A Concise Review: Antioxidant Effects and Bioactive Constituents of Grape

Üzümün Biyoaktif Bileşenleri ve Antioksidan Etkileriyle İlgili Kısa Bir Derleme

Aysun Çetin
Assist. Prof., M.D.
Department of Biochemistry and Clinical Biochemistry
Faculty of Medicine, Erciyes University
aysuncetin@yahoo.com

Osman Sağdıç
Assoc. Prof., Ph.D.
Food Engineering
Faculty of Engineering, Erciyes University

Abstract
Grape (Vitis Vinifera), one of the most widely consumed fruit worldwide, contain many bioactive constituents including flavonoids, polyphenols,anthocyanins and stibene 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 benefical 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, antiinflamatuar, 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

Corresponding Author:
Yard. Doç. Dr. Aysun Çetin
Department of Biochemistry and Clinical Biochemistry
Faculty of Medicine, Erciyes University
38039- Kayseri / Turkey

E-Mail : aysuncetin@yahoo.com

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) (Figure1).

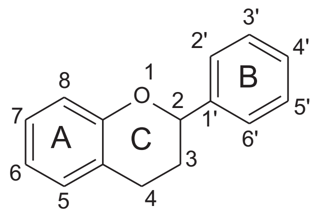

Figure 1. Structure of flavonoid.

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).

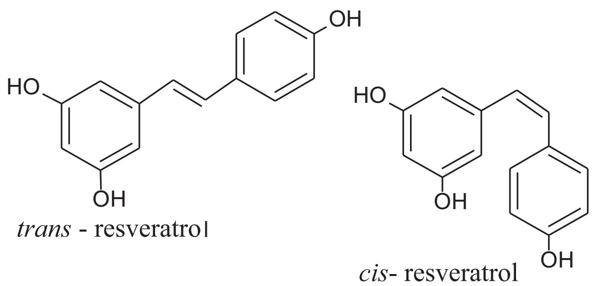

Figure 2. *Trans*-resveratrol and *cis*-resveratrol.

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

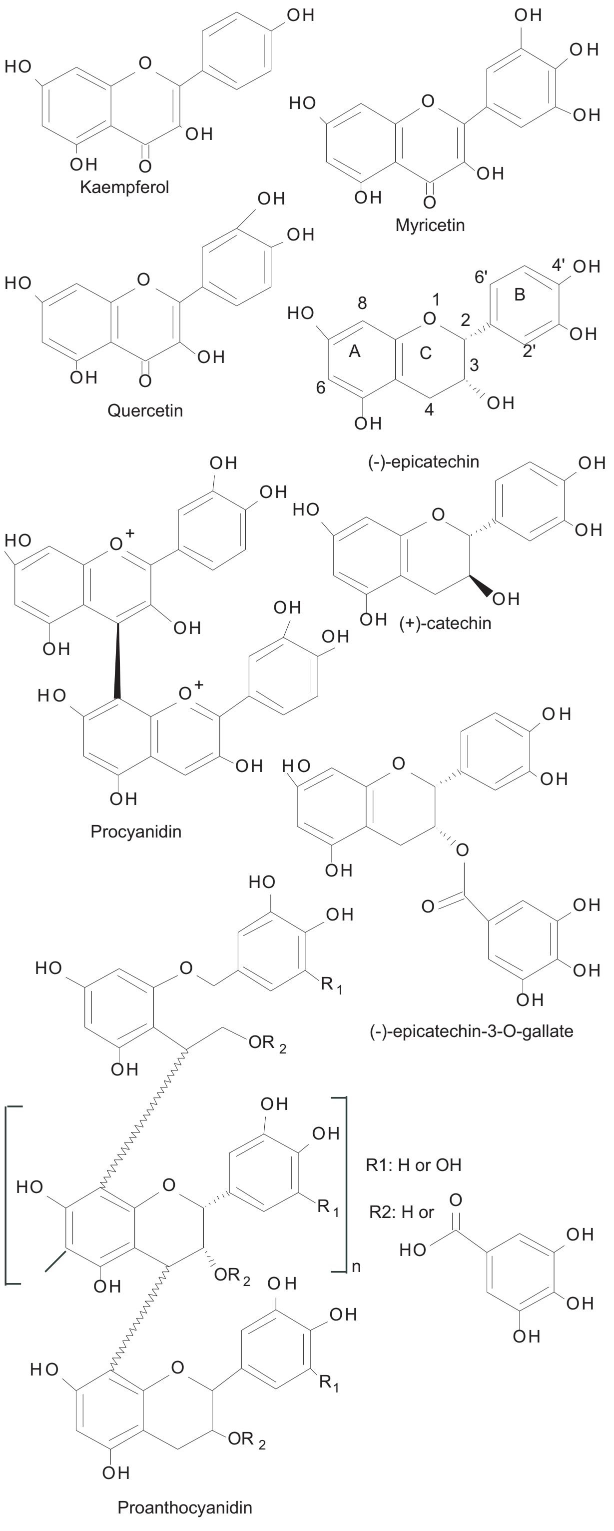

Figure 3. Chemical structures of some important biologically active compounds from grapes.

lipid alkoxyl and peroxyl 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 ß–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 peroxyl 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 hypercholestemic 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 µmol/1, 25 µmol/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 µmol/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_{50} 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_2O_2 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_2 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/1) 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.

