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Health Benefits of Grapes Polyphenols

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Abstract: Diet based therapies and other regimens from fruits are being used to recover from health disorders since centuries. Grape (*Vitis vinifera* L.) is not only used for nutritional purposes, but also for exclusive therapeutics, owing to its antimicrobial, antioxidant and anti-inflammatory perspective. Grapes are non-climacteric fruits and grown on the deciduous and perennial woody vines. Grapes are abundant in polyphenols, which are known for numerous biological activities and health-promoting benefits. Resveratrol, a phytoalexin antioxidant produced when plants are exposed to various abiotic and biotic stresses. Red grapes and its juices and wine are the major source of dietary resveratrol in humans and have both chemo-preventive and therapeutic properties against various ailments. Therefore have numerous implications for human health. Grape has been useful for reducing the extent of diabetes mellitus, cardiovascular disorders and digestive problems. This review elaborates the health claims of various chemical components of grapes and their functional roles, with special reference to antioxidant potential, immune-nutrition, anticancer perspectives and cardiovascular cure.

Keywords: Grape, phytochemicals, antioxidant potential, anti-aging, nutraceutical value, stilbenes, phytoalexins, functional roles, viniferins.

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1. Grape Polyphenols

Plants are sources of nutrients and several bioactive moieties (Brenes al., 2016), responsible for vital functions in humans, therefore possess numerous health prospects (Joshi et al., 2001; Weseler and Past, 2017). Energy and dietetic regimes linkages are mostly reported in literature; however, the extraction of bioactive moieties and their impacts on human metabolism need systematic and coherent research investigations, for establishment of meticulous and persuasive association for consumers (Waet al., 2013). Grape (*Vitis vinifera* L.) is a leading fruit crop producing 70 million metric tons grapes annually in the world with extraordinary taste and flavor (Nowshehri et al., 2015). Various food products are produced from its fruit. Its seeds and leaves are also utilized for production of herbal medicines, as well as dietary supplements (Ben-Arye et al., 2016; Liperoti, et al., 2017; Saad et al., 2006; Sap Sapwarobol et al., 2012)..

Phytochemicals such as tannins, anthocyanins, flavonols, flavan-3-ols, epicatechin, epigallocatechin, catechin, gallocatechins, and epicatechin gallate, proanthocyanidins (typically hexamers) or procyanidins (Pezzuto, 2008) obtained from grape fruit have been reported for their bioactive properties (Doshi et al., 2006). Acylated procyandin, an ester of gallic acid is obtained from grape seeds extract (GSE) (Fuleki and Ricardo-da-Silva, 1997); while, epicatechin monomers epicatechin-3-O-gallate, catechin, 11 trimeric, 14 dimeric and 1 tetrameric procyanidin are present in grapes (Gabetta et al., 2000).

Flavonoids are phenylpropanoid derivatives with tri-ring (C 6 -C 3 -C 6) structure. Their central ring is responsible for the degree of oxidation and substitution in flavonoid structure. Flavonoids are comprised of flavonols, flavan-3-ols, proanthocyanidins and anthocyanins. In grapes, large numbers of structural modifications of flavonoids are possible due to multiplicity of various innate products (Kitamura, 2006). The flavonoids and their conjugates exist in several plants, and these compounds can be accumulated in plants and differ based on plant phenological period, their localization in organ and tissue and cell types (Schwinn and Davies, 2004).

Flavonoids prevent from UV rays, production of reactive O_2 and signaling molecules, because they are responsible for color to flowers, fruits and seeds, as well as also prevent from the microbial contamination (Kitamura, 2006). Anthocyanins, tannins, flavonols and flavan-3-ols are major classes of flavonoids. They give organoleptic properties to wine and other by-products (Adams, 2006). The anthocyanins contents range from 11.5 to 29.8 mg/g in different cultivars of red grape. Moreover, grape peel consists of free flavan-3-ol monomers e.g., epicatechin and catechin (Downey et al., 2003).

These polyphenols also possess numerous biological activities and health-promoting potential. Grape skins primarily comprise of anthocyanins, flavonols, flavanols, phenolic acids and stilbenes (resveratrol) (Chacona et al., 2009). Different parts of grapes such as seeds, leaves, stems and peels contains flavonoids predominantly (+)-catechins, (−)-epicatechin and procyanidin polymers. Cardiovascular diseases and various kinds of cancers can be cured by using polyphenoles from different fruits in diet (Shanmuganayagam et al., 2007).

