

## A Review on Antioxidant, Anti-Tumor and Other Qualitative Properties of Grape Seed Extract

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### Abstract

One of the most popular fruits consumed worldwide is the grape. The leaves and sap of grape plants have long been employed in traditional medicine in ancient Europe. The skin and seeds of grapes are a great source of vitamins and fibre, but they are also particularly high in polyphenols, namely proanthocyanidins, which can be used as a functional component to treat a variety of health conditions by enhancing the body's natural bio-processes. Protection against oxidative damage, as well as anti-diabetic, anti-cholesterol, and anti-platelet activities, are among the possible health advantages of these compounds. People are turning to grape seeds as a source of proanthocyanidins due to their growing conscious of the positive effects these compounds may have on their health. This article presents some of the diverse pharmacological and qualitative properties of grape seed extract in brief.

**Keywords:** Grape Seed Extract (Gse); Antioxidant; Polyphenols; Proanthocyanidins

### Introduction

Grapes are one of the most consumed fruits in the world in one way or another (wine, raisins, vinegar, jam jelly). Numerous studies on the composition and characteristics of grapes revealed that they contain significant levels of phenolic chemicals. These substances have a variety of beneficial impacts on human health, including a decrease in heart disease and cancer risk as well as a reduction in human low-density lipoprotein. GSE as a nutritional supplement is offered in powder, liquid, pill, and tablet formats [1]. It is made by removing the seeds of various grapes (*Vitis vinifera*), drying, and grounding it [2]. Surprisingly, grapes' seeds contain the highest proportion of the fruit's total polyphenols. As a result, GSE includes fibre (35%), fat (13%), protein (11%), water (7%), various vitamins and minerals (3%), and a heterogeneous variety of polyphenolic chemicals, including monomers (5-30%), oligomers (17-63%), and polymers (11-39%) [3]. According to a chemical investigation, proanthocyanidins are the primary polyphenolic components of GSE. Proanthocyanidins have been found to have antioxidant, anti-inflammatory, anti-hypertensive, anti-platelet, antithrombotic, and cholesterol-lowering properties. Fascinatingly, in-vitro studies have shown that their antioxidant properties are even higher than those of vitamin C and vitamin E. Commercially accessible grape seed extract is made from the fruit's seed. When compared to the polyphenols in red wine, the proanthocyanidins in grape seed extract are widely recognised as having the most potent antioxidant effect [4, 5]. Typically sold as 50- or 100-mg capsules or tablets, oral grape seed extract is accessible over-the-counter in pharmacies and grocery shops. Wine also contains grape seed extract, although red wines have far more (177 mg/L vs. 8.75 mg/L) than white wines [5].

### Bio Active Compounds In Gse

About 35% of dried grape seeds are fibre, while another 29% are extractable components such phenolic compounds, proteins, minerals, and water [6].

The bioactive compounds are found in plants, but they are locked away in insoluble structures like plant cell vacuoles and lipoprotein bilayers, which makes it hard to extract them [7]. There are many methods to get bioactive components out of plant-based materials. These methods have been used in a variety of ways to find out how they work and how selectively they extract things from different

natural sources. The goals of developing and improving the extraction procedure are to get the highest possible yield of the target compounds, to separate the useful compounds from the unwanted compounds (impurities, toxic ingredients), to keep the useful compounds from breaking down, getting worse, or losing their usefulness during processing, and to keep the process in line with regulatory as well as industrial requirements so that the final product is food grade [8].

Conventional solvent extraction is still the most common way to get bioactive compounds out of plant materials on a large scale for industrial use. [9, 10, 11, 12, 13] say that some of the problems with these techniques include long extraction times, loss of compounds due to hydrolysis and oxidation during extraction, and possible pollution of the environment from using large volumes of organic solvents (Table 1).

In general, solid-liquid extraction is the method most often mentioned for obtaining polyphenols out of grape processing waste. During the solid-liquid extraction process, analytes in a solid matrix move into a solvent phase that is in contact with the matrix. This moves mass from the solid phase to the liquid phase. Changes in concentration gradients, diffusion coefficients, or the boundary layer can improve the efficiency of extraction depending on the sample and the compounds that are being sought. The extraction method, solvent type, temperature, extraction time, particle size, and matrix composition can all affect these parameters [14, 15, 16].

