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Review Article

Grapes and their Bioactive Compounds: Role in Health Management Through Modulating Various Biological Activities

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ABSTRACT

Grape is one of the important plant and its implication in health management has been proven. Grapes are used in the production of grape juice, food products and in other form. The fruits leaves and seeds of the plant are confirmed its role in diseases management based on *in vivo* and *in vitro* study. Leaves, fruits and seeds of grape are rich source of bioactive compounds and such compound play role in diseases cure and management. Grapes leaves, fruits and seeds shows therapeutic implications as antioxidant, anti-inflammatory, anti-diabetic, hepatoprotective effect and antimicrobial. Grapes leave, fruit and seed and their active compounds play significant role in inhibition of cancer. Its bioactive compound has designated its role in tumour management through modulating genes activity. This review comprehensively summarizes the role of grapes fruits, seeds and leaves in diseases management through modulating different biological activities based on *in vivo* and *in vitro* study.

Key words: *Vitis vinifera*, Proanthocyanidins, Antioxidant, Anti-tumour, Anti-inflammatory.

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INTRODUCTION

Grapes fruits, seed and leaves have proven its role in diseases management through their active compounds. Grapes has been found to have vital bioactive ingredients and such ingredients are rich in antioxidant potentiality. Several health promoting and diseases management activity of grapes seed, fruits, seeds and leaves have been explained. Leaves, fruits and seeds of grapes has been proven its role through animal model and *in vitro* study. The role of grape juice consumption on the antioxidant capacity as well as the interleukin-6 blood level was examined. Antioxidant capacity was higher in the grape juice group than in the control group. Overall, study established that consumption of grape juice in the period of lactation increases the antioxidant capacity in lactating and seems proficient to decrease the inflammatory activity.[1] Red grape juice consumption increased the antioxidant capacity of plasma without affecting concentrations of uric acid or ascorbic acid. Furthermore, juice supplementation displayed decrease in LDL-cholesterol and apolipoprotein B-100 concentrations, while increasing the concentrations of HDL cholesterol and apolipoprotein A-I.[2] Grapes role in heaptoproteion has been explained as extract with dose of 200 mg/kg caused an important protective effect via decreasing the levels of SGPT, SGOT, alkaline phosphatase and total bilirubin. Furthermore, extract with this dose increases the level of total protein.[3] The antimicrobial efficacy of active compounds towards methicillin-resistant Staphylococcus aureus (was investigated. Result concluded that root extracts of grapevines showed good antimicrobial activities towards some strains of Gram-positive pathogens. Heyneanol A, the major antimicrobial compound, is particularly active towards MRSA.[4] The protective effects of juice extract against thalidomide and carboplatin induced-brain and renal damage was linked with the minimization of oxidative stress.[5] Grapes and its active compound has proven its role in tumour prevention based on laboratories experiment. This review comprehensively summarizes the role of grapes fruits, seeds and leaves in diseases management through modulating different biological activities based on *in vivo* and *in vitro* study.

THE VARIOUS PHARMALOGICAL ACTIVITIES OF GRAPES FRUITS, SEEDS AND LEAVES ARE DESCRIBED AS FOLLOWINGS

Antioxidant activity

Investigators and food manufacturers had become more and more interested in polyphenols from grapes due to their antioxidant properties as well as great abundance in diet.[6,7] Antioxidant-rich fractions were extracted from grape seeds through several various solvents. Result confirmed that at 100 ppm concentration, numerous extracts designated 65–90% antioxidant activity. Moreover, mixtures of ethyl acetate and water at different concentrations showed more antioxidant activity than other extracts. Besides, grape seed extracts may be useable for the maintenance of food products and for health supplements as well as nutraceuticals.[8] Phenolic antioxidants and the insulinotropic effect of extracts of seed, skin as well as stems of red wine grape was examined. Result demonstrated that Pusa Navarang cultivar has revealed high amounts of total phenolics (95.8 mg per ml), flavonoids (30.5 mg per ml) and flavan-3-ols (21.8 mg per ml) in seed extract and total anthocyanin (4.9 mg per ml) in its skin extract as compared to Merlot cultivar. Largely, the seed, skin

