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The Multifaceted Health Benefits of Grape Seed Extract: A Comprehensive Review

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ABSTRACT:
Vitis vinifera L. commonly known as grapes, is a widely cultivated and consumed fruit worldwide. This review article provides a comprehensive overview of the phytochemistry, pharmacological properties, and therapeutic applications of *Vitis vinifera*. The plant's various parts, including roots, leaves, seeds, juice, and skin, exhibit anti-inflammatory, antioxidant, anti-bacterial, and anti-diabetic activities. Grape seed extract has been shown to possess multifaceted health benefits, including improving cardiovascular health, immune function, and cognitive performance. The extract's proanthocyanidins have been found to regulate LDL cholesterol, inhibit α-amylase and α-glucosidase enzymes, and exhibit anti-hypertensive, antidiabetic, and anti-oxidant effects. This review highlights the potential of *Vitis vinifera* as a natural remedy for various diseases and emphasizes the need for further research to fully explore its therapeutic potential.

KEYWORDS: Grape seed extract, Vitis vinifera, Antioxidant, Antihypertensive

INTRODUCTION:

Vitis vinifera L. (GRAPES):

Grapes are the berry fruit produced by plants from the *Vitis* genus which consists approximately 60 species. *Vitis vinifera L*. is the most common species which is producing more than 90% of the grape berries present in the market. Grapes are consumed as both fresh and processed products including juice, jam, wine, jelly, dried grape, grape seed extract, grape seed oil and vinegar. Grapes are one of the most popular fruits which are produced in mostly China, Italy, and United states. Also, India and Turkey are more focused on table and dried grapes. (1) Approximately 80% of all grapes are used for the making of wine and 13% are consumed as table grapes. Mostly the 60 species of *Vitis vinifera* are found between America and Asia. (2) Grapes are produced in more than 80 countries in 7,572,237 hectares. (3) *Vitis vinifera* is valuable source of raw materials in the pharmaceutical industry due to its various health benefits including antioxidant properties, cardioprotective effects, hepatoprotective effects, anticancer properties, antibacterial, and antiviral activities. The plant is also useful to treat various health issues including cancer, cholera, smallpox, nausea, eye infections, sore throats, and treats the problems of liver and kidney. (4)

PHYTOCHEMISTRY: Different parts of the plant of *Vitis vinifera* is used for its pharmacological action.
Grape root extract: It is the extract obtained from the roots of *Vitis vinifera.* The main chemical constituents are resveratrol, vitisins A, vitisins B and Piceatannol which are responsible for the Anti-inflammatory activity. (5)
Grape leaves extract: Grape leaves extract is the extract of the lobed, deciduous leaves of the common grapevine (*Vitis vinifera*). Main chemical constituents are Hydroxybenzoic acid, Hydroxycinnamic acid, caffeic acid, procyanidins, quercetin, kaempferol, myricetin. It shows the Anti-inflammatory activity. (6)
Grape seed extract: Grape seed extract is obtained from the seeds of *Vitis vinifera*. Main Chemical constituents are Procyanidin, Gallic acid, epicatechin, catechin, resveratrol, anthocyanidins, linoleic acid. It is responsible for the Antioxidant, Anti-inflammatory, Anti-bacterial activities. (6)
Grape juice: Grape juice is obtained by crushing and blending grapes into a liquid. Main Chemical constituents are caffeic acid, coumaric acid, ferulic acid, caftaric acid, fertaric acid, epicatechin, catechin. It is responsible for Anti-bacterial activity. (6)
Grape skin extract: Grape skin extract is the extract used as a coloring material that is produced from the common grape *Vitis vinifera.* main Chemical constituents are Flavanols, anthocyanins, flavan-3-ols, stilbenes, phenolic acid, quercetin, vanillic acid. It is responsible for Antioxidant activity. (7)
Grape seed oil: Grape seed contains 20% of oil and yield depends on the various factors such as extraction technique, type of solvent and the environmental factors. Main Chemical constituents are Phenolic compounds,

vitamin E, unsaturated fatty acid, phytosterols. It is responsible for Anti-oxidant, Anti-inflammatory, Antimicrobial activities. [8]

Raisins: Raisins are dried Thompson seedless grapes. There are two methods for drying grapes to produce raisin. The first one is Sun drying of grapes for 2 to 3 weeks and second one is short exposure to hot water followed by placement in dehydration tunnel. Raisins are mainly consisting of phenol, polyphenol and tannins which are helpful in the cardiovascular disease, diabetes and for sugar metabolism. [9]

MORPHOLOGY: Grapevines are climbing plants with woody stems. They use tendrils to cling to nearby structures. They grow rapidly, producing long shoots and tendrils that coil around objects for support. Grape leaves are of various shapes and sizes, depending on the species or cultivar, and can be large or small, lobed, or rounded. The plant's buds and flowers are small and green, growing in clusters, some species produce over 100 flowers at a time. The fruit is a small, round, or oblong berry with 2-4 seeds, often coated in a thin layer of wax. Some grape varieties produce multiple clusters of fruit per shoot, requiring. The color of the grape skin, which can range from green to dark purple, is determined by the presence of anthocyanin compounds. [1]

