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Review

Biological and Medicinal Properties of Grapes and Their Bioactive Constituents: An Update

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ABSTRACT The grape is one of the most valued conventional fruits, worldwide. Although most of the parts of the grapevine are useful, primarily, the grape is considered as a source of unique natural products not only for the development of valuable medicines against a number of diseases, but also for manufacturing various industrial products. Over the last few decades, apart from the chemistry of grape compounds, considerable progress has been made towards exploring the biological activities of various grape-derived constituents. Today, it is well established that in addition to serving as food, the grape is a major source of several phytochemicals. The main biologically active and well-characterized constituent from the grape is resveratrol, which is known for various medicinal properties in human diseases. This review discusses the roles of various grape-derived phytochemicals in relation to various diseases.

KEY WORDS: • ***biological functions*** • ***grapes*** • ***phytochemicals*** • ***resveratrol***

INTRODUCTION

SINCE THE BEGINNING of human civilization, medicinal plants have always remained a part and parcel of human society to combat and treat different diseases. In particular, in the Indian systems of medicine Rigveda, Charak Samhita, and Sushruta Samhita such descriptions have been documented. According to estimates of the World Health Organization nearly 75% of the world's population currently uses herbs and other traditional medicines to treat diseases of different natures.[1] Nevertheless, currently medical as well as pharmaceutical research is being carried out towards characterization and development of plant-derived natural components to treat various human ailments.[2]

The grape has been well recognized worldwide for over 2,000 years as one among the edible sweet fruits and recognized for its wide spectrum of biological properties.[3] Its taxonomic position is as follows: Group Thalamifloreae, Order Rhamnales, Family Vitaceae, Genus *Vitis*, Species *vinifera.* Various chemical studies on the products of the fruit and other parts of the grape plant have been attempted, mainly during the 1950s. Chemical structures of some of the important biologically active grape-derived compounds are given in Figure 1.

GRAPE: A GOOD SOURCE OF NUTRIENTS

The grape belongs to the berry family as it is found attached to the stem. Many berries make up a cluster or bunch of grapes. The fruit of the grape is one of the most palatably edible foods, having many established nutritional and medicinal properties for consumers. The grape is a good source of water (∼82%), 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 small amount of calcium (0.01–0.02%) and phosphorus

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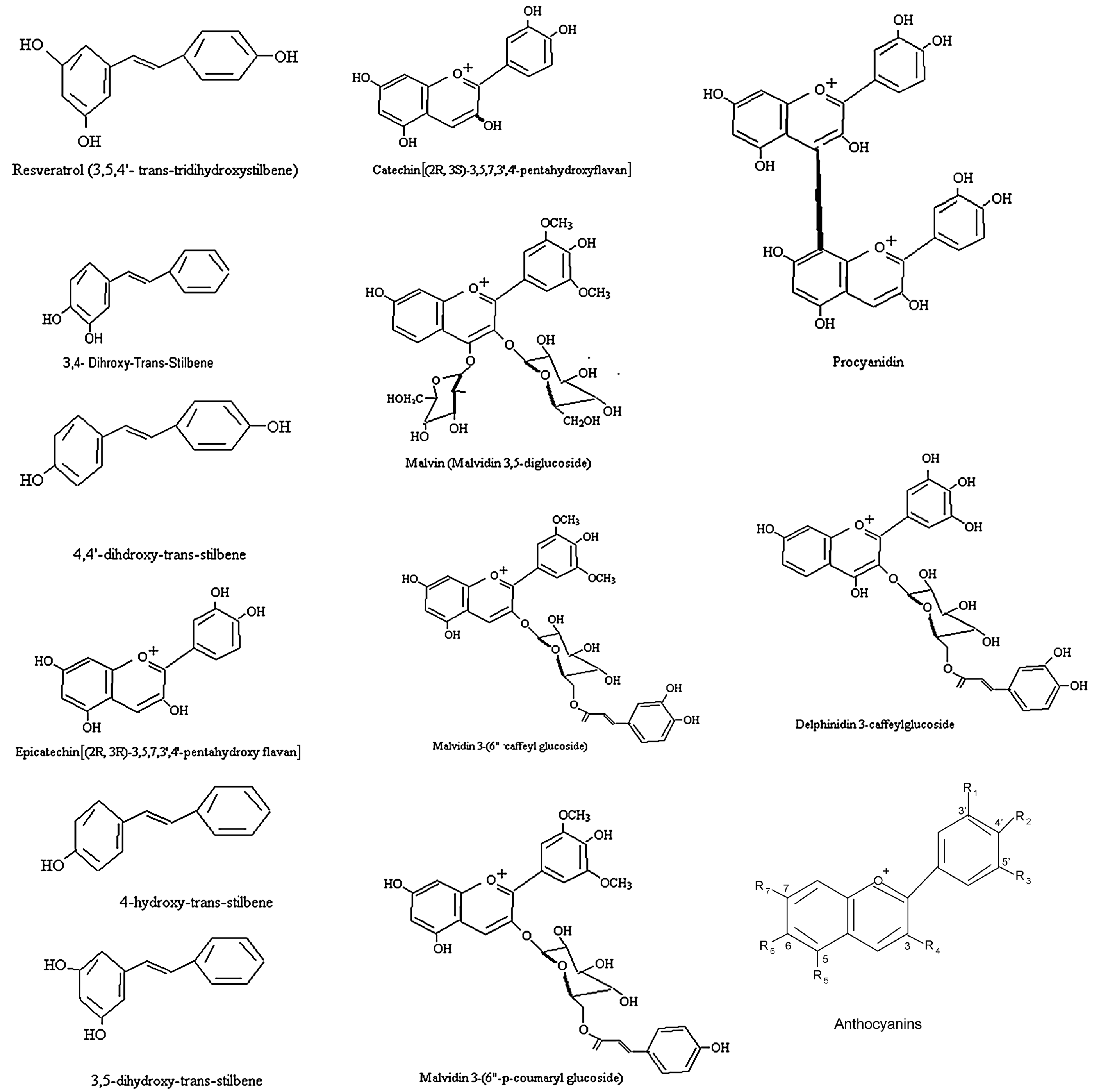

FIG. 1. Chemical structures of well identified biologically active compounds from grapes.