References

1.Harman D. Free radical theory of aging: an update: increasing the functional life span. Ann NY Acad Sci 2006; 1067:10-21.

2.Hallıwell B, Gutterıdge JM, Cross CE.Free radicals, antioxidants and human disease; where are we now? J Lab Clin Med 1992; 199 : 598–620.

3.Ames BN,Gold LS.Environmental pollution, pesticides, and prevention of cancer:misconceptions FASEB J 1997; 11:1041-1052.

4.Sarı I, Çetin A, Kaynar L,et al. Disturbance of Pro–oxidative/Antioxidative Balance in Allogeneic Peripheral Blood Stem Cell Transplantation. Annals of Clinical Laboratory Science 2008 ;38: 120–125.

5.Park YK,Lee SH,Park E,Kim JS,Kang MH.Changes in antioxidant status,blood pressure,and lymphocyte DNA Damage from Grape Juice Supplementation.Ann NY Acad Sci 2009;1171: 385-390 .

6.Iriti M, Faoro F. Bioactivity of grape chemicals for human health. Nat Prod Commun 2009;4: 611–634.

7.Pezzuto JM.Grapes and Human Health:A Perspective.J Agric Food Chem 2008;56: 6777-6784.

8.Yadav M, Jain S, Bhardwaj A, et al. Biological and Medicinal Properties of Grapes and Their Bioactive Constituents: An Update. J. Med Food 2009;12 : 473–484.

9.Demir BS, Serindağ O. Determination of boron in grape (Vitis vinifera) by azomethine H spectrophotometric method. Eurasian J Anal Chem 2006; 1: 11–18.

10.Sağdıç O, Ekici L. Üzüm (Vitis Vinifera) Çekirdeğinin Fenolik Bileşikleri ve Biyoaktif Özellikleri.Hasad Gıda 2005;Yıl: 21 Sayı: 244.

11.Baydar NG, Sagdic O, Ozkan G, Çetin S. Determination of antibacterial effects and total phenolic contents of grape (Vitis vinifera L.) seed extracts. International Journal of Food Science and Technology 2006;41: 799–804.

12.Wiel A,Golde PH,Harth HC.Blessings of the grape .Eur J Intern Med 2001; 12: 484-489.

13.Nasirsi-Asl M,Hosseinzadeh H. Review of the pharmacological effects of Vitis Vinifera and its bioactive compounds.Phytother Res 2009;23: 1197-1204 .

14.Iriti M, Faoro F. Grape phytochemicals: A bouquet of old and new nutraceuticals for human health. Med Hypothesis 2006;67: 833–838.

15.Shi J,Yu J,Pohorly JE,Kakuda Y. Polyphenolics in Grape Seeds–Biochemistry and Functionality . J Med Food 2003;6 : 291–299.

16.Makris P, Kallithraka S, Kefalas P. Flavonols in grapes, grape products and wines; Burden, profile and influential parameters, Journal of Food Composition and Analysis 2006;19 : 396–404.

17.Bagchi D, Garg A, Krohn RL, Bagchi M,Tran MX,Stohs SJ Oxygen free radical scavenging abilities of vitamins C and E, and a grape seed proanthocyanidin extract in vitro. Res Commun Mol Pathol Pharmacol 1997;95: 179–189.

18.Esterbauer H, Schaur RJ, Zollner H. Chemistry and biochemistry of 4-hydroxynonenal, malonaldehyde and related aldehydes. Free Radic Biol Med 1991;11: 81–128

19.Kushi L, Lenart EB, Willet WC. Health implications of Mediterranean diets in light of contemporary knowledge.1.Plant foods and dairy products. Am J Clin Nutr 1995; 61: 1407–1415

20.Bouhamidi R, Prevost V, Nouvelot A. High protection by grape seed proanthocyanidins (GSPC) of poylunsaturated fatty acids against UV–C induced peroxidation. CR Acad Sci 1998;321: 31–38.

21.Stein JH, Keevil JG, Wiebe DA,Aeschlimann S,Folts JD. Purple grape juice improves endothelial function and reduces the susceptibility of LDL cholesterol to oxidation in patients with coronary artery disease. Circulation 1999;100: 1050–1055.

22.Bagchi D, Sen CK, Ray SD, et al. Molecular mechanisms of cardioprotection by a novel grape seed proanthocyanidin extract. Mutat Res 2003;523–524: 87–97.

23.Sano A, Uchida R, Saito M, et al. Beneficial effects of grape seed extract on malondialdehyde–modified LDL. J Nutr Sci Vitaminol 2007; 53: 174–182.

24.Berti F, Manfredi B, Mantegazza P, Rossoni G. Procyanidins from Vitis vinifera seeds display cardioprotection in an experimental model of ischemia–reperfusion damage. Drugs Exp Clin Res 2003;29: 207–216.