Makris et al., (2008) reported approximately 2178.8 mg/g, 374.6 mg/g, 23.8 mg/g and 351.6 mg/g total phenols in seed, skin, flesh, and leaf of probus, frankovka and rumenika grape varieties, respectively. However, the quantity of polyphenols in a particular cultivar may vary with climate, geographic condition, soil composition, and cultivation practices.

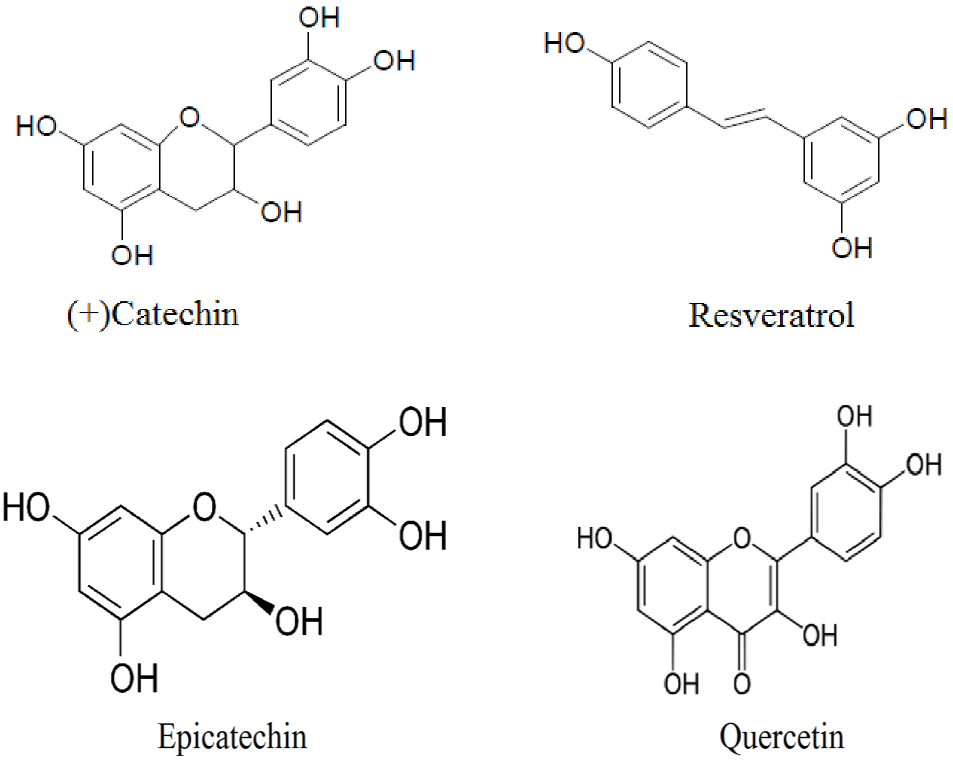
Grape juice phenolics can also prevent from the carcinogen-induced DNA and DNA amalgamation in case of breast cancer cells, and also induce apoptosis in prostate cancer cell lines. Despite several beneficial effects, the elevated concentration these compounds may cause toxic effects and can induce cell death. These polyphenolic antioxidants scavenge the free radicals prevent oxidative damage to organs and tissues. Releasing of dopamine from striatal muscles and cognitive performance were observed in rats after consumption of 10% of grape juice. Rats fed with diet supplemented with GSE (100 mg/kg BW) for a month prevented from the age-related oxidative DNA indemnity, and lowered the free radical-induced lipid peroxidation in neural tissue (Balu et al., 2006).

2. Antioxidant Potential of Grape Polyphenols

Toxic effects of oxidant metabolites caused oxidative stress and ultimately developing chronic diseases. Absolute prevention of oxidative damage is rarely achieved through endogenous defence mechanism. Therefore role of dietary antioxidants is very crucial in prevention and management of chronic diseases. Dietary vitamins (A, C and E), polyphenols and minerals are of significant implications for stress and disease management (Landete, 2012).

Wide range of flavonols is found in grapes mainly flavonol glycosides such as kaempferol 3-O-galactoside, kaempferol 3- Oglucoside, quercetin 3-O-glucoside and quercetin 3-O-glucuronide (Lu and Foo, 1999). Grape juice contained minute quantity of quercetin glycosides (7.2 to 9 mg/L) (Spanos and Wrolstad, 1992) flavonol glycosides (5.7 to 8.6 mg/L rutin equivalents) Frankelet al., (1998).