(0.08–0.01%). Grapes are also a major source of other nutrients like boron,[4] a possible substance for bone health. The essential parts of the berry include skin, pulp, and seeds. The composition of the grape, in terms of nutrients, is summarized in Table 1. Nutritional analysis per serving with grape halves gives ~78 calories of energy, ~0.3 g of protein, ~19 g of carbohydrate, ~0.23 g of fat (~3% calories from fat), ~0.18 mg of sodium, ~155 mg of potassium, ~0.4 g of fiber, ~20 ng of calcium, ~30 ng of phosphorus, and ~1 mg of vitamin C.

BIOLOGICAL ACTIVITIES OF GRAPE

Although a large number of compounds have been isolated from the grape, only some of them have been found to be having biological/medicinal activities, as summarized in

Table 1. Nutrients from Grapes (per 100 g)[3]

Nutrient	*Level*
Proximates	
Water	74.796 g
Energy	61.740 kCal
Energy	257.600 kJ
Protein	0.580 g
Lipid (fat)	0.322 g
Ash	0.524 g
Carbohydrate (by difference)	15.778 g
Fiber (total dietary)	0.920 g
Minerals	
Calcium	12.880 mg
Iron	0.267 mg
Magnesium	4.600 mg
Phosphorus	9.2 mg
Potassium	175.72 mg
Sodium	1.840 mg
Zinc	0.037 mg
Copper	0.037 mg
Manganese	0.661 mg
Selenium	0.184 μg
Boron[4]	0.748 mg
Vitamins	
Vitamin C (total ascorbic acid)	3.680 mg
Thiamine	0.085 mg
Riboflavin	0.052 mg
Niacin	0.276 mg
Pantothenic acid	0.022 mg
Vitamin B6	0.101 mg
Folate (total)	3.680 μg
Vitamin A (IU)	92.00 IU
Vitamin A (RAE)	4.600 μg RAE
Vitamin E	0.313 mg ATE
Lipids	
Fatty acids (total saturated)	0.105 g
14:0	0.003 g
16:0	0.090 g
18:0	0.012 g
Fatty acids (total monounsaturated)	0.013 g
18:1 (undifferentiated)	0.01 g
Fatty acids (total polyunsaturated)	0.094 g
18:2 (undifferentiated)	0.073 g
18:3 (undifferentiated)	0.022 g
Amino acids	
Tryptophan	0.003 g
Threonine	0.016 g
Isoleucine	0.005 g
Leucine	0.012 g
Lysine	0.013 g
Cysteine	0.009 g
Phenylalanine	0.012 g
Tyrosine	0.010 g
Valine	0.016 g
Arginine	0.042 g
Alanine	0.024 g
Aspartic acid	0.071 g
Glutamic acid	0.121 g
Glycine	0.017 g
Proline	0.019 g
Serine	0.028 g

This composition is an approximation (obtained from the Nutrition Data website[5]); it may vary with regard to various species of grapes, age, region of growth, and storage. ATE, α-tocopherol equivalents; RAE, retinol activity equivalents.

Table 2. The major medicinal properties of grape and its constituents are antioxidant, anticarcinogenic, immunomodulatory, antidiabetes, anti-atherogenic, neuroprotective, anti-obesity, anti-aging, and anti-infection (Fig. 2). In particular, several biological activities of resveratrol, a major compound extracted from the skin and seeds of grape, have been reported.

Antioxidant property

Oxidative stress is a hallmark of various health problems. Resveratrol (3,5,4′-*trans*-trihydroxystilbene) is a natural phytoalexin abundantly found in grapes and red wine, which has potent antioxidant property. Over the years several analogs, *i.e.*, 3,4-dihydroxy-*trans*-stilbene (3,4-DHS), 4,4′-DHS, 4-hydroxy-*trans*-stilbene, and 3,5-DHS, of resveratrol have been synthesized and have been found to have an attenuating effect on free radical-induced peroxidation of rat liver microsomes.[6] Thus, all these *trans*-stilbene derivatives are potent antioxidants against both 2,2′-azobis (2-amidinopropane hydrochloride)- and iron-induced peroxidation. The most potent antioxidant activity was noticed with 3,4-DHS, followed by 4,4′-DHS, resveratrol, 4-hydroxy-*trans*-stilbene, and 3,5-DHS respectively.[6] Further, resveratrol was also reported to show a strong inhibitory effect on 2,3,7,8-tetrachlorodibenzo-*p*-dioxin-induced aryl hydrocarbon receptor DNA binding activity as well as on the expression of cytochrome P450 1A1 and 1B1, which are known to oxidize 17β-estradiol to produce catechol and estrogens.[7] Thus, resveratrol protects the tissues from oxidative stress as well as catechol estrogen-induced damage. In another study, proanthocyanidin, a variant of resveratrol, isolated from grape seed extract also exhibited antioxidant protection in smokeless tobacco-induced cellular injury, and this activity has been ascribed to be due to alteration in Bcl-2 and p53 expression in *in vitro* and *in vivo* systems.[14]