### Extraction and Composition

To make GSE, grape seeds were physically extracted from the grapes, air-dried for a week at 25 to 30 °C in the shade, and then crushed into a fine powder. The powdered grape seed powder was macerated for

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**Table 1:** Conventional extractions mechanisms applied for the recovery of bioactive compounds.

Extraction conditions	Solvent used	Bio active compound	References
Maceration, overnight shaking	80% Ethanol (solvent-to-solid ratio 10:1)	Phenolic compounds	Hogan et al. 2010
Maceration and shaking, at 20 and 60°C, 2 h	Acetone concentrations of 50, 70, and 100%	Anthocyanins	Vatai et al. 2008
A matrix solid-phase dispersion (MSPD) process	Methanol ethanol and ethyl acetate, as well as mixtures of methanol and water, acidified with HCl to pH = 1	Polyphenols	Lores et al., 2012
Maceration, triple extraction, room temperature	Water and acidified methanol (0.1% formic acid)	Anthocyanins and other polyphenols	Lee and Rennaker 2011
Classic maceration at room temperature and hot (Soxhlet) extraction for 4 h at 65°C	Hexane	Tocopherols	Bydar and Ozkan 2006
Maceration, stirring, 10 min	Methanol/acetone/water (6:3:1) (acidified 0.1% HCl) solvent-to-solid ratio 10:1	Total polyphenols	Markis et al., 2007
Single-step batch extraction at 20, 40, and 60°C, 2 h	Acetone [20, 40, 60, 80, and 100% (v/v)] and ethanol [50, 70, and 100% (v/v)] mixtures with water	Total phenolics and anthocyanins	Vatai et al., 2009

three days at room temperature in 25% w/v, 70% ethanol. The filtrate was dried to remove the ethanol at room temperature (about 25°C), yielding powdered GSE [17].

Mechanical processes or organic solvents have historically been used to extract the oil from grape [18]. Product quality is higher in mechanical extraction; however, the yield is reduced due to the extraction method. Organic solvent extraction does provide a better yield, but it needs distillation for solvent recovery, and the finished product still has some trace amounts of residual solvent [18]. Whereas mechanical and organic solvent extractions are limited in their oil output and quality, the supercritical approach is seen as a viable alternative. Grape seed oil is extracted using cold pressing, which does not involve the use of chemicals or high temperatures [19]. It is true that cold pressing often results in a lesser yield than other standard solvent extraction methods, but it may be more effective and safer since no solvent residues are left in the grape seed oil [20].

### Antioxidant Properties

Studies have reported that grape seeds exhibit a broad spectrum of pharmacological properties against oxidative stress. Their potential health benefits include protection against oxidative damage, and anti-diabetic, anti-cholesterol, and anti-platelet functions. Recognition of such health benefits of proanthocyanidins has led to the use of grape seeds as a dietary supplement by the consumers. Polyphenols and flavonoids present in the GSE have been shown remarkable interest based on positive reports of their antioxidant properties and ability to serve as free radical scavengers [21]. Grape seed polyphenols have a higher antioxidant activity as compared to other well-known antioxidants (such as vitamin C, vitamin E, and b-carotene) [22] Grapes have a high level of catechin, gallic acid, epicatechin, proanthocyanidin, and procyanidins, which is likely the cause of their high antioxidant capacity.

### Dental Re-Mineralization

In order to avoid dental caries, which are the most common chronic disease in both children and adults around the world, it is essential to promote evidence-based preventative care. Regular fluoride usage has historically and successfully prevented caries, but there are also potential to halt and restore cavities using different agents. Due to

its concentrated quantities of proanthocyanidins, grape seed extract (GSE), a widely accessible plant-based supplement, offers intriguing properties that may help prevent dental caries. Proanthocyanidin, which is abundant in GSE and helps to reinforce collagen-based tissues (by increasing the collagen cross links). Additionally, GSE boosts collagen production and the process by which soluble collagen becomes insoluble. Research was conducted to determine the impact of GSE on the artificial enamel caries in the primary human teeth. The results indicated that the GSE accelerates the re-mineralization process, supporting the re-mineralization process on teeth via proanthocyanidins [23].