Total flavonols in white grape extract ranged between 1.6 to 10.4 mg/L, which significantly differ among grape genotypes (Breksa et al., 2010; Burns et al., 2001; Karakaya and Nehir 1999; Weidner et al., 2013). In juice of red grapes, relatively higher total flavonols contents (21.1 to 24.6 mg/L) whereas myricetin, quercetin, and kaempferol contents ranged from 13.4 to 100.9 mg/L (Frankel et al., 1998; Talcott and Lee, 2002).


(+)Catechin

Resveratrol

Epicatechin

Quercetin

Figure 1: Active compounds in grapes

Cantos et al., (2000) reported that concord and de chaunac grapes contained an average of 34.95 mg/kg quercetin 3-O-galactoside, whereas Napoleon cultivar contained 21.6 mg/kg quercetin 3-Oglucoside and quercetin 3-Oglucuronide, each. Similarly, Cabernet Sauvignon and two Merlot grapes cultivars contained 84.6 and 327.9 nmol/g flavonols in free and conjugated (kaempferol, myricetin, quercetin, and iso-rhamnetin) forms, respectively.

Grape polyphenols employ antioxidant mechanism through (i) scavenging peroxyl radicals and lipid alkoxyl (ii) chelating metal ions (iii) producing α-tocopherol during reduction of the α-tocopheroxyl radical (Bors et al., 1990).

3. Bioavailability of Resevratrol

Resveratrol (3, 5, 4'-trihydroxy-Trans-stilbene) is a polyphenolic parent compound of diversified family of molecules, consisting of polymers and glucosides exist in both *trans* and *cis* configurations (Soleas et al., 1997). Glycosylated piceid (3-O-B-d-glucosides) is generally existing form of resveratrol in a variety of plants, while some forms are conjugated, having sulfate group, methyl groups (pterostilbene) and a fatty acid (*trans*-resveratrol-3-sulfate).

Resveratrol is involved in inducible as well as constitutive defense mechanisms of plants and produced as stress metabolite in response to various biotic e.g., pathogenic attach (Dixon and Paiva, 1995; Jeandet et al., 1995; Hassan and Bae, 2017), injury and abiotic stresses e.g., UV-irradiation, O_3, growth hormone and heavy metals (Soleas et al., 1997; Bavaresco, 2003; Chong et al., 2009; Hassan and Bae, 2017). Resveratrol is believed to be a precursor of viniferins, which is antifungal stress metabolites, and potentially have significant role in disease resistance of grape plants (Langcake and McCarthy, 1979).

Although resveratrol found in almost 70 plant species (berries, grapes, peanuts and pines) however, it is found in very limited range of edible materials mainly skin of red grapes, juice and red wine produced from these grapes (Kundu et al., 2004; Hassan and Bae, 2017).

Genotype, grape cultivar, location of cultivation, growing season, environmental conditions and nutrient supplementation significantly influence resveratrol accumulation (Hassan and Bae et al., 2017; Zhu et al., 2017). Different parts including grapevine leaf, shoot, stem, bud, root, seed and grape skin differ in their resveratrol contents (Li et al., 2006; Zhu et al., 2017). However, higher resveratrol concentration found in grape skin as compared to its wine and juice.

Red grapes contain higher concentration of resveratrol than white grapes, consequently red grapes and its products are considered as major source of resveratrol in human diet (Delmas et al., 2006). Skin of fresh grapes has resveratrol in range of 50 to 100 µg/g of fruit weight, which results in a comparatively higher resveratrol concentration in red wine and grape juice (Baliga et al., 2005).

Since 1997, resveratrol received intense scientific attention as it was believed to be cure for various interconnected but broad range of diseases or health issues including cancer and aging, neurodegenerative and heart diseases, inflammation, diabetes and obesity, and ultimately promotes human health (Borriello et al., 2014; Brisdelli et al., 2009; Joseph et al., 2016). Resveratrol-induced effects on various pathways e.g., angiogenesis, antioxidant production, apoptosis, inflammation, mitochondrial dysfunction, oxidative stress or pro-survival have serious implication in the pathogenesis of age-related ocular, dermal glycemic, neural, kidney, hematological and cardiovascular disorders (Abou-Amero et al., 2016; Baxter, 2008; Bhatt et al., 2012; Das and Das, 2010; Diaz et al., 2016; Kelkel et al., 2010; Phyu et al., 2016; Pinheiro et al., 2017; Saldanha et al., 2013).