GRAPE SEED EXTRACT

Grape seed extract is a dietary supplement and a rich source of antioxidants obtained from the seeds of grape. As grape seed extract contains lots of polyphenols it is considered as superior natural antioxidant and used as a health promoting agent. [10] Grape seeds are considered as waste if the extract is not made from it. [11] procyanidins and prodelphinidins are extracted from the seeds and skins of the grapes during the process of fermentation in the wine making. [12] Total phenols, flavonoids, and proanthocyanidins in the 100 gm of dried mass of red grape seed extract was found to be 8.58gm,8.36gm and 5.95gm respectively. [13]

Extraction method

Different methods are used for the extraction such as microwave assisted extraction [14], super critical fluid extraction [15], Sub critical water extraction [16], Ultra sound assisted extraction. [17] Generally grape seed extract is extracted by liquid-liquid extraction method in which organic solvents are used for extraction method. Different preferable solvents for the extraction of different chemical compounds are shown in the table below. [18]

No	Solvent	Compounds
1	Acetone	procyanidins
2	Ethanol	Gallic acid
3	Methanol	Catechin

Table 1-Solvents used for the extraction of various chemical compounds. [18]

Solvents like hexane and methanol mixture, ethanol benzene combination, ethyl acetate and sulfur dioxide can show toxic effect in humans in large doses. To avoid this toxicity membrane processing method is used to decrease the use of organic solvent and its concentration in the final extract. Ultra filtration membrane is used to separate polyphenolic compounds and reject the particles with the molecular weight more than 1000. [19]

Taxonomic classification [20]

Rank	Scientific name
Kingdom	Plantae
Subkingdom	Tracheobionta
Superdivision	Spermatophyta
Division	Magnoliophyta
Class	Magnoliopsida
Subclass	Rosidae
Order	Rhamnales
Family	Vitaceae juss.
Genus	*Vitis* L.
Species	*Vitis vinifera* L.

Table 2- Taxonomic classification of *Vitis vinifera.* [20]

Physicochemical Properties [21]

Parameter	Value
Protein content	0(%)
Viscosity	87.8 ± 2.75(cP)
Density	0.965 ± 0.02(gm/ml)
Acid value	2.25±0.75(mg KOH/gm oil)
Saponification value	185.5 ± 7.45(mg KOH/gm oil)
Iodine value	176.4±5.85(mg KOH/gm oil)
Refractive index	1.55 0.002(nD)

Table 3- physicochemical properties of *Vitis vinifera.* [21]

Pharmacological properties: Proanthocyanidins are the compounds present in the grape seeds grabbing attention of consumer because of their multifaceted health benefits such as their antioxidant activity, modulation of Immune function, platelet activation and vasorelaxation. [22] In addition, proanthocyanidins regulates LDL and cholesterol level in the body thus inhibits the progression of atherosclerosis. [23]

Various pharmacological properties are shown by the consumption of proanthocyanidins obtained from grape seeds presented below:

Anti-diabetic activity: In study by Montagut et al. It was reported that treatment of female Wister rats with 25 mg grape seed procyanidin extract / kg of body weight per day for 30 days shows improvement in the glucose homeostatic and improve insulin resistance index. [24] In another study he also demonstrated that procyanidin extracts can induce auto phosphorylation of insulin receptor and activate them to stimulate the glucose uptake. [25] Grape seed extract also shows the hypoglycemic effect by inhibiting α-amylase and α-glucosidase enzymes. [26]

Anti-oxidant activity: Grape seed extract contains the antioxidant activity by which it neutralizes the oxygen free radical and reduces the risk of spreading of chronic diseases. [27] Different methods are used to evaluate the antioxidant properties of grape seed extract including, 1,1-diphenyl-2-picryhidrazyl (DPPH) method and oxygen radical absorbance capacity (ORAC). The antioxidant capacity of grape seed extract is found in range of 17-92 mmol TE/g by DPPH method and 42 mmol TE/g is observed by ORAC method. [28] Highest antioxidant capacity was found in grape seeds followed by leaves, skins, and pulps. [29]

Anti-hypertensive activity: Grape seed extract shows beneficial effect on the blood pressure. In a meta-analysis of 16 randomized controlled trials, it was found that the grape seed extract has significant effect on blood pressure by reducing both Systolic Blood Pressure & Diastolic Blood Pressure. [30] In another study, consumption of grape seed extract beverage for 6 weeks results into reduction of Systolic Blood Pressure and Diastolic Blood Pressure by 5.6% and 4.7% respectively. [31]

Improvement in blood flow: Grape seed extract improves the blood flow by showing the blood thinning effect which is helpful to reduce the risk of blood clots. A study on 17 healthy postmenopausal women taking 400 mg of grape seed extract daily for 8 weeks, the grape seed extract shows the blood thinning effect and risk of blood clotting is reduced. [32] In another study on 8 healthy young women taking 400 mg proanthocyanidin from grape seed extract immediately followed by six hours of sitting shown that the swelling of leg is 70% reduced compared with not taking grape seed extract, in the same study women who took 133 mg dose of proanthocyanidin from grape seed extract daily for 14 days experienced 40% less leg swelling after 6 hours of sitting. [33]