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and stem byproducts of both cultivars are good sources of phenolics as well as antioxidants and signify a source of new insulin secretagogues.[9] The role of grape juice consumption on the antioxidant capacity as well as the interleukin-6 blood level of lactating rats was investigated. Finding of the study revealed that antioxidant capacity was higher in the grape juice group than in the control group. Overall, study concluded that consumption of grape juice in the period of lactation increases the antioxidant capacity in lactating rats and appears capable to decrease the inflammatory activity.[1] Study was performed to evaluate the protection of organic and conventional purple grape juices in brain, liver, and plasma from adult Wistar rats against the oxidative damage induced through carbon tetrachloride (CCl(4)). Result revealed that in view of the treatment groups, it was noticed that in all tissues and plasma, CCl(4) treatment increased the lipid peroxidation levels. Moreover, grape juices were capable to reduce lipid peroxidation levels in cerebral cortex and hippocampus; however, in the striatum and substantia nigra only the organic grape juice reduced lipid peroxidation level. CCl(4) caused an increase in catalase activity in cerebral cortex, hippocampus, and substantia nigra and in superoxide dismutase activity in substantia nigra.[10] The antioxidant action of grape juice on preneoplastic lesions induced by azoxymethane was evaluated. It was observed that azoxymethane decreased the expression of catalase and manganese superoxide dismutase enzymes. Moreover, it was noticed that increase expression of catalase and manganese superoxide dismutase after grape juice administration. Overall, study advocates that independent action of each enzyme and a probable antioxidant action of the grape juice components in the diet being capable to balance the body to counteract the superoxide radicals.[11]

Anti-inflammatory effect

Study was performed to assess the mechanisms of action of phenolic compounds of grape juice on colitis. Result confirmed that TNF-a and inducible NO synthase mRNA expression were noticed in the groups treated with grape juice after inducing experimental colitis. Moreover, grape juice reduced the harmful effects induced by colitis caused by 2,4,6-trinitrobenzene sulphonic acid, particularly at the 1 % dose.[12] Another pioneer study was performed to evaluate whether phenolic compounds of grape juice might reduce the inflammatory effects caused by experimental colitis. TNF-immunoexpression and iNOS were decreased after drinking grape juice and cyclooxygenase 2 was reduced in the groups exposed to 1% grape juice. overall, the grape juice primarily at 1% dose showed anti-inflammatory effects in chronic colitis induced by TNBS as an outcome of down regulation in the expression of pro-inflammatory cytokines.[13] The consumption of the grape pomace-supplemented diet was established to decrease the lipopolysaccharide/ and galactosamine-induced activation of NF-κB and expression of inducible nitric oxide synthase and ccox-2 proteins. These finding propose that red grape pomace may hold a great quantity of effective ingredients for anti-inflammatory action.[14] Study investigated the hepatoprotective effect of fresh grape juice prepared using a low-speed masticating juicer or a high-speed centrifugal juicer in mice. Result confirmed that low-speed masticating grape juice showed higher antioxidant and anti-inflammatory activities than high-speed centrifugal juice. These finding propose that low-speed masticating juicer grape juice can exert hepatoprotective effects, partly via improving insulin resistance and promoting antioxidant and inflammatory activities.[15] Study was performed to evaluate the effects of dietary supplementation with red grape juice on lipoprotein profile, antioxidant capacity and inflammatory biomarkers. In both healthy subjects as well as hemodialysis patients, red grape juice consumption increased the antioxidant capacity of plasma without affecting concentrations of uric acid or ascorbic acid. Moreover, juice supplementation showed decrease in LDL-cholesterol and apolipoprotein B-100 concentrations, whereas increasing the concentrations of HDL cholesterol and apolipoprotein A-I.[2]