Resveratrol posses wide range of anti-aging properties. As a phenolic compound it stimulates expression and activity of endothelial nitric oxide synthase (eNOS), causing increased nitric oxide (NO) and may provide protection to cardiovascular tissues. These modifications are vital in the in cardiovascular disease prevention in humans (Bonnefont-Rousselot, 2016; Delmas et al., 2005; Frémont, 2000; Li et al., 2012; Wallerath et al., 2002). Moreover it regulates lipid metabolism and cause inhibition of lipoproteins oxidation and platelets adhesion and aggregation (Bonechi et al., 2017). Resveratrol has potential to curtail the development of three basic stages in carcinogenesis and inhibit phosphorylation of extracellular signal-regulated kinase and inflammatory diseases (Borriello et al., 2014; Frémont, 2000). Beta-amyloid breakdown by resveratrol and direct influence on neural tissues can improve Alzheimer's patients (Baxter, 2008).

Considering its chemopreventive properties and diversified role in various stresses resveratrol family have numerous implications for disease resistance and human health (Chong et al., 2009). However, limited bioavailability of resveratrol along with its rapid metabolization is key issues and cause of criticism (Abou-Amero et al., 2016). Oxidative deprivation of resveratrol can be avoided by a process glycosylation, which makes glycosylated resveratrol highly stable, and be readily solublized and absorbed in gastrointestinal tract (Regev-Shoshani et al., 2003). Subsequent to absorption of glycosylated resveratrol is quickly metabolized (in liver) by the activity of phase-II drug metabolizing enzymes, which ultimately biotransforms it into water-soluble *trans*-resveratrol-3-O-sulfate and trans- resveratrol-3-O-glucuronide, and thus predominantly excreted through urine (Walle et al., 2004).

Plasma half-life of resveratrol varies from 8 to 14 min, however its metabolites posses 9.2 h plasma half-life (Walle et al., 2004). Efficacy and bioavailability of resveratrol metabolites are not well known (Baur and Sinclair, 2006; Soleas et al., 2001). Administration of trans-resveratrol significantly increased resveratrol concentration in plasma in rats and humans (Crowell et al., 2004; Soleas et al., 2001).

Resveratrol is rapidly increasing globally, however its natural synthesis and accumulation are very low in grapes. Consequently, consistent research efforts may induce accumulation of resveratrol in grape skin (Hassan and Bae, 2017).

4. Health Perspectives of Grape Polyphenols

4.1 Anticancer properties

Cancer is associated with the uncontrolled growth of cells in human body. There are multiple categories of cancer, but the most frequent human sarcoma is skin cancer (Bode and Dong, 2000; Baliga and Katiyar, 2006). Administration of resveratrol (25 µmol) in bald mice hindered the ultraviolet B (UVB) (180 mJ/cm^2)-mediated phototoxicity, including augmentation of bifold thickness and edema of skin in SKH-1 (Afaq et al., 2003).

Aziz et al., (2005) found that resveratrol lowered the expressions of cyclins D1 and D2; Cdk 2, 4 and 6; and multiplication cell nuclear antigen, but can be amplified the p21WAF1/CIP1. It also suppressed the anti-apoptotic proteins e.g., tumor promotion markers, survivin, ornithine decarboxylase and cyclo oxygenase. Kapadia et al., (2002) reported that resveratrol caused 98% diminution in skin tumors such as TPA-promoted and DMBA-initiated murine skin cancer model, and also in the SKH-1 bald mouse model.

