ISSN : 0974 - 7532 Volume 7 Issue 5

Research & Reviews in BioSciences

Trade Science Inc.

Review

RRBS, 7(5), 2013 [175-180]

A review on benefits and uses of *Vitis vinifera* (Grape)

N.S.S.A.Valli Kanagarla*, I.J.Kuppast, T.Veerashekar, Chindala Laxman Reddy
Department of Pharmacology, National College of Pharmacy, BalrajUrs Road, Shimoga, Karnataka, (INDIA)
E mail: amrutha.valli01@gmail.com

ABSTRACT

Herbs have been used by people for longer than we have been keeping written record. Originally they were found in the wild, by the gatherers and used for a lot of different things. They were used to flavour food, as a source of nutrition, as medicines[1].

Over the years, natural products have contributed to the development of important therapeuticdrugs used currently in modern medicine. The study of plants that have been traditionally used should still be seen as a fruitful and logical research strategy, in the search.

*Vitisvinifera*is a perennial woody, climbing tree belongs to family *Vitaceae*. It is commonly known as grape and draksha. The ripe fruit is laxative and purgative, fattening, diuretic, aphrodisiac, appetizer, and the throat; cures thirst, asthma, "vata" and "vatarakta", jaundice, strangury, blood disease. The ashes of stem are goodfor pains in joints, swelling of the testicle, and piles. The flowers are expectorant and haematinic, and are useful in bronchitis. In Iran, grape leaves are used in a traditional food and for treatment of diarrhea and bleeding[2]. In this review, several pharmacological and clinicalstudies of the *Vitisvinifera*fruit, commonly known asgrape and its active components are described[3].

KEYWORDS

Vitisvinifera;
Antioxident activity;
Antidiabetic;
Antimicrobial and antiviral effect;
Anticarcinogenic activity;
Hepatoprotective activity.

INTRODUCTION

Fruits of *Vitisvinifera*have been used for thousands of yearsbecause of their nutritional and medicinal benefits. Theyare rich in sugars,flavonoids, anthocyanins and proanthocyanins, organic acids, tannin,mineral salts and vitamins. Grapes skin, especially from the red and black species is rich inresveratrol which is a derivative of stilben. Studies have shown that resveratrol is one of the strongest knownnatural antioxidants. It is found in a large quantity in black grape juice, skinand seed[4]. The seeds and the leaves ofthe grapevine are used in herbal medicine and its fruitsare utilized as a dietary supplement[3].

ORIGIN AND DISTRIBUTION

The grapevine (*Vitisvinifera*) is indigenous to southernEurope and Western Asia and is cultivated today in alltemperature regions of the world[3] which comprises about 60 inter-fertile wild*Vitis* species distributed in Asia, North America and Europe under subtropical, Mediterranean and continental–temperate climatic conditions[5].

DESCRIPTION

*Vitisvinifera*is a perennial, woody climbing vine; stems up to 35 m long, but in cultivation usually reduced by annual pruning to 1–3 m; leaves thin, circular to circular-ovate, 5–23 cm broad, margins dentate or jagged, basal sinus deep and lobes often overlapping, 5–7-lobed, glabrescent above, often with persisten tomentum beneath; tendrils branched, normally opposite 2 leaves out of three; flowers numerous, in dense panicles or thyrses opposite leaves; flower clusters and tendrils absent at every third node; calyx very shortly 5-lobed; petals about 5 mm, pale green, sweet-scented; fruit a soft, pulpy berry, skin adhering to pulp, oval or oblong, ellipsoid to globose, skin green, yellow, red or purplish-black, in large, long clusters; seeds 2–3, sometimes none, pyriform, with rather long beak.

ECOLOGY

Requirements are for long, warm to hot dry summers and mild winters. Plant damage occurs at -18°C; frost kills young shoots. Daily mean temperature should be at least 18°C. This species will not endure the high temperatures coupled with high humidity of tropics. Humidity promotes disease. *Vitisvinifera* is reported to tolerate annual precipitation of 0.9 to 27.2 dm (mean of 12.1 cases = 134) annual temperature of 8.3 to 28.5°C (mean of 21.8 cases = 133) and pH of 4.5 to 8.7 (mean of 6.8 cases = 66)[6].

ACTIVE CONSTITUENTS

Flavonoids:Grape seeds contain flavonoids (4–5%),including kaempferol-3-O-glucosides, quercetin-3-O-glucosides,quercetin and myricetin.

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 B5-32 -gallate.