### Skin Care

The extract that is prepared from the seeds of grapes (*Vitis vinifera*) is rich in polyphenolic proanthocyanidins, which are potent free radical scavengers found in various berries, green and black tea, red wine, and red cabbage. The topical application of grape seed extract has been shown to enhance the sun protection factor in human volunteers. Grape seed extract is thought to be a significantly more potent scavenger of free radicals than vitamins C and E. The bioflavonoids in grape seed extract appear to foster the body's ability to absorb vitamins, thus providing a symbiotic environment for other nutrients. Grape phenolics are often employed in cosmetic products because of their potent antioxidant properties. Additionally, resveratrol is said to help with skin thickness, elasticity, flexibility, brightness, glow, and plumpness as well as with the look of wrinkled, lined, dry, flaky, aged, or photodamaged skin. Resveratrol has been shown to suppress keratinocyte proliferation and promote differentiation in skin epidermal cells. Additionally, it was discovered that this phenolic reduced skin irritation that may be brought on by alpha-hydroxy acids and inhibited melanin formation by skin cells [24].

### Anti Viral (Covid)

The mechanisms through which the GFSE can combat viruses are still largely unexplored. Although the antiviral components of GFSE have not been found, aglicons such as flavonoid glycoside, apigenin, limonoids, quercetin, naringin, hesperidin, unsaturated or saturated fatty acids, kaempferol, and naringin are possibilities [25,26]. According to research, the nose may serve as the major entrance and SARS-main CoV-2's site of replication; in Furthermore, droplet-based

modes of transport have also discovered to be efficient. An available ready-to-use nasal spray, Xlear Nasal Spray, including GFSE and xylitol, was theorised by a researcher to be useful as an adjuvant therapy for Covid-19. In a recently released research, three symptomatic, low- to moderate-risk Covid-19 patients were treated as a result of intranasal combination treatment addition to existing pharmaceuticals. This trio of patients was administered twice every six hours by nasal spray. When utilised repeatedly All of the intranasal swab tests that used PCR displayed a quick turnaround in terms of the patient's clinical condition. No problems During the course of the treatment were found. These findings confirm that the components have a significant antiviral function [27].

It was also studied in vitro whether or not Xlear nasal drops had a deleterious impact on SARS-CoV-2. Experiment 1 tested the efficacy of Xlear, whereas experiment 2 examined the efficacy of a repeatable medication in neutralising SARS-CoV-2. Only Xlear with 0.2% GFSE was effective in reducing SARS-CoV-2 to undetectable levels in laboratory tests [27].

Naringenin, a flavonoid found in grapefruit, has been investigated for its potential antiviral effects on a variety of viruses. These include dengue, Zika, hepatitis C, Semliki Forest, chikungunya, yellow fever, herpes simplex 1 and 2, and human immunodeficiency virus. In vitro studies have revealed that naringenin inhibits viral growth both before and after infection [28,29,30].

### Anti Cancer

Phenolic chemicals are abundant in GSE, and these compounds have been shown to have anticancer and cell cycle modulating action [31]. These phenolic compounds have cytotoxic action against cancer cells but have no harm on normal healthy cells [32]. Pro-angiogenic factor expression, such as that of angiopoietins and vascular endothelial growth factor, and the inactivation of the phosphoinositide 3-kinase (PI3K)/protein kinase B (PKB) signalling pathway, leading to the induction of apoptosis of cancer cells, have been proposed as mechanisms of anticancer activity [32]. Using the tumour cells of the MDA-MB 231 and HeLa cell lines and the normal cells of the L929 and B16 cell lines, [33] created lipid nanocarriers of Grape seed oil and laurel leaf oil (natural oils) and assessed their efficacy in battling specific tumour cells and counteracting free radicals. Cancer cell growth was shown to be significantly slowed. As a result, lipid nanocarriers derived from natural oils like Grape seed oil and laurel leaf oil may greatly enhance the therapeutic effectiveness of anticancer medicines in therapeutic trials [33].