Grape polyphenols caused arrest of G1-phase cell cycle, decreased the cell cycle regulators such as cyclins D1/D2/E and C (dks, hyperphosphorylated pRb proteins, AP-1, and MEK1 > ERK1/2 signaling) and enhanced the p21WAF1/CIP1. Moreover, increased production of 8-oxo-7, 8-dihydro-2′-deoxyguanosine in UVA-irradiated genomic DNA of HaCat human keratinocyte cells is also reported (Ahmad et al., 2001; Adhami et al., 2001; Kim et al., 2006). UVA stimulates DNA strand splintering and cell death in presence of resveratrol (Seve et al., 2005). Resveratrol administration (1 mg/L; 4 µg/mouse) prevented from the development of mammary tumor *in vitro* (Provinciali et al., 2005). Resveratrol administration (25 mg/kg/day) in MDA-MB-231 tumors of experimental mice and human breast cancer xenografts inhibited the tumor growth, reduced angiogenesis and induced apoptotic cell death (Mahady and Pendland, 2000; Atten et al., 2005). Similarly, resveratrol in cancer cells caused arrest of cell cycle, induced apoptosis during nitric oxide development (Holian et al., 2002; Atten et al., 2005; Riles et al., 2006).

Grape polyphenols triggered a variety of caspases and induced apoptosis, accretion of the pro-apoptotic proteins Bax and Bak, as well as reorganization of the Fas receptor in membrane rafts of colon cancer cells (Delmas et al., 2003). Tessitore et al. (2000) reported that administration of drinking water contained resevratrol (200 µg/kg/day) decreased the AOM-induced anomalous crypt foci (ACF) linked with alterations in Bax and p21 appearances (Tessitore et al., 2000). Administration of resveratrol (0.01% in the drinking water) in Min mice exhibited 70% reduction in tumors development in small intestine via down regulating the genes (DP-1 transcription factor, cyclins D1 and D2, and Y-box binding protein) (Schneider et al., 2001).

In xenograft gastric tumor models of Apc(Min+) mouse, resveratrol exhibt the suppressive effect on progress of adenomas and significantly prevented from the development of tumors in colons and small intestines (Zhou et al., 2005; Sale et al., 2005; Schneider et al., 2001). Resevratrol can slow down FGF2-induced angiogenesis and hindered the platelet/fibrin clot-promoted human colon and fibrosarcoma tumor enlargement in the chick chorioallantoic membrane tumor model. Oral treatment of resveratrol (1 mg/kg/day) reduced the proliferation of murine T241 fibrosarcoma in C57Bl6/J mice (Mousa et al., 2005).

4.2 Cardioprotective properties

Cui et al., (2002) found that the oral dose of grape extracts (100 and 200 mg/kg) provides significant cardio protection by enhancing post-ischemic ventricular recuperation and reduction of rat myocardial infarction. Similarly, Tebib et al., (1994) reported that tannins obtained from grape seed exhibited anti-hypercholesterolemic properties by reducing cholesterol transportation, increasing bile acid excretion and reduced absorption of intestinal cholesterol in rats.

Low reperfusion damages of heart after procyanidin supplementation, along with increased antioxidant activity of blood plasma in rat and rabbit (Berti et al., 2003). In human internal mammary aortic rings aperoxynitrite damage to vascular cells could be prevented by layering on the facade of coronary endothelial cells, and increasing the relaxation of endothelial NO- synthase-mediated (Aldini et al., 2003).

Table 1: Phenolic compounds in different parts of grape and its product

Resources	Phenolic compounds	References
Stem	rutin, trans-resveratrol, quercetin 3-O-glucuronide, astilbin	Makris et al., 2008
Seed	(+)-catechin, dimeric procyanidin, epicatechin, proanthocyanidins, gallic acid	Huang et al., 2005; Nowshehri et al., 2015
Skin	myricetin, proanthocyanidins, ellagic acid, kaempferol, trans-resveratrol, quercetin,	Hernandez-Jimenez et al., 2009; Li et al., 2006
Leaf	gallic acid, myricetin, kaempferol, ellagic acid, quercetin	Laurent et al., 2007
Red wine	petunidin-3-glucoside, malvidin-3-glucoside, cyanidin-3-glucoside, peonidin-3-glucoside, catechin, resveratrol, hydroxycinnamic acid, quercetin	Rivero-Perez et al., 2008; Panico et al., 2006

Mendesa et al., (2003) reported that the catechin and epicatechin from grape help in maintenance of endothelium integrity, and released nitric oxide (NO). Furthermore, Edirisinghe et al., (2008) demonstrated that GSE contained polyphenolic complexes, which caused AKT/PI3 kinase induced blood vessels endothelium relaxation. Similarly, GSE rich in proanthocyanidins had cardioprotective properties to reduce reperfusion-induced damages in secluded hearts of rats (Pataki et al., 2002; Sato et al., 2001). Quercetin (50 to 100 mol /L) and catechin (10 to 20 mol /L) can synergistically reduced platelet linkage to collagen and collagen-induced platelet combination (Pignatelliet al., 2000) together with resveratrol inhibited platelet combination, in vivo as well as in vitro (Wang et al., 2002).