Grape seeds contain procyanidins or proanthocyanidins (mostly hexamers). All of the acylatedprocyandins of grape seeds areesters of gallic acid (Fuleki and Ricardo da Silva, 1997);however, monomers of (+)-catechin, (□–)-epicatechin, and (□–)-epicatechin-3-O-gallate, 14 dimeric, 11 trimeric, andone tetramericprocyanidin have also been reported.

Anthocyanins:The anthocyanins that have been reportedfor *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.

Stilbene derivatives:Trans-Resveratrol (trans-3,5,40-trihydroxystilbene) has also been reported in grapes[3].

USES

Fresh fruits, eaten or processed into wine, raisins, juice, with some cultivars adapted for the canning industry. Grape seeds contain 6–20% oil, used for edible purposes, soaps, and as a linseed substitute. The leaves of this and other species are eaten in other cultures. Sap of young branches used as remedy for skin diseases. Leaves astringent, used in diarrhoea. Juice of unripe fruit astringent, used in throat affections. Dried fruit as demulcent, cooling, sweet, laxative, stomachic, used in thirst, heat of body, coughs, hoarseness, consumption and in wasting diseases. Amalagma made from the seed is said to be a folk remedy for condylomata of the joints. The fruit, prepared in various manners, is said to remedy for mola, uterine tumors, hardness of the liver, tumours, and cancer. The juice, prepared in various manners, is said to remedy for tumours of the tonsils, excrescences of the seat, tumours of the fauces, indurations, tumours of the neck, chronic tumors[6].

PHARMACOLOGICAL ACTIVITIES

Antioxidant effects

Grape seed extract has antioxidant and free radical scavenging activity[7]. The sparing/recycling effect of procyanidins from *V. vinifera*seeds on alpha-tocopherol was established in phosphatidylcholine liposomes and red blood cells. Procyanidines, in addition to scavenging free radicals, strongly and non-competitively inhibit xanthine oxidase activity, the enzyme which triggers the oxy-radical cascade[8]. In one study, polyunsaturated fatty acid peroxidation was inhibited by low concentrations of grape seed proanthocyanidins (2 mg/l). Other studies have confirmed that grape seed proanthocyanidinextract (GSPE) (50 mg/l) provided protection against free radicals in *in vitro* free radicalscavenging assay and this effect was better than vitamins C and E. Moreover, GSPE (100 mg/kg), compared to other antioxidants, provided significantprotection against 12-O-tetradecanoylphorbol -13- acetate (TPA)-induced oxidative damage.

In addition, procyanidin B4, catechin, and gallic acid at low concentrations (10μmol/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 (150μmol/l). Similarly, GSPE demonstrated significant protective ability against oxidative damage in rat leukocytes. 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 week. Also, pretreatment with resveratrol (10 μmol) prevented ethanol-induced disruption of embryonic development in blastocysts and ESC-B5 embryonic stem cells. Resveratrol has also shownprotective effects against ischemia reperfusion in the skeletal muscles of rat due to its potent antioxidant properties.

Cardioprotective effects

Oral consumption of standardized grape extract (100 and 200 mg/kg) providedsignificant cardioprotection by improving post-ischemic ventricular recovery and reducing the amount of myocardial infarction in rats. 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. Dietary grape seed tannins (2%monomers 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. Procyanidin supplementation in rat and rabbit reduced ischemia/reperfusion damage in the heart and this was associated with an increase in plasma antioxidant activity. Also, it was able to prevent a peroxynitrite attack to vascular cells by layering on thesurface of coronary endothelial cells, and enhancing endothelial NO-synthase-mediated relaxation in human internal mammary aortic rings. On the other hand, it was shown that the modest vascular relaxations observed with catechin and epicatechin arenot endothelium-dependent, but rather the relaxing effects of procyanidin from grape seed and anthocyaninswere both related to the integrity of the endothelium and the synthesis and release of nitric oxide (NO). 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 eNOSrabbit aortic rings. Similarly, proanthocyanidins-rich extract of grape seed had cardioprotective effects against reperfusion-induced injury in isolated rat hearts. The ability to reduce or remove, directly or indirectly, freeradicals in myocardium that is reperfused after ischemia has been suggested as a possible mechanism. 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. Quercetin (50–100 μmol/l) and catechin (10–20 μmol/l) synergistically inhibited platelet adhesion to collagen and collagen-induced platelet aggregation. Also, resveratrol-inhibited platelet aggregation (10–1000μmol/l) and (4 mg/kg.d) respectivelyboth *in vitro* and *in vivo*.