Moreover, skin and seeds of grape are good sources of phytochemicals like gallic acid, catechin, and epicatechin, which are appropriate raw substrates for the production of antioxidative dietary supplements.[21] Antioxidant thioconjugates could also be obtained from the white grape pomace.[23] Analysis of Concord grape juice has shown that it is a rich source of flavonoids, having greater antioxidant efficacy, as seen *in vitro,* than α-tocopherol (vitamin E).[24] Further, Concord grape juice has also been found to increase serum antioxidant capacity and thereby be more protective than α-tocopherol against low-density lipoprotein (LDL) oxidation in healthy adults. Thus, O'Byrne *et al.*[24] concluded that Concord grape juice flavonoids are potent antioxidants that protect the host against oxidative stress and reduce the risk of free radical damage and onset of chronic diseases. Surprisingly, dried grape seeds, obtained after the color extraction and alcohol distillation of wine pomace, still kept considerable flavanol content with high antioxidant activity, even after exposure to high temperatures.[15] The polyphenol diprim is a natural polyphenol from Amur grape crest, and it has been documented to promote inhibition of lipid peroxidation and to have a glutathione-saving effect that might be due to the

Table 2. Summary of Bioactive Compounds from Grapes and Their Biological Functions

Grape compound(s)	*Source*	*Model*	*Activities*	*Biological activity*	*Biomarkers*	*Major results*	*Reference*
Resveratrol	Fruit skin and seeds	Rat liver microsomes	*Ex vivo*	Antioxidant	TBARS	Decreased	6
		MCF-10A cells	*In vitro*	Antioxidant	ROS	Decreased	7
					DNA damage	Decreased	
					CYP1A1	Decreased	
					CYP1B1	Decreased	
		Human ovarian carcinoma cell line	*In vitro*	Anticarcinogenic	Cell growth	Decreased	8
					Cell death	Increased	
					Cytochrome *c* release	Increased	
					Autophagocytosis	Increased	
		Mice	*In vivo*	Anticarcinogenic	Tumor number	Decreased	9
					Tumor volume	Decreased	
					p53	Increased	
					Bax	Increased	
					Bcl-2	Decreased	
					Survivin	Decreased	
					Cytochrome *c* release	Increased	
					Caspase activation	Increased	
					Apaf-1	Increased	
					PI3K/Akt	Increased	
		Rats	*In vivo*	Anti-inflammatory	Neutrophil infiltration	Decreased	10, 11
					PGE_2	No change	
					PGD_2	Decreased	
					COX-1 and -2	Decreased	
					IL-1β	Decreased	
		Rats (ischemia)	*In vivo*	Cardioprotective	NO	Decreased	12
					Lactate dehydrogenase	Decreased	
		Donryu rats	*In vivo*	Cardioprotective	Triglyceride	Decreased	13
					VLDL	Decreased	
					LDL	Decreased	
					Fecal neutral sterols	Decreased	
					Fecal bile acids	Decreased	
Proanthocyanidins	Seed extracts	NHOK cells	*In vitro*	Antioxidant	Cell viability	Increased	14
					DNA damage	Decreased	
					Bcl-2, p53	Increased	
		TBARS and TEAC assay	*In vitro*	Antioxidant	TBARS	Decreased	15
					TEAC	Decreased	
		Rats (ischemia)	*In vivo*	Cardioprotective	Apoptotic rate	Decreased	16
					ROS	Decreased	
					JNK-1	Decreased	
					c-Jun	Decreased	
		Rats (STZ-induced)		Antidiabetic	Gray value	Increased	17
					RAGE	Decreased	
					NF-κB p65	Decreased	
Anthocyanins	Fruit skin and seeds	Wistar rats	*In vivo*	Antioxidant	TBARS	Decreased	18
					Catalase	Decreased	
					SOD	Decreased	
					Carbonyl	Decreased	
		Rats	*In vivo*	Anticarcinogenic	Aberrant crypt foci	Decreased	19, 20
					Cell proliferation	Decreased	
					DNA damage	Decreased	
					COX	Decreased	

Gallic acid, catechin, epicatechin	Fruit skin and seeds		*In vitro*	Antioxidant	ORAC	Decreased	21
					Hydrogen donor activity	Increased	
					Peroxy radical scavenging activity	Increased	
Epigallocatechin 3-gallate	Skin and seed	HEp-2 laryngeal carcinoma cells, LoVo colon carcinoma cells, HeLa cervical carcinoma cells, and normal myoepithelial cell line		Antineoplastic	Neoplastic activity	Decreased	22
					Apoptosis	Increased	
Thioconjugates	White grape	Chemical assay	*In vitro*	Antioxidant	DPPH scavenging assay	Increased	23
Flavonoids	Concord grape juice	Human	*In vivo*	Antioxidant	α-Tocopherol	Increased	24
					Serum O_2 radical absorbance capacity	Increased	
					Plasma protein carbonyls	Decreased	
					LDL oxidation	Decreased	
		Rats	*In vitro* and *ex vivo*	Antidiabetic	β-Cell regeneration	Increased	25
		CHO cells and mice	*In vitro* and *in vivo*	Anticarcinogenic	Aromatase activity	Inhibited	26
					Tumor weight	Decreased	
					Estradiol	Decreased	
					Estrone	Decreased	
Diprim	Amur grape crest	Rats		Cardioprotective	Triglyceride	Decreased	27
				Antioxidant	Cholesterol	Decreased	
					Liver triglyceride	Decreased	
					TBARS	Decreased	
					GSH	Increased	
					Fatty acid oxidation	Increased	
Melanin		Rats (adjuvant-induced disease)		Antioxidant	Peroxidation in rat liver microsomes	Decreased	11
					Tissue TBARS	Decreased	
				Anti-inflammatory	IL-2	No change	28
				Immunosuppressive	IL-1	Decreased	
					IL-6	Decreased	
					TNF-α	Decreased	
					Serum globin fraction	Decreased	
					$T4^+$ and $T8^+$	Decreased	
Oleanolic acid and aleanilic acid	Grape skin	INS-1 cells	*In vitro*	Insulin secretor	Insulin secretion	Increased	29
					COX activity	Decreased	
Tannins		Rats	*Ex vivo* and *in vivo*	Blood pressure regulator	SBP	Decreased	30
					GSH	Increased	
					GSSG	No change	
					COX-2	Increased	
					Thromboxane B_2	Increased	
					Contraction	Decreased	
					Relaxation	Increased	