Improvement in bone strength: Grape seed extract shows effects on bone and improve the strength of it. In an experiment on tibial bone in rats, it was found that the grape seed extract increases the bone density, mineral content, and bone strength. [34] In another experiment on mice suffering from inflammatory autoimmune arthritis the bone destruction can be suppressed by using proanthocyanidin from grape seed extract. [35]

Improving function of brain: The grape seed extract contains gallic acid which shows the inhibition of the formation of fibrils by β-amyloid peptide which is helpful to prevent the brain from the Alzheimer's disease. [36] The 12-week long study on 111 healthy older adults taking 250mg of grape seed extract daily, it is found that attention, language, immediate memory, and delayed memory is improved. [37]

Improving function of kidney: Grape seed extract shows its effect on the kidney of rats and reduces the kidney damage and improve the renal function by reducing oxidative stress and inflammatory damage. [38] In another study of 23 people diagnosed with chronic renal failure were treated with 2 gm of grape seed extract daily for 6-month resulted into improvement in kidney filtration by 9% and decrease in urinary protein by 3%. [39]

Safety aspect

"The food and drug administration" (FDA) approved the grape seed extract as "generally recognized as safe" (GRAS) and sold commercially as a dietary supplement listed on the "everything added to food in the United States" (EAFUS) data base. [40] In majority of the studies proanthocyanidin were ingested between 75–300mg may modify risk factors associated with cardiovascular diseases, but also that the rare side effects have been observed only after the ingestion of pharmacological doses. For example, stomach discomfort was noted in subjects taking about one gram per day epigallocatechin gallate supplements. [41]

Different formulations containing grape seed extract

Cosmetic serum: For the preparation of serum containing grape seed extract, the Carbopol ultras 30 is dispersed in demineralize water and then homogenized. Triethanolamine is added to obtain the gel base. Methyl paraben and propyl paraben are dissolved in propylene glycol. This mixture is added to gel base and then homogenized. Sodium metabisulphite is dissolved in demineralized water and then added to the gel base. after the formulation of gel, concentrated phytosomes grape seed extract is added to it. It is then homogenized for 15 min. [42]

Herbal syrup: 100gm of each of the sample powder (*Vitis vinifera, Cucurbita* maxima seeds and leaves of *Psidium guvagua* and *Solanum trilobatum*) is taken and mixed with 2000 ml of water then boiled until the total volume becomes ¼th of initial volume then cooled and filtered. Filtrate is taken to prepare final herbal syrup. One part of filtrate is mixed with 5 parts of simple syrup. 0.5 gm of methylparaben and 0.08 gm of propylparaben are added as preservatives. [43]

Herbal emulsion: There are 2 phases in the emulation the aqueous phase contains 98% pure water and 2% grape extract while oily phase contains 80% pure water + 16% paraffin oil and 4% abil EM90® both phases are heated up to 75 ± 1°C using water bath. The aqueous phase is added to oily phase with continuous mechanical starring at 2000 rpm for 15 min than 1000 rpm for 5 min and 500 rpm for next 5 min. [44]

Marketed formulations

NO	Product name	Company name	Use
1	Herbal face wash	Jovees herbal	Brighter and glowing skin
2	Sensitive tooth paste	Biomed	Sensitivity reduction in tooth
3	Grape seed face mask	Guam	Skin tightening
4	Shubhar grape seed with vitamin C cream	Blue nectar	For oily and acne prone skin
5	Grape seed cold press oil	Caraway	For growth of hair
6	Moisturizing shampoo	Petal fresh pure	Replenishes dry and damaged hair
7	Grape seed extract body lotion	Skinfood	Moisturizing skin
8	Anti-oxidant, multivitamin supplement with grape seed extract (syrup)	Grapovit	Obtain the antioxidant effect
9	Grape seed extract capsules	GNC herbal plus	Provides antioxidant support
10	Multivitamin, multimineral with grape seed extract	Zincobert	To work as health supplement

Table 4 -Marketed formulations containing grape seed extract.

Conclusion: *Vitis vinifera L.*, a fruit species with a rich history of culinary and medicinal use, has been extensively studied for its phytochemical composition and pharmacological properties. The evidence presented in this review underscores the vast therapeutic potential of *Vitis vinifera*, with its various constituents exhibiting anti-inflammatory, antioxidant, anti-bacterial, and anti-diabetic effects. Grape seed extract has emerged as a promising nutraceutical entity, with its proanthocyanidins demonstrating multifaceted health benefits, including cardiovascular protection, immunomodulation, and cognitive enhancement. Further research is warranted to fully elucidate the pharmacological mechanisms and clinical applications of *Vitis vinifera*, with a focus on optimizing extraction methods, standardizing dosing regimens, and exploring synergistic interactions with other phytochemicals. Ultimately, the integration of *Vitis vinifera* into preventive and therapeutic strategies may contribute significantly to the promotion of human health and well-being.

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