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. 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. 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.

Anticarcinogenic effects

Topical application of a polyphenolicfraction isolated from grape seeds or commercialgrape seeds resulted in highly effective protection against phorbol ester induced tumor promotion inchemical carcinogen-initiated mouse skin. This effect may belargely due to the significant antioxidant activity of theprocyanidins. In recent studies, mixed polyphenolic fractions on atoyopearlmatrix (TP-2, TP-4, and TP-6) from grapecell culture acted as potent catalytic inhibitors in ahuman DNA topoisomerase II assay for cancer chemoprevention. Treatments that combined anthocyaninrichfractions (TP-2; 0.5 or 2.0 μg of dried material/ml),fractions containing catechins, procyanidin dimers, andflavanones (TP-4; 0.25 μg of dried material/ml), and/orfractions enriched with procyanidin oligomers and polymers (TP-6; 0.15 or 0.5 μg of dried material/ml) showedadditive effects toward catalytic inhibition of the enzyme. TP-6, a procyanidin-rich fraction,and its subfractions were selectively cytotoxic tocancerous cell lines tested (maximal toxicity = 67.2%;ED (50) = 50.5 μM).

The red grape skin polyphenolic extract (25 μg/ml) also prevented and inhibited angiogenesis in the Matrigelmodel by decreasing the basal motility of endothelialand cancer cells, and reversing the chemotactic effectof sphingosine-1-phosphate (S1P) and vascular endothelialgrowth factor (VEGF).

Antimicrobial and antiviral effects

Antimicrobial activityhas been reported in several components of grapes including gallic acid, hydroxycinnamicacids, flavanols[9], trans-resveratrol, and tannins. Moreover, antilisterial activity has been reportedfor grape seed extract (1%). Theseed and skin of Ribier grapes extracts decreased L.monocytogenes numbers from 106–107 CFU/ml to nodetectable colonies within 10 min.

CNS effects

Grape seed extract (50 mg/kg) reducedthe incidence of free-radical-induced lipid peroxidationin the central nervous system of aged rats and reducedhypoxic ischemic brain injury in neonatal rat. Grape seed extract (60 mg/kg) also showedneuroprotective effects on neuronal injury inducedby transient forebrain ischemia in gerbil achieved byinhibiting DNA damage in the gerbil hippocampus. Furthermore, the extract (100 mg/kg, 30 days) could inhibit the accumulation of agerelatedoxidative DNA damage in the spinal cord andin various brain regions. The administrationof grape seed extract (100 mg/kg, 30 days) toaged rats increased memory performance and reducedreactive oxygen species production, which may be related to enhancement of the antioxidant status in thecentral nervous system. Proanthocyanidin intake (75 mg/kg, 9 weeks) waseffective at up-regulating the antioxidant defense mechanismby attenuating lipid peroxidation and protein oxidation in the adult rat brain. Changes in the cholinergicsystem, however, indicated an increase in the Ach concentration with a moderate reduction in AChEactivity, further suggesting that proanthocyanidin mayhave a potent role in enhancing cognition in older rats.

Dermatological studies

The combination GSPE containing 5000 ppm resveratrol could accelerate wound contraction and healing in mice. The application of topical GSPE facilitates oxidantinduced vascular endothelial growth factor (VEGF) expression in keratinocytes by modulating pathways that are common to both H_2O_2 as well as TNF-a signalling[3].

Antidiabetic effects

GSPE has been reported to beeffective in treating diabetic nephropathy, though little is known about the functional protein changes. AfterGSPE 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. GPSE (250 mg/kg body weight/d) also ameliorated glycation-associated cardiac damage in diabetic rats[10].

Other effects

Administration of grape seed extract,which contains 38.5% procyanidins, to hereditary cataractousrats (ICR/f rats) prevented the progression of cataract formation by their antioxidative action. Studies by 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 andincreases 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.

TOXICITY

Acute oral toxicity, dermal toxicity, dermalirritation, and eye irritation studies have been performedwith GSPE. The LD_{50} of GSPE was found to be greaterthan 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. Furthermore, administration of the grape seed extract ActiVin to rats in the feed at levels of 0.5, 1.0, or 2.0% for 90 days did not induce any significant toxicological effects. Similarly, it was reported that there was no observed adverse effect of the dietary concentration of grape seedextract or grape skin extract in rats.

CONCLUSION

In summary, *V. vinifera*and its bioactive compounds have several pharmacological activities such as antioxidative, anti-inflammatory and antimicrobial activities, *aswell 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[3].

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