CHO, Chinese hamster ovary; CYP, cytochrome P450; DPPH, 2,2-diphenyl-1-picrylhydrazyl; GSH, reduced glutathione; GSSG, oxidized glutathione; JNK, c-Jun N-terminal kinase; ORAC, oxygen radical absorbance capacity; PI3K, phosphoinositide 3-kinase; RAGE, receptor of advanced glycation end products; ROS, reactive oxygen species; SBP, systolic blood pressure; SOD, superoxide dismutase; STZ, streptozotocin; TBARS, thiobarbituric acid-reactive substances; TEAC, Trolox equivalent antioxidant capacity.

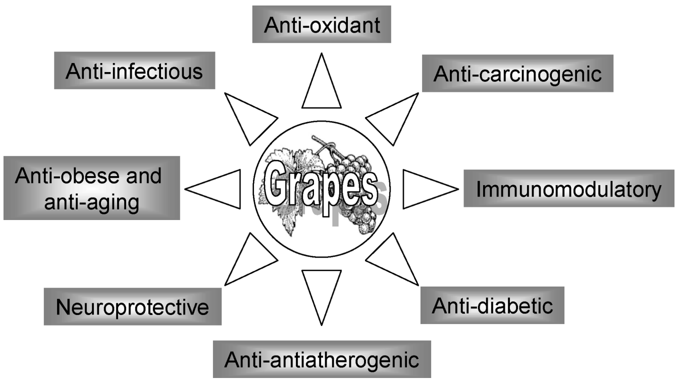

FIG. 2. Medicinal properties of grapes and their ingredients.

contents of polyphenols, which capture free radicals.[27] On the basis of these observations the consumption of fruit of the grape and/or its constituents may be part of therapeutic regimens to suppress oxidative stress-related threats. Another important group of components present in grapes is the anthocyanins, which belong to the flavinoid family. In recent years, several studies have shown that anthocyanins displays a wide variety of biological activities, including antioxidant, anti-inflammatory, antimicrobial, and anticarcinogenic activities.[31] Antioxidant activity of anthocyanins have been extensively studied and reviewed elsewhere.[18]

Anticarcinogenic activity

Cancer is a rapidly growing health problem that is the biggest challenge to researchers and medical professionals regarding various prevention and therapeutic strategies. Dietary intake of many vegetables and fruits, including grapes, has been found to reduce the risk of occurrence of cancer.[32] Resveratrol is well characterized as having anticarcinogenic effects as well as antineoplastic properties. Various molecular mechanisms for anticarcinogenic effects of resveratrol have been proposed, and one of these is supposed to be associated with mitochondrial release of cytochrome *c*, formation of the apoptosome complex, and caspase activation.[33]

The antiproliferative and pro-apoptotic effects of resveratrol in breast cancer cells are thought to be through accumulation of ceramide and the phenolic moiety of stilbenoids, which is necessary to induce ceramide-associated growth inhibition.[34] The inhibitory effects of red wine polyphenolics on human breast cancer cells have been demonstrated to be due to inhibition of cell proliferation by flavonoids, which in turn could be related to the inhibition of calcium/calmodulin-associated phosphodiesterase activity, indicating that flavonoids interfere with the function of the second messenger calcium. Thus, certain grape wine ingredients that have anticancer properties may be helpful for developing functional neutraceuticals with anticancer properties.[35] Resveratrol has also been reported to suppress the proliferation of human prostate cancer cells with a typical apoptotic feature, interfering with the expression of heat shock protein 70.[9] Kubota *et al.*,[36] in their experiments with A549, EBC-1, and Lu65 lung cancer cells, found that resveratrol could inhibit (by 50%) the growth of cells and could enhance the activity of paclitaxel, a chemotherapeutic agent for lung cancer treatment; based on these findings, they recommended that resveratrol could be involved in an adjuvant to anticarcinogenic therapy for lung cancer. Recently Roy *et al.*[37] reported that resveratrol inhibits mouse skin tumors by regulation of mitochondrial metabolism and the phosphoinositide 3-kinase/Akt pathway.