**Gse And Skin Cancer:** Family history, UV sensitivity, prolonged sun exposure and environmental exposures to carcinogens, and immune suppression are major etiological factors for skin cancer [34]. [35] used GSE to test the anti-tumor effect of GSE polyphenolic fraction (GSP) in a two-stage SENCAR mouse skin carcinogenesis model in which a single application of 7,12-dimethylbenz[a]anthracene (DMBA) was used to start a tumour and repeated applications of 12-O-tetradecanoyl-phorbol 13-acetate were used to make the tumour grow. When GSP was put on the dorsal skin of mice that had been exposed to DMBA, 12-O-tetradecanoylphorbol 13-acetate could not cause skin tumours to grow. This was shown by a significant decrease in the number of tumours, their size, and the number of tumours. In a model of mouse skin cancer caused by UVB radiation, GSP in the diet stopped photocarcinogenesis at both the start-up and growth stages and stopped skin papillomas from turning into cancerous skin cancers [36,37, 38].

**GSE and prostate cancer:** Although other cancers in men have increased in prevalence, prostate cancer is still the most prevalent kind detected. Prostate cancer rates have levelled down in recent years because to advances in detection and therapy. Resistance to apoptosis is a common barrier in the treatment of prostate cancer that has progressed to an advanced stage. On top of that, in the latter stages of the disease, prostate cancer cells have angiogenic capability, which aids in their proliferation and spread to new locations. Therefore, medicines that may either trigger apoptosis in cancer cells or block their ability to form new blood vessels can have significant benefits on preventing cancer from progressing to a more advanced state [39, 40]. In this way, we found that GSE has antiproliferative and antiangiogenic effects and interferes with IGF-1 signaling in DU145 xenografts by different means. This slows the growth of DU145 xenografts in nude mice as a whole [41].

### Anti Microbial

Grape seeds have demonstrated potential as novel microbial agents since they are abundant sources of polyphenols. According to a study, defatted grape seed extracts had an antibacterial impact on the microorganisms *Bacillus cereus*, *Bacillus subtilis*, *Staphylococcus aureus*, *Bacillus coagulans*, *Escherichia coli*, and *Pseudomonas aeruginosa* [42]. It is also revealed that these extracts totally inhibited both Gram-positive and Gram-negative bacteria at concentrations of 850 to 1000 ppm and 1250 to 1500 ppm, respectively. According to [43], grape seed extract had a minimum inhibitory concentration of 0.26 against *Listeria monocytogenes* (*L. monocytogenes*), indicating that it might be exploited as a low-cost source of natural antilisterial combinations.

Many bacteria, including *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Enterococcus faecalis*, have favourable antimicrobial activity in response to resveratrol [44]. When resveratrol is topically applied to healthy skin, more cathelicidin is produced. Cathelicidin inhibits the development of *Staphylococcus aureus* and promotes the synthesis of antimicrobial peptides [45]. Resveratrol has been shown to have antibacterial properties that entail the induction of oxidative damage to bacterial membranes without harming host cells, particularly in *E. coli*. These results provided insight into how resveratrol may be used to support conventional treatments when antibiotics failed or proved inefficient [46]. According to [47], changes in cell shape and DNA content are what give GSE its antibacterial properties.

### Cardiovascular Diseases

One of the biggest issues brought on by today's unhealthy lifestyle, which is the leading cause of mortality globally, is cardiovascular illnesses (CVD). CVD may be prevented in large part by a healthy lifestyle. Regular exercise, a healthy diet full of organic fruits and vegetables, and other factors all lower the risk of CVD. Risk factors for the development of atherosclerosis and CVD include things like diabetes mellitus, high blood pressure, and dyslipidemias, which may be lessened by altering one's lifestyle [3]. Deposition of lipoprotein in the intimal layer of the arteries leads to the formation of atherosclerotic plaque. Particles of oxidised lowdensity lipoprotein (Ox-LDL) are important in the progression of atherosclerosis. When endothelial cells are exposed to Ox-LDL, monocytes go into the subendothelial layers where they mature into macrophages and produce growth factors. Along with these actions, exposure to Ox-LDL also causes the proliferation of smooth muscle cells and fibroblasts, platelet aggregation, and angiotensin II-like effects [48]. The pathogenesis of CVD in this situation is heavily reliant on the free radical scavenger