25.Soares De Moura R, Costa Viana FS, Souza MA, et al. Antihypertensive, vasodilator and antioxidant effects of a vinifera grape skin extract. J Pharm Pharmacol 2002; 54: 1515–1520.

26.Fan PH, Lou HX. Isolation and structure identification of grape seed polyphenols and its effects on oxidative damage to cellular DNA. Yao Xue Xue Bao 2004;39: 869–875.

27.Morin B, Narbonne JF, Ribera D,Badouard C,Ravanat JL. Effect of dietary fat–soluble vitamins A and E and proanthocyanidin–rich extract from grape seeds on oxidative DNA damage in rats. Food Chem Toxicol 2008;46: 787–796.

28.Feng Y, Lin YM, Fratkins JD,Le Blanch MH. Grape seed extract suppresses lipid peroxidation and reduces hypoxic ischemic brain injury in neonatal rats. Brain Res Bull 2005;66: 120–127.

29.Balu M, Sangeetha P, Murali G, Panneerselvam C. Modulatory role of grape seed extract on age–related oxidative DNA damage in central nervous system of rats. Brain Res Bull 2006; 68: 469–473.

30.Balu M, Sangeetha P, Muralli G. Age–related oxidative protein damages in central nervous system of rats: modulatory role of grape seed extract. Int J. Dev Neurosci 2005;23: 501–507.

31.Devi SA, Jolitha AB, Ishii N.Grape seed proanthocyanidin extract(GSPE) and antioxidant defense in the brain of adult rats. Med Sci Monit 2006; 12 : 124–129.

32.Yamakoshi J, Saito M, Kataoka S,Tokutake S. Procyanidin rich extract from grape seeds prevents cataract formation in hereditary cataractous (ICR/f) rats. J Agric Food Chem 2002;50: 4983–4988.

33.Nandakumar V,Singh T,Katiyar SK.Multitargeted prevention and therapy of cancer by proanthocyanidins. Cancer Lett 2008;269:378-387.

34.Khan N , Afaq F , Mukhtar H . Cancer chemoprevention through dietary antioxidants: progress and promise. Antioxid Redox Signal 2008 ;10: 475 – 510.

35.Ratnam DV , Ankola DD , Bhardwaj V , Sahana DK, Kumar MN. Role of antioxidants in prophylaxis and therapy: a pharmaceutical perspective. J Control Release 2006; 113: 189 – 207 .

36.Conklin KA.Dietary antioxidants during cancer chemotherapy: impact on chemotherapeutic effectiveness and development of side effects. Nutr Can 2000; 37: 1–18.

37.Shacter E, Williams J.A, Hinson R.M, Sentürker S,Lee YJ. Oxidative stress interferes with cancer chemotherapy: inhibition of lymphoma cell apoptosis and phagocytosis. Blood 2000;96: 307–313.

38.Lee YJ, Shacter E. Oxidative stress inhibits apoptosis in human lymphoma cells. J Biol Chem 1999;274: 19792–19798.

39.Ferreira PR , Fleck JF , Diehl A , et al . Protective effect of alpha-tocopherol in head and neck cancer radiation-induced mucositis: a double-blind randomized trial. Head Neck 2004 ;26 : 313 – 321 .

40.Lesperance ML , Olivotto IA , Forde N , et al . Mega-dose vitamins and minerals in the treatment of non-metastatic breast cancer: an historicalcohort study . Breast Cancer Res Treat 2002 ;76 : 137 – 143 .

41.Cetin A, Kaynar L, Kocyigit I, et al.Role of grape seed extract on methotrexate induced oxidative stress in rat liver. Am J Chin Med 2008; 36: 861–872.

42.Cetin A , Kaynar L, Koçyigit I, et al .The effect of grape seed extract on radiation-induced oxidative stres in the rat liver.Turk J Gastroenterol 2008;19: 92-98.

43.Velioglu, Ogunc A, Sehirli O, Toklu HZ, Resveratrol protects against irradiation–induced hepatic and ileal damage via its anti–oxidative activity. Free Radic Res 2009 ; 25:1-12.

44.Delmas D, Jannin B, Latruffe N. Resveratrol :preventing properties against vascular alterations and ageing. Mol Nutr Food Res 2005; 49: 377–395.

45.Elmali N, Esenkaya I, Karadag N, Tas F,Elmali N. Effects of resveratrol on skeletal muscle in ischemia–reperfusion injury. Ulus Travma Acil Cerrahi Derg 2007;13: 247–280.

46.Huang LH, Shiao NH, Hsuuw YD,Chan WH. Protective effects of resveratrol on ethanol–induced apoptosis in embriyonic stem cells and disruption of embryonic development in mouse blastocysts. Toxicology 2007;242: 109–122.

47.Delmas D,Lancon A,Colin D,Jannin B,Latruffe N.Resveratrol as a chemopreventive agent:a promising molecule for fighting cancer.Curr Drug Targets 2006;7:423-442.