Aromatase is considerably expressed in breast cancer tissue compared to normal tissue. Procyanidin B dimers from red wine extract fraction also have good inhibitory action on aromatase activity, and it was suggested that these dimers could play a role in treating breast cancers.[26] Epigallocatechin 3-gallate, another component from grapes, has been demonstrated to possess high antineoplastic potential due to its programmed cell death induction.[22] In addition, one more bioactive component of grapes, anthocyanin, has also been reported to have anticarcinogenic potential.[19,20] In conclusion, grapes may be considered as an alternative/complementary therapeutic regimen to prevent and/or suppress tumor progression in various cancer types.

Effect on apoptotic cell death

Apoptosis is an important cellular process that participates in the homeostasis of various pathophysiological conditions. Various signaling pathways involved in cell proliferation and cell death (apoptosis) are presented schematically as a summary in Figure 3, which will allow readers to easily understand the mechanisms of action of active ingredients from grapes. Various natural components are characterized as playing an important role in regulating the apoptotic rate *in vitro* and *in vivo*, and here we discuss the role of grape constituents in relation to apoptosis. Resveratrol has been reported to induce activation of apoptosis signal-regulating kinase 1, which activates the downstream kinases c-Jun N-terminal kinase and p38 mitogen-activated protein kinase and leads to regulation of apoptotic cell death.[38] Also, Su *et al.*[38] have reported that resveratrol activates the small GTP-binding protein Cdc42 and apoptotic signal-regulating kinase 1/c-Jun N-terminal kinase/Fas ligand signaling cascade in HL-60 cells, which leads to subsequent apoptosis. Regarding the effect of resveratrol on cell growth, resveratrol has been found to inhibit the growth of human prostate carcinoma cells[34] and the human breast cancer cell line MCF-7.[35] This type of antiproliferative effect of resveratrol has been associated with the inhibition of D-type cyclins and cyclin-dependent kinase 4 expressions and with the induction of tumor suppressor p53 and cyclin-dependent kinase inhibitor p21WAF1/CIP. Moreover, the kinase activities of cyclin E and cyclin-dependent kinase 2 are known to be inhibited by resveratrol without alteration of their protein levels. Further, resveratrol treatment has also been demonstrated to up-regulate Bax protein and mRNA expression in a dose-dependent manner without significantly affecting Bcl-2 and Bcl-xL levels. It is considered

