antioxidative, anti-inflammatory and antimicrobial activities, *as well as in vitro* activity against several cancer cell lines and hepatoprotective and cardioprotective effects. It seems that grape seed extract and its active components such as proanthocyanidins, resveratrol, and quercetin are potent antioxidants. The consumption of grapes and grape juice is likely to have positive effects on human health and especially in postmenopausal women. These results suggest that grape seeds and their active components should be studied in more detail for development as agents to assist in the treatment of cardiovascular, gastrointestinal, and neurodegenerative diseases.

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