Hepatoprotective effect

The antioxidant and hepatoprotective effect of the chronic use of conventional or organic grape juice evaluated. The results established that high-fat diet induced an increase in thiobarbituric acid-reactive substances, catalase activity and 2′,7′-dihydrodichlorofluorescein oxidation and a decrease in sulfhydryl content and superoxide dismutase and glutathione peroxidase activities. These changes were prevented by both type of juice, where organic juice was more effective.[16] The efficiencies of grape skin and seeds on hepatic injury induced by dimethylnitrosamine was assessed. Treatment with dimethylnitrosamine increased levels of serum alanine transaminase, aspartate transaminase as well as, alkaline phosphatase. Diet supplementation with grape skin or seeds prevented such elevations. The grape skin and seeds also restored serum albumin and total protein levels, grape skin and seeds reduced dimethylnitrosamine -induced collagen accumulation. Besides, grape skin and seeds showed *in vivo* hepatoprotective and antifibrogenic effects against dimethylnitrosamine -induced liver injury, proposing that grape skin and seeds may be valuable in inhibiting the development of hepatic fibrosis.[17] The antioxidant activity of grape juices such as organic purple grape juice and conventional purple grape juice was evaluated. The group treated with organic grape juice showed the highest SOD and catalase activities in both plasma and liver when compared with the conventional and control groups. Moreover, in plasma, it was noticed a positive correlation among SOD and catalase activities, resveratrol, and all anthocyanin contents, suggesting that these polyphenols responsible for this increased antioxidant defence.[18] The root of *Vitis vinifera* was investigated for hepatoprotective activity in rats with liver damage caused by carbon tetrachloride. The extract with dose of 200 mg/kg caused an important protective effect via decreasing the levels of SGPT, SGOT, alkaline phosphatase and total bilirubin. Moreover, extract with this dose increases the level of total protein.[3]

Anti-diabetic effect

Hypoglycaemic and antihyperglycaemic effect of aqueous extract from the leaves of *Vitis vinifera* L. were examined. The results revealed that extract was rich in polyphenolics and possessed a significant antihyperglycaemic and antioxidant activity equipotent with the reference tolbutamide when evaluated in diabetic rats.[19] High concentration of glucose induced cytotoxicity and oxidative stress in cultured LLC-PK1 cells, but treatment with GSPs, particularly oligomer grape seed polyphenols, had powerful protective effects against high glucose-induced oxidative stress. besides, high glucose induced nuclear translocation of nuclear factor-kappa B, and increased expression of cyclooxygenase-2 as well as inducible nitric oxide synthase. These results indicate that grape seed polyphenols have protective effects against high glucose-induced cytotoxicity, and among them, oligomer GSPs have more potent effects than other GSPs on high glucose-induced renal cell damage.[20] The effects of supplementing meals of subjects with muscadine grape juice (MJ), muscadine grape wine, and dealcoholized muscadine grape wine on glycemic indices, blood constituents, lipid profile was evaluated. Result demonstrated that diabetics given muscadine grape wine and dealcoholized muscadine grape wine designated lower levels of blood glucose, insulin, and glycated hemoglobin, indicating better glycemic control. Moreover, daily intake of 150 mL of muscadine grape wine or dealcoholized muscadine grape wine with meals improved several metabolic responses among diabetics compared with diabetics given MJ.[21]

Anti-microbial effects

A pioneer study was performed to examine antibacterial and antifungal activity of black grape peel extracts against antibiotic-resistant pathogenic bacteria and toxin producing molds. Finding

revealed that as compared to other solvent extracts, methanol extracts possessed high antibacterial and antifungal activity. Maximum zone of inhibition was found in case of S. aureus, followed by E. faecalis and E. aerogenes. Besides, maximum and minimum percent of growth inhibition was shown by P. expansum and A. niger as 73% and 15% at 1080 TAE/ml concentration of grape peel extract, respectively.[22] The antimicrobial effect of a white grape juice extract against a range of Gram-positive and Gram-negative bacteria, yeasts, and the fungus was evaluated. Juice extract was also tested on the production of bacterial biofilms *in vitro*. Juice extract inhibited most Gram-positive bacteria tested, *Staphylococcus aureus* ATCC 6538P being the most sensitive strain (MIC values of 3.9 μg/mL). The effect was bactericidal at the concentration of 500 μg/mL. Moreover, juice extract employed both bacteriostatic and bactericidal activity *in vitro*[23] The antimicrobial efficacy of active compounds towards methicillin-resistant Staphylococcus aureus (was investigated. Result concluded that root extracts of grapevines showed good antimicrobial activities towards some strains of Gram-positive pathogens. Heyneanol A, the major antimicrobial compound, is particularly active towards MRSA. Besides, great quantity of heyneanol A and other stilbenes in the roots of grapevines make it possible to produce natural antimicrobial compounds from this plant species.[4]