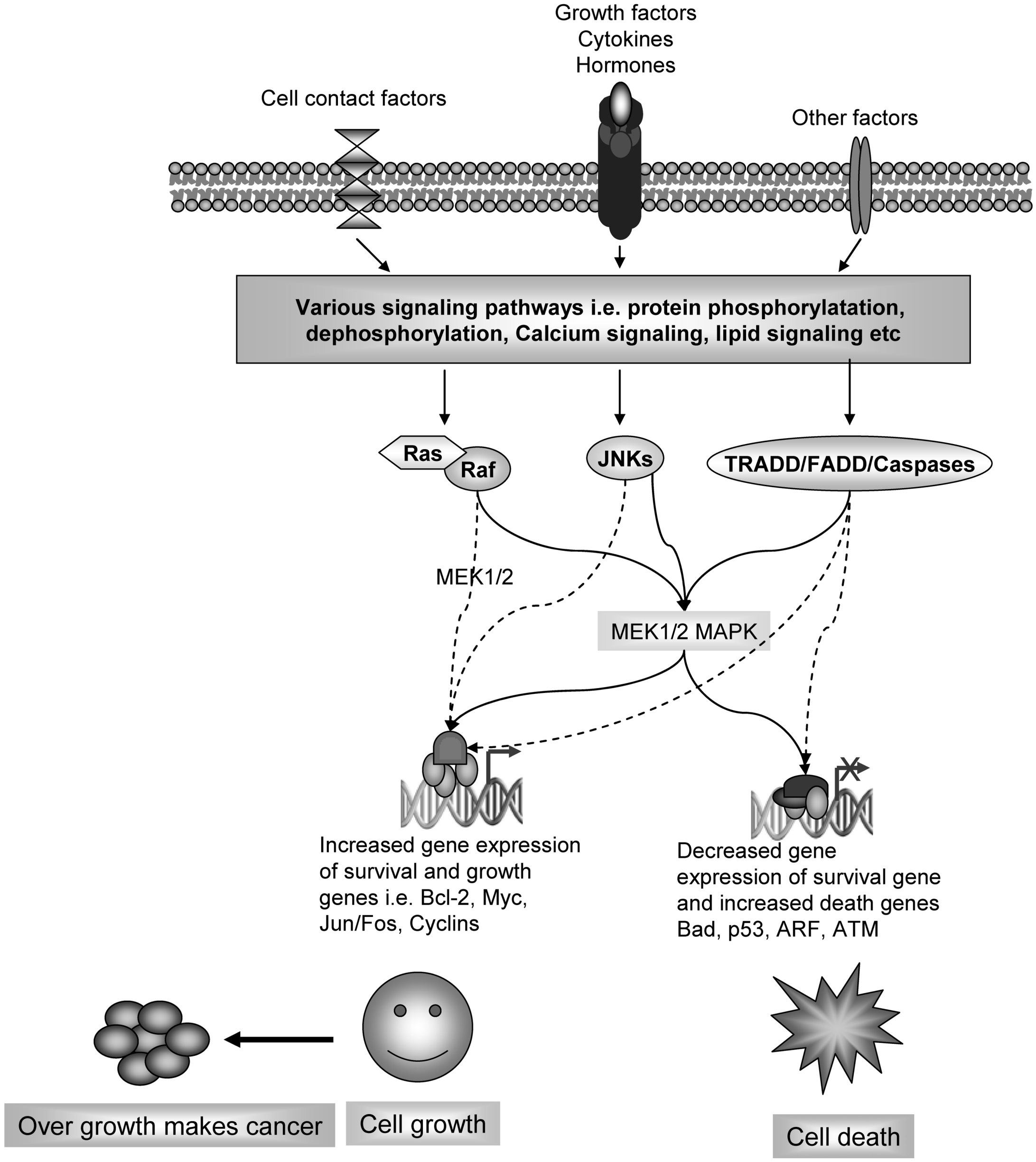

FIG. 3. Schematic representation of the fate of cell survival and apoptosis during cell growth and functioning. The path of cell survival versus apoptosis (cell death) depends on the extracellular (cell contact factors, growth factors, cytokines, hormones, and other factors) and intracellular (signaling mediators [*i.e.*, Ras, c-Jun N-terminal kinases (JNKs), tumor necrosis factor receptor-1 associated death domain/Fas-associated death domain (TRADD/FADD), caspases, mitogen-activated protein kinases (MAPKs)]) signals. These signals regulate cell survival genes (Bcl-2, Myc, Jun/fos, cyclins) and apoptotic genes (Bad, p53, ARF, ATM) and push the cells to their respective ways. Normally aged, virus-infected, damaged, and competent cells go to apoptosis, and the remaining cells go to cell survival to function in normal work and after completion of their life span again turn over by apoptosis. If cell survival factors are overactivated and dominated by apoptotic genes, then cells continuously keep proliferating, and cancer develops. MEK, mitogen-activated protein kinase kinase.

that these effects are caused through involvement of activation of caspase-3 and caspase-9.[8] Kim *et al*.[8] and Hayashibara *et al*.[39] have reported that resveratrol inhibited the growth of human T cell lymphotrophic virus-1-infected cell lines, at least in part, by inducing apoptosis mediated by down-regulation in survivin expression. In a study with breast cancer cells resveratrol has been found to induce apoptosis via p53-dependent pathways.[40] Additionally, heyneanol A, a tetramer of resveratrol, isolated from the roots of *Vitis amurensis*, has been found to induce cytochrome *c* released from mitochondria into the cytosol and subsequent caspase activation.[41]

Anti-inflammatory and immunomodulatory properties

The role of inflammation is widespread in various immunopathophysiological conditions. The main target of current research is to identify anti-inflammatory natural components to treat various inflammatory diseases. Thus far several findings have established that resveratrol has potent anti-inflammatory and immunomodulatory activities.[42] Martin *et al.*[10] reported that resveratrol considerably reduced the colonic injury, index of neutrophil infiltration, and levels of cytokines *in vivo*. However, resveratrol could not reverse the increased prostaglandin (PG) E_2 levels but produced a significant fall in PGD_2 levels. It targeted the PGH_2 synthases, cyclooxygenase (COX)-1 and COX-2, that catalyze the synthesis of PGs via sequential COX enzymes while peroxidase reactions were inhibited.[11,43] Resveratrol inactivated COX-1 and offered a design for a selective COX-1 inactivator that worked at the peroxidase active site.[43,44] Resveratrol inhibited phorbol myristate acetate ester-mediated induction of COX-2 in human mammary glands and oral epithelial cells. Treatment of cells with phorbol myristate acetate induced COX-2, causing a marked increase in PGE_2. Resveratrol also inhibited phorbol myristate acetate-mediated activation of protein kinase C.[45]

Resveratrol and quercetin have been identified as novel non-steroidal compounds with anti-inflammatory activity that have applications for the treatment of inflammatory diseases. These molecules inhibit both interleukin (IL)-8 and granulocyte-macrophage colony-stimulating factor release from A549 cells. Resveratrol, but not estradiol, inhibited cytokine-stimulated inducible nitric oxide (NO) synthase expression and nitrite production in human primary airway epithelial cells.[43] Grape melanin also interferes with PG-, leukotriene-, and complement system-mediated inflammation.[28] Melanin also reduced levels of the cytokines IL-1, IL-6, and tumor necrosis factor-α (TNF-α) in adjuvant-induced diseased rats.[28]

The inhibition of COX, induction of CD95 signaling-dependent apoptosis, effects on cell division cycle, and modulation of nuclear factor κB (NF-κB) activation suggest a possible effect of resveratrol on the immune system. Resveratrol induces the development of cytokine-producing $CD4^+$ and $CD8^+$ T cells by stimulating peripheral blood mononuclear cells with anti-CD3/anti-CD28 *in vitro*.[46] The phagocytosis rate has been found to increase in a human promonocytic cell line, when treated with resveratrol and quercetin, whereas both polyphenols demonstrated cytostatic activity and a pro-intraphagocytic effect on U937 cell growth.[47]