Likewise, purple grape juice (4 to 8 mL/kg/day, 4 weeks) administered to coronary heart disease patients increased the flow-mediated vasodilatation (FMD) of the brachial artery. Moreover, treatment of purple grape juice (7 mL/kg/day) for about 14 days lowered the superoxide release, augmented platelet-derived NO production and inhibited platelet aggregation (Freedman et al., 2001).

Drinking pure red grape juice (twice a day 50 mL, for 14 days) enhanced the antioxidant capability of plasma, reduced the oxidation of low density lipoprotein concentration and increased the high-density lipoproteins in healthy persons and patients suffering from hemodialysis. The red grape juice consumption lead to remarkable reduction in plasmamonocyte chemo attractant protein 1, an inflammatory biomarker linked with cardiovascular disease in hemodialysis patients (Castilla et al., 2006; Coimbra et al., 2005). It also exhibited antithrombotic effects in patients. Similarly, proanthocyanidin-rich GSE administration (300 mg) prevented from the postprandial oxidative stress via diminishing the oxidation and escalating the antioxidant plasma level (Natella et al., 2002).

4.3 Healing of Wounds

Resveratrol (5000 ppm) administration in mice speed up wound tightening and curing in mice (Khanna et al., 2002). It assisted oxidant induced vascular endothelial growth factor appearance in keratinocytes by transformation of pathways, which are pervasive equally to H_2O_2 and signaling of TNF-a. Likewise, Khanna et al. (2001) reported that GSE exhibited the healing of wounds through regulating oxidant-induced modifications in keratinocytes. Resveratrol markedly suppresses the murine fibrosarcoma growth in mice, and lead to impediment of angiogenesis-dependent healing of wounds (Bråkenhielm et al., 2001; Kumar et al., 2007).

4.4 Diabetes Prevention

Involvement and influence of dietary polyphenols in carbohydrate metabolism forced to support finding about their antihyperglycemic effects and significant potential for diabetes management and prevention in animals and humans (Bahadoran et al., 2013; Gonzalez-Abuin et al., 2015; Han and Lao, 2007; Hanhineva et al., 2010; Johnston et al., 2005; Kim et al., 2016; Zunino et al., 2007). Procyanidin present in GSE acts as insulinomimetic agent as it induces phosphorylation of insulin receptor and ultimately enhanced uptake of glucose (Pinent et al., 2004). This induced phosphorylation pathway is different from that of insulin (Montagurt et al., 2010).

Polyphenols rich GSE has been found efficient in curing diabetic nephropathy, through changes in body functional proteins (Weidner et al., 2013; Vislocky and Fernandez, 2010). The exposure of GSE to diabetic rats returned the nine kidney proteins to their normal levels. These proteins were linked with glycosylation damage, oxidative stress and amino acid metabolism (Li et al., 2008; Cheng et al., 2007).

Similarly, quercetin supplemented for 56 days exhibited marked reduction in serum glucose level and glycated hemoglobin in C57BL/KsJdb–db mice (Kim et al., 2011). Likewise, quercetin has been found to prevent the diabetic rats glucose level (Coskun et al., 2005). Quercetin based diet significantly prevented from the destruction of β-cells damage in streptozotocin-induced diabetic mice (Kobori et al., 2009). It also protected from the oxidatively stressed human erythrocytes and depleted concentrations of antioxidant enzymes. In diabetic rats antidiabetiv effect of resveratrol is attributed to increased uptake of glucose and enhanced expression of the insulin-dependent glucose transporter (GLUT4) (Penumathsa et al., 2008; Chi et al., 2007).

5. Conclusion

Grapes have been renowned for remedial properties throughout human history. Current advancements in the fields of immuno-nutrition, pharmacology and physiology have further emphasized their significance as a nutraceutical food against various ailments. Much research work has been carried out on the health promoting potential of grapes, often referred to its bioactive component, i.e. resveratrol. Grapes bioactive compounds maintain cell integrity through scavenging free radicals and protecting membranes from damage.

Competing Interest: The authors declare that there is no potential conflict of interest.

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