Cardioprotective effects

A study was performed to know whether the grapes were equally cardioprotective. Result demonstrated that with dose 100 mg/kg and at 200 mg/kg, grapes provided significant cardioprotection as showed by improved postischemic ventricular recovery and reduced amount of myocardial infarction. Moreover, *in vitro* studies revealed that the grapes extract might directly scavenge superoxide and hydroxyl radicals that are formed in the ischemic reperfused myocardium.[24] Another study was performed to evaluate whether proanthocyanidins derived from grape seeds possess cardioprotective properties. Finding revealed that proanthocyanidin-fed animals were resistant to myocardial ischemia reperfusion injury as proven by improved recovery of post-ischemic contractile functions. The proanthocyanidin-fed group revealed reduced extent of myocardial infarction compared to the control group. Overall, finding advocates that the results grape seed-proanthocyanidins possess a cardioprotective effect against ischemia reperfusion injury.[25] A study was made based on rat model to examine whether grape seed proanthocyanidins protect the heart against myocardial injury induced by isoproterenol. Finding revealed that that prior administration of proanthocyanidins maintained the levels of the marker enzymes in all the treatment groups when compared to ISO-injected rats. Finding advocates that proanthocyanidins has a significant effect in the protection of heart against myocardial injury induced by isoproterenol.[26]

Neuroprotective effects

Neuroprotective effects of grape seed extract in the gerbil hippocampus was examined. Neuronal cell density in extract-treated ischemic animals was meaningfully increased as compared with vehicle-treated ischemic animals. Moreover, it was found that GSE had neuroprotective effects on neuronal injury through inhibiting DNA damage in the CA1 region after ischemia. Besides, results advocate that extract can protect ischemic neuronal damage via inhibiting DNA damage after transient forebrain ischemia.[27] An experiment was performed to examine the possible neuroprotective role of a polyphenolic white grape juice extract in an experimental mice model of autoimmune encephalomyelitis. Finding revealed that oral administration of juice extract showed neuroprotective effects, diminishing both clinical signs and histological score typical of disease.[28] Neuroprotective and anticonvulsant effects of organic and conventional grape juice treatments in rats against pentylenetetrazole -induced damage was examined. Study result demonstrated that neither organic nor conventional grape juice altered the behavior parameters, and no statistical differences were observed in the seizure characteristics of the groups. However, both juice types were able to protect from lipid and protein oxidative damage, decrease nitric oxide content and increase enzymatic as well as non-enzymatic antioxidant defenses in brain tissues subsequent pentylenetetrazole-induced seizures.[29]

Nephroprotective effect

The role of grape seed extract in renal toxicity, oxidative stress, and Bcl-2 expressions was examined. Finding revealed that juice extract administered to normal mice did not produce any signs of toxicity. Posttreatment of Eltroxin-induced hyperthyroidism mice with juice extract improved all examined biochemical or histopathological features. Furthermore, serum urea, creatinine, and electrolyte levels were significantly improved.[30] Another study finding demonstrated that grape seed proanthocyanidin extract co-treatment with thalidomide and carboplatin decreased their brain and renal damage, oxidative stress, reduced cytokines, p53, and inhibited brain and renal cell apoptosis. Moreover, finding advocates that protective effects of juice extract against thalidomide and carboplatin induced-brain and renal damage was linked with the minimization of oxidative stress.[5]

Lipid lowering effect

Cholesterol-lowering activity of polyphenolic compounds found in grape seed was investigated. The finding demonstrated that gallic acid, catechin, and epicatechin significantly inhibited pancreatic cholesterol esterase in a concentration-dependent way. Additionally, concentration of 0.2 mg/mL, gallic acid, catechin, and epicatechin reduced the formation of cholesterol micelles 27.26 ± 2.17%, 11.88 ± 0.75%, and 19.49 ± 3.71%, respectively.[31] The protective effect of red grape dried seeds on antioxidant properties, lipid metabolism, and liver and kidney functions of rats with paracetamol induced hepatotoxicity was examined. The results designated an important decrease in levels of serum cholesterol, triglycerides, low density lipoprotein, and very low density lipoprotein, with a significant increase in level of high density lipoprotein for red grape dried seeds groups compared to induced control. Rats administered a diet containing red grape dried seeds levels produced noteworthy hepatoprotection.[32]