Antidiabetic property

Currently a large part of the adult population worldwide is suffering from diabetes, and prevalence of the disease is increasing day by day. Until now no therapy has been available to treat diabetes, and various therapeutic strategies have also been applied to suppress its increasing prevalence. Among these strategies the use of various natural components is common, of which which grapes and its constituents are one. Bolton *et al.*[48] demonstrated that the insulin response to the whole fruit of the grape was significantly higher than that to juice alone. This led to speculation that the glucose in grapes is more insulinogenic than those in oranges and apples. The plasma insulin and glucose responses to fruit depended on the fiber and glucose content.[48] Oleanolic acid and aleanolic aldehydes present in grape skin have insulin secretor activities.[29] Resveratrol inhibits the uptake of glucose by transformed human myelocytic cells.[49] Grape seed extract, chromium polynicotinate, and zinc monothionine combinations enhance insulin sensitivity and lowers levels of glycosylated proteins.[50] In addition, these combinations can markedly lower systolic blood pressure in normotensive rats and lessen oxidative damage and decrease glycosylated hemoglobin without any toxicity.[51] Flavonoids and epicatechin isolated from grapes stimulate β-cell regeneration and ameliorate chemically induced diabetes in animals.[25] Recently, it has been shown that resveratrol activates SIRT-1 deacylase (an enzyme that deacetylates various proteins involved in glucose homeostasis) and protects against high fructose-induced diabetes.[52] Milne *et al.*[53] reported that analogues of resveratrol improved energy homeostasis and insulin sensitivity. Recently, Xu *et al.*[17] reported that feeding an extract of grape seed proanthocyanidins down-regulates the receptor for glycation end products and/or NF-κB p65.

Cardioprotective effects

Among the biggest health problems today is cardiovascular diseases, which affect around 12% of the adult population worldwide. The pathophysiology of cardiovascular diseases is very complex, and therefore it is termed as metabolic syndrome. Cardioprotective effects of various natural components have been investigated; here we discuss the role of grapes. Purple grapes have partial antithrombotic effects due to the availability of phytochemicals.[54] Epidemiologic studies suggest that red wine from grapes is associated with a reduced incidence of mortality and morbidity from coronary heart diseases, which might be due to changes in lipid metabolism, antioxidative effect, and changes in hemostasis. It has been reported that moderate intake of red wine increases high-density lipoprotein cholesterol, decreases LDL cholesterol, decreases the fibrinogen level, and inhibits platelet aggregation; this could positively influence stress, fear, anxiety, and depression.[55] A study from the University of Wisconsin reported that grape juice improved blood flow by 6.4% and protected LDL from oxidation.[56] Research revealed that the flavonoids in grape juice decreased the tendency of blood to clot and that regular use of grape juice could reduce the risk of cardiovascular disease, a safer way to achieve protection against heart disease than wine.[56] Grape juice also inhibits platelet activity and protects against epinephrine activation of platelets as well as enhances endothelial production of NO.[57,58]

Grape seed extract reduced malonaldehyde content of the heart, indicating reduction of oxidative stress during ischemia and reperfusion.[59] The hearts of the grape seed extract-fed individuals are resistant to myocardial ischemia reperfusion injury, suggesting a cardioprotective role of grapes.[59] The cardioprotective effect has been attributed to antioxidants present in the polyphenol fraction of red wine. The wine extract, resveratrol, and proanthocyanidins are equally effective in reducing myocardial ischemic reperfusion injury, which suggests that polyphenolic antioxidants in wine play a vital role in cardioprotection.[16] Grape seed proanthocyanidin extract significantly reduced the appearance of apoptotic cardiomyocytes and appearance of reactive oxygen species in the ischemic/reperfused hearts, while functioning as an *in vivo* antioxidant.[60] The proanthocyanidin-fed animals were resistant to myocardial ischemia reperfusion injury as evidenced by improved recovery of postischemic contractile functions.[61,62] A plausible mechanism of action of grape red wine for cardioprotection was found to be through inhibition of the c-Jun N-terminal kinase-1 and c-Jun pathway, which might lead to inhibition of production of reactive oxygen species and rate of apoptosis.[61] The flavonoids in grapes are good inhibitors of plasminogen activator *in vitro*, which are present in grapes in the form of proanthocyanin. Hence grape juice may be a useful alternative dietary supplement to red wine without concomitant intake of alcohol.[63]

Resveratrol is a potent anti-arrhythmic agent with cardioprotective properties, and the same could be correlated with up-regulation of NO production.[12] Resveratrol suppresses levels of serum triglyceride and very-LDL (VLDL) and LDL cholesterol. This hypocholesterolemic action of resveratrol is partly attributed to an increased excretion of neutral sterols and bile acids into feces.[13] The increase in tyrosine phosphorylation of Iκ-Bα, p50-NF-κB, and p65-NF-κB suggests the involvement of such alterations in the modulation of NF-κB transcription activity, which shows the cardiovascular protective effects and suggests anti-atherogenic activities of the compound on endothelial cells.[64] Resveratrol has been found to pharmacologically precondition the heart through the up-regulation of NO.[65] NO, being a free radical with vasodilator properties, exerts dual effects on tissues and cells in biological systems. The high levels of flavonoids, catechins, tannins, and other polyphenolics in red wine induce NO formation in endothelial cells to improve circulation and suppress induction of inducible NO synthase.[30] Its beneficial effects in focal cerebral ischemia may be due to its antiplatelet aggregation activity, vasodilating effect, or antioxidant property or by collective effects of all of these.[66] In ovarectomized rats, resveratrol acts like mammalian estrogens, thus lowering blood pressure and increasing dilatory responses to acetylcholine.[67]

Neuroprotective property

The increasing prevalence of neurodegenerative diseases has attracted researchers to examine various components that can be used to treat/prevent neurodegeneration. Investigations of whether polyphenolic antioxidants offer protective effects beyond the cardiovascular system and whether polyphenols from other plant sources offer beneficial effects to human health of interest are useful. Animal models have provided information clearly indicating the ability of grape polyphenols to ameliorate neuronal damages due to chronic ethanol consumption. Resveratrol has shown protective effects on neuron cell death induced by ethanol and other oxidative agents.[68] Resveratrol is a potent neuroprotective agent in focal cerebral ischemia.[67] Recently, it has been reported that resveratrol protects against ethanol-induced neurotoxicity.[69] The neuroprotective effect of resveratrol might be due to its antioxidant and ion channel regulatory (Ca^{2+} channels) properties. Aruoma *et al*.[70] also reported that the low-molecular-weight proanthocyanidin dietary biofactor Oligonol® (Maypro Industries, Inc., Tokyo, Japan) also exhibited neuroprotective effects by modulating oxidative stress and other factors.