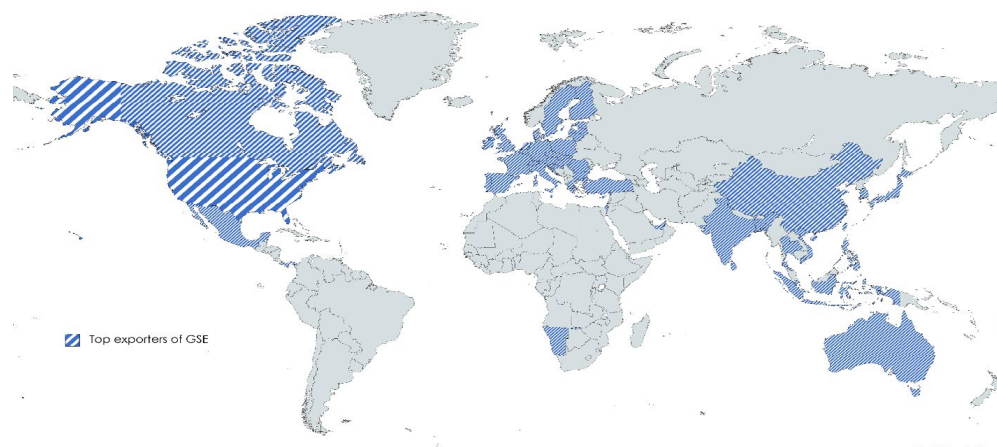


Figure 1: Grape Seed Extract Global Market.

[49, 50]. GSE's promising lipid-lowering abilities have been researched in several animal studies as well as some human investigations.

Numerous epidemiological studies have been conducted, and the results imply that eating grapes high in polyphenols lowers the death rate from cardiovascular disease. Inhibiting or limiting the oxidation of low-density lipoprotein (LDL), decreasing blood pressure, reducing inflammation, preventing platelet aggregation, and activating certain proteins that prevent cell senescence are only a few of the methods through which GSE inhibits atherosclerosis [51].

### Grape Seed Extract Global Market

In 2018, the global market for grape seed extract was worth USD 120.6 million, and it is expected to grow at a rate of 7.6% per year from 2019 to 2025. The growing importance of grape seed extract as a functional ingredient that helps people lose weight, get rid of cellulite, and boost their immune systems is expected to have a big effect on the growth of the market [52-55]. Also, these extracts are recommended for treating conditions like candidiasis, throat infections, earaches, and diarrhoea because they are exceptionally effective at their anti-bacterial and anti-fungal properties (Figure 1).

The Indian Council of Medical Research (ICMR) said in a report that nearly 17% of all deaths in the South Asian country are caused by heart problems. Every year, about 10 million individuals die on average in India. In the coming years, health supplement makers are likely to use more grape seed extracts in their products in an effort to decrease the number of individuals who get cardiovascular related diseases. Because grape seed extracts are high in oligomeric procyanidins (OPC), most supplement makers use them as an ingredient. Diseases like atherosclerosis, high cholesterol, poor blood flow, macular degeneration, and nerve damage can be helped by these traits. Some companies are making their functional drinks healthier by adding more grape seed extract to them. Youthy Forever, for example, has added more grape seed extract to its pineapple juice, which is a mix of pear, passion fruit, and prickly pear juices. Each 8-oz serving of this ingredient has 40 mg [56-61]. These components have a lot of omega-6 fatty acids and linoleic acid, which help treat acne by making pores less likely to get clogged. It also kills bacteria and reduces inflammation, which makes it a great way to treat breakouts. Grape seed extracts in these products help keep the skin moist, reduce inflammation, and get rid of fine lines and wrinkles.

### Conclusion

Grape seed extract (GSE) is rich in compounds that may provide a safe, natural, and cost-effective treatment. It can also be used in the treatment of diseases by developing it into successful pharmaceuticals formulation. The potential health benefits of consuming grape seed consumption are thought to arise mainly from bioactivities of their polyphenols. Grape seeds have high antioxidant potential and their potential health benefits include protection against oxidative damage, and anti-diabetic, and cardiovascular diseases. Given this, not only may it be used as a nutraceutical or cosmeceutical, but it may also have the potential to replace or supplement already used medications in the treatment of disorders if it is further developed into additional effective pharmaceutical formulations. The pharmaceutical industry in India stands to gain much from future GSE research.

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