Anti-obesity effect

Anti-obesity effect of resveratrol-amplified grape skin extracts on adipocytes was investigated. Treatment with extracts of resveratrol-amplified grape skin decreased lipid accumulation and glycerol-3-phosphate dehydrogenase activity. Besides, grape skin extract treatment caused in considerably decreased expression of important adipogenic transcription factors.[33] Combined effects of grape seed flour, a prebiotic, and lactic acid bacteria derived from kefir, a probiotic, on obesity-related metabolic disease in high-fat diet (HFD) induced obese mice was investigated. The combination of 10% grape seed flour and lactic acid bacteria showed synergistic effects on body weight gain, plasma insulin and total cholesterol concentrations, and cecum propionate contents.[34] The role of grape seed and skin extract and Xenical on high fat diet -induced obesity and brain lipotoxicity was examined. Finding showed that as expected high fat diet -induced body and adipose tissue weight gain, dyslipidemia, accumulation of lipid into the brain, a drop in adiponectin. Moreover, grape seed and skin extract per se showed poweful anti-obesity effect while the combination (grape seed and skin extract and Xenical), by acting in concert, was the most efficient against obesity.[35]

Role in respiratory infection

Anti-inflammatory effects of grape seed proanthocyanidin extract on airway epithelial cells infected with Respiratory syncytial virus. Airway

epithelial cells were pretreated with grape seed proanthocyanidin extract and its effects on cytokine production during Respiratory syncytial virus infection were examined. Respiratory syncytial virus infection induced significant increases in proinflammatory cytokine expression. Though, grape seed proanthocyanidin extract pretreatment decreased the mRNA and protein expression levels of IL-1ß, IL-6 as well as IL-8. Grape seed proanthocyanidin extract controlled the immune response through decreasing the Respiratory syncytial virus -induced transcription of proinflammatory cytokines in airway epithelial cells.[36]

Role in reproduction

Long-term grape juice concentrate consumption discussing a protective effect against cadmium -induced damage to the epididymis, totally preserving sperm profile was investigated. Cadmium had a devastating effect established by reduced sperm count in testes and epididymis, sperm production and normal sperm count, besides increased epididymis sperm transit time. Moreover, such changes were credited to higher cadmium levels in the testes and a lipid peroxidation process. Consumption of juice plus cadmium intoxication was effective, reducing metal accumulation. Furthermore, juice extends its protective effect to the epididymis, allowing complete re-establishment of its morphology, ensuring successful sperm maturation process.[37] The effects of long-term grape juice concentrate consumption, in two dosages, on the reproductive parameters of cadmium-exposed male rats was examined. The results designated that cadmium changed all reproductive and antioxidant parameters. whereas at dosage II (2·36 g/kg BW), the GJC improved the gonadosomatic index, serum testosterone levels, the relative weight of epididymis, the percentage of normal sperm. Furthermore, at this dosage, normalisation of the enzymatic activity of superoxide dismutase and of testicular levels of glutathione were noticed.[38]

Immunomodulatory effect

A study was performed to explain the molecular mechanisms involved in the antitumor therapeutic as well as immunomodulating effects of grape seed proanthocyanidins via *in vivo* and *in vitro* models. The results displayed that grape seed proanthocyanidins might meaningfully inhibit the growth of Sarcoma tumor cells *in vivo*. Besides, Grape seed proanthocyanidins might stimulate lymphocyte transformation, increased lysosomal enzyme activity and phagocytic capability of peritoneal macrophages, and significantly promote the production of TNF-α.[39] Another study was made to investigated the synergistic immune-enhancing activity of Lycium barbarum polysaccharide and grape seed procyanidins. *In vitro* based study reported that the proliferation rate of splenocytes was higher in Lycium barbarum polysaccharide+ grape seed procyanidins group (64.16%), rather than the sum of Lycium barbarum polysaccharide group (13.01%) and grape seed procyanidins group (43.61%) individually used. The synergistic effects of Lycium barbarum polysaccharide and grape seed procyanidins on immunomodulatory were better than the sum of the effects of the individual agents both *in vitro* and *in vivo*.[40] Proanthocyanidin has anti-tumor activity and increases the anti-tumor activity of doxorubicin, and the mechanism might be related partially to immunopotentiating activities via the increase of lymphocyte proliferation, NK cell cytotoxicity, CD4+/CD8+ ratio, and IFN-gamma productions.[41]

Effect on hypertension

A recent study investigated whether 100% concord grape juice lowers blood pressure in patients with prehypertension and stage 1 hypertension. Study based on finding concluded that no effect of grape juice on ambulatory blood pressure in this cohort of relatively healthy individuals with modestly elevated blood pressure. Secondary analyses proposed favorable effects on nocturnal dip and glucose homeostasis.[42] The effect of whole red grape juice on blood pressure at rest and on the magnitude of post-exercise hypotension was evaluated. **Results demonstrated that blood pressure** at rest did not change in the experimental group, but when this group was subdivided by initial blood pressure, the subjects with controlled initial BP achieved a significant reduction in contrast, the experimental group with borderline hypertensive BP values did not. Overall, finding concluded that juice promotes a reduction in BP at rest and is also capable of improving PEH in individuals with hypertension.[43]