Effect on obesity and aging

Obesity is the main growing health problem leading to immature morbidity and mortality in a major part of the world's population. The main cause of obesity is high energy (fat) intake through food. One of the strategies to inhibit prevalence of obesity may be suppression of fat absorption from the gastrointestinal tract. Grape seed extract enriched with compounds that inhibit gastrointestinal digestion of lipids through inhibition of lipase enzymes (pancreatic lipase, lipoprotein lipase, and hormone-sensitive lipase *in vitro*) may provide a safe, natural, and cost-effective weight control treatment. Thus, grape seed extract may have its potential application as a treatment for obesity.[71] Recently it has been reported that various analogs of resveratrol have the capacity to reduce insulin resistance by enhancing energy homeostasis.[53] Resveratrol is also known to interact with numerous proteins and pathways involved in pathogenesis of obesity, including mitochondrial ATP synthase and complex III, fatty acid synthase, protein kinase C, p53, mitogen-activated protein kinase kinase1, TNF-α, and NF-κB, all of which are candidates for mediating its *in vivo* effects. In particular, activation of AMP kinase by resveratrol protects against atherosclerosis and liver damage in diabetic mice, suggesting a likely mechanism for the observations reported by Moreno, de la Lastra, and their colleagues.[71,72]

Accelerated aging is another health threat, affecting whole populations and sometimes leading to premature mortality. Aging is a progressive accumulation of changes as time progresses and is responsible for the ever-increasing likelihood of disease and death. The precise cascade of pathological events responsible for aging mainly is the enhanced production of free radicals. The deleterious effects of free radicals on proteins, nucleic acids, and fats as well as enhanced glycosylation of proteins and DNA are prevalent during aging. Partial insulin resistance may be a common etiology, behind the pathobiological alterations of advancing age. Grape seed proanthocyanidin extract has been demonstrated to improve insulin sensitivity and ameliorate free radical formation by reducing the signs/symptoms of chronic age-related disorders.[51] Resveratrol and various anthocyanins of grapes have been well established as having anti-aging effects through various mechanisms, of which the antioxidant property is the major one.[72]

Hormonal agent and antipyretic property

Resveratrol has been shown to be a non-flavonoid phytoestrogen and to act as an estrogen receptor superagonist in MCF-7 cells, transiently transfected with estrogen-responsive reporter constructs. Several additional hydroxystilbenes, including diethylstilbestrol and piceatannol, were tested, and all showed estrogen receptor agonism, but superagonism was specific to resveratrol.[73] Grape seeds and anthocyanins inhibited apyrase (an enzyme that hydrolyzes ATP and ADP) and ecto-ATPase, which is related to the integrity of the endothelium and the synthesis and release of NO. In addition, grape seeds and anthocyanins activate P2Y1 and/or P2Y2 purinoceptors of endothelial cells, triggering the synthesis and release of NO, which leads to relaxation and reducing the body temperature.[74]

*Antiviral and anti-*Encephalitozoon *activities*

Resveratrol has been found to show anti-herpes simplex virus activity as a cream with 12.5% and 25% resveratrol, which effectively suppressed lesion formation.[75] Hepatitis is a widespread form of disabling viral infection of the liver. Grapes have been shown to improve the systemic condition of hepatitis-affected liver in experimental animals.[76] Resveratrol synergistically enhances the anti-human immunodeficiency virus type 1 activity of the nucleoside analogs zidovudine, zalcitabine, and didanosine. Moreover, resveratrol at $10\,\mu M$ was not toxic to cells and by itself reduced viral replication by 20–30%.[77] Stilbenes are phenolic molecules that have antifungal effects in plants.[78]

Microsporidians of the genus *Encephalitozoon* are an important cause of disease in immunocompromised patients. Resveratrol at $50\,\mu M$ showed significant sporicidal activity, while at $10\,\mu M$ resveratrol also inhibited intracellular development of the parasite, without affecting host cell viability.[79]

Other health beneficial effects of grapes

Resveratrol is suggested to be a potent anti-glomerulonephritic food factor capable of suppressing proteinuria, hypoalbuminemia, and hyperlipidemia.[80] The glycosylation of resveratrol by resveratrol glucosyltransferase is distinct from glycosylation by the glucosyl transferase(s) active on the other phenolics.[78] Resveratrol diffuses rapidly across the intestinal epithelium.[81]

CONCLUSIONS AND PERSPECTIVES

The fruit of the grape is liked by consumers worldwide for its taste and is blessed with a bundle of nutritional properties. The health-favorable properties of active ingredients are prevalent in different parts (*e.g.*, fruit, stems, and seeds) of grapes. This further adds to the benefits of this fruit, thereby tempting the consumer for its addition in the diet of humans to avoid disease, infections, and relaxants. Keeping in mind all the facts described here, it is worthwhile mentioning that intake of grapes in the regular diet of humans could help a lot in maintaining good health. Similarly, the purified products obtained from the fruit could prove to be potential agents in prevention and treatment of several diseases.

AUTHOR DISCLOSURE STATEMENT

No competing financial interests exist.

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