Photo-protection effect

The protective effect of grape stem extract against UVB-induced oxidative damage in mice was evaluated. Grape stem extract was administered topically one week before UVB irradiation and continued until the termination of the experiment. Result demonstrated that grape stem extract evidently recovered skin damage induced by the UVB radiation via the prevention of epidermal hyperplasia, erythema, collagen degradation and COX-2, and HO-1 expressions. Moreover, study confirmed in C57BL mice that grape stem extract reduces UVB-induced oxidative damage and hereafter can play a protecting role in skin photo-damage.[44]

Anti-cancer activity

Natural compounds or active compound of medicinal plants play a vital role in cancer inhibition through modulating various biological and cell signalling pathways.[45-52]

The efficiency of grape seed procyanidin on antiproliferative effects related to p53 functional status of oral squamous cell carcinoma for its chemoadjuvant potential was investigated. The findings advocate that grape seed procyanidin on OEC-M1 cells leads to cell cycle arrest through increasing the expression of $p21^{Cip1}$/$p27^{Kip1}$ protein while grape seed procyanidin on SCC-25 cells inhibits cell proliferation through both G1-phase arrest and mitochondria-mediated apoptosis in a dose-dependent manner as a result of alterations of Bcl-2.[53] The chemotherapeutic effects of bioactive proanthocyanidins from grape seeds (GSPs) as investigated through *in vitro* and *in vivo* models based study. Treatment of human pancreatic cancer cells with proanthocyanidins from grape seeds *in vitro* decreased cell viability and increased G2/M phase arrest of the cell cycle leading to induction of apoptosis in a dose and time dependent way. The proanthocyanidins from grape seeds -induced apoptosis of pancreatic cancer cells were associated with a decrease in the levels of Bcl-2 and Bcl-xl and an increase in the levels of Bax and activated caspase-3. Overall, finding advocates that proanthocyanidins from grape seeds may have a possible chemotherapeutic effect on pancreatic cancer cell growth.[54] The chemopreventative/antiproliferative potential of a grape seed proanthocyanidin extract based on colon cancer cells was investigated. Extract with dose of 10-100 microg/ml suggestively inhibited cell viability and increased apoptosis in cancer cells. Moreover, the increased apoptosis observed in extract-treated colon cancer cells correlated with an attenuation of PI3-kinase and decreased PKB Ser(473) phosphorylation.[55] The anti-tumor promoting activity of a polyphenolic fraction from grape seeds was examined in CD-1 mouse skin epidermis. Pretreatment of mouse skin with 5, 10, 20 and 30 mg of GSP resulted in a dose-dependent reduction in TPA-induced epidermal ODC activity compared to controls. besides, pretreatment of mouse skin with 1, 5, 10 and 20 mg of GSP resulted in a significant 43, 39, 54 and 73% inhibition of MPO activity, respectively, compared to controls Moreover, studies advocate that grape seed holds anti-tumor promoting activity when applied to CD-1 mouse skin prior to treatment with TPA.[56] Another study based on animal models reported that grape seed proanthocyanidins meaningfully inhibited azoxymethane-induced colonic aberrant crypt foci, a precursor lesion for colon cancer in rat dual-organ tumor model.[57] The *in vivo* efficacy of grape seed extract against prostate cancer and associated molecular

events was examined. Result designated that extract feeding strongly inhibited tumor growth that accounted for 59-73% inhibition in tumor volume and 37-47% decrease in tumor weight at the end of the experiment and extract decreases proliferation index and increases apoptotic index. Based on finding study advocates that extract holds *in vivo* anticancer efficacy against hormone-refractory human prostate cancer, which is linked with its antiproliferative, proapoptotic and antiangiogenic activities.[58] The inhibitory effect of Grape seed extract on the expression of vascular endothelial growth factor (VEGF) and the mechanism underlying this action. It was reported that extract inhibited VEGF messenger RNA and protein expression in U251 human glioma cells and MDA-MB-231 human breast cancer cells. Moreover, grape seed extract inhibited transcriptional activation of the VEGF gene via reducing protein of hypoxia-inducible factor 1alpha. altogether, results designate that seed extract inhibits VEGF expression through reducing HIF-1alpha protein synthesis via blocking Akt activation.[59] The chemopreventive efficacy of grape seed extract (GSE) against prostate cancer was evaluated. Results of the study confirmed that noteworthy reduction in the weight of genitourinary tract organs in the extract-fed mice. The extract-fed group of mice had a higher incidence of prostatic intraepithelial neoplasia but showed strong reduction in the incidence of adenocarcinoma compared with mice in control group. Besides, extract strongly decreased the protein levels of cyclin B1, cyclin A, and cyclin E.[60] The effect of grape seed extract on constitutive and TNFalpha-induced NF-kappaB DNA binding activity and apoptotic death in advanced human prostate carcinoma cell was investigated. Constitutive and TNFalpha-induced NF-kappaB DNA binding activity was inhibited by GSE. A strong induction of apoptosis was also noticed following extract treatment, whereas a combination with TNFalpha strongly potentiated apoptosis induction.[61]

CONCLUSION

Grapes fruits, seed and leaves have proven its role in diseases management through their active compounds. Grapes has been found to have vital bioactive ingredients and such ingredients shows health promoting effect through modulating various biological cascades. Several health promoting and diseases management activity of grapes seed, fruits, seeds and leaves have been noticed in animal studies as well *in vitro* study. Grapes shows therapeutic implications as antioxidant, anti-inflammatory, anti-diabetic, hepatoprotective effect, antimicrobial and anti-tumour activity.

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CONFLICT OF INTEREST

There is no conflict of interest.

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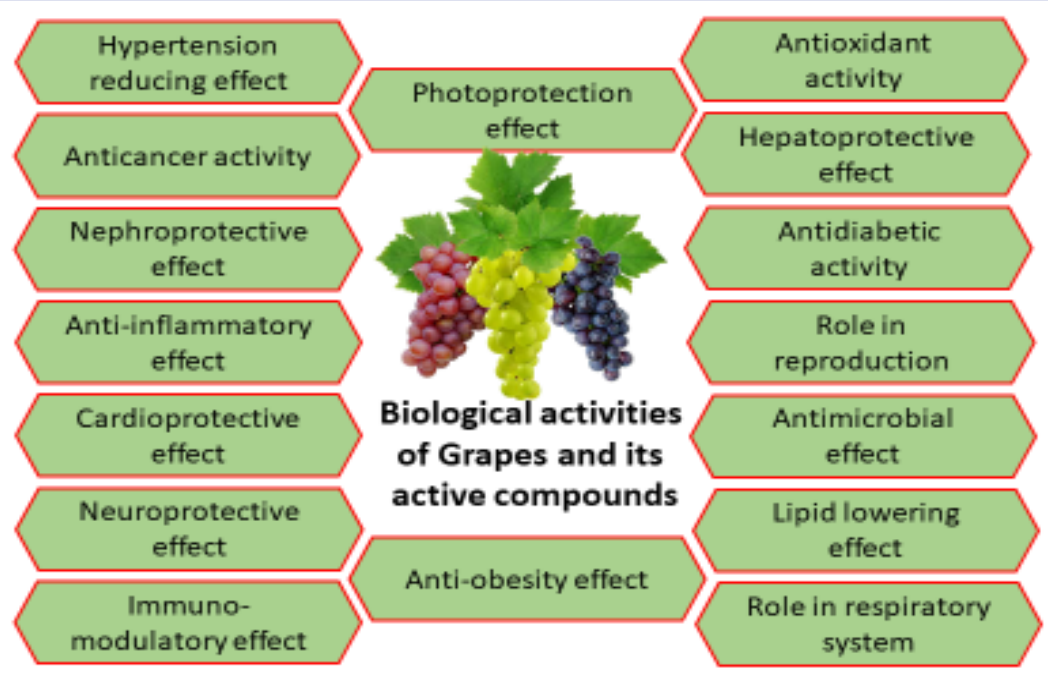
GRAPHICAL ABSTRACT



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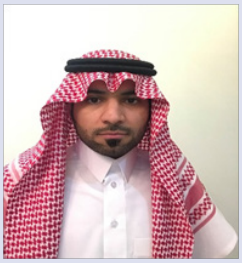

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