

## A Review on Grape Seed: Phytochemical Composition and Biological Activities

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### Abstract:

Grape seeds, one of the major by-products from the industrial processing of grapes, are a source of numerous bioactive compounds that could have biological and therapeutic significance. Grape seeds contain phytochemicals like polyphenols, flavonoids, phenolic acids, catechin, epicatechin, tannins, and proanthocyanidins. The review will focus on exploring the major bioactive compounds in grape seeds and their biological activities, which include antioxidant, antibacterial, antimicrobial, anti-inflammatory, and anticancer properties. Antioxidant activity in grape seeds is due to high levels of polyphenols that help in scavenging the free radicals and oxidative stress in the body. The antimicrobial property may be responsible for inhibiting microbial activity, while anti-inflammatory activities result from the ability to regulate inflammatory mediators and cellular pathways. Additionally, grape seed proanthocyanidins have been shown to exhibit anticancer effects through oxidative damage, cellular signalling, and apoptosis in experimental studies. Besides having biological significance, there is a lot of scope of sustainable usage of agricultural waste as grape seeds in pharmaceutical, nutraceutical, cosmetic, and food industries.

**Keywords** — Grape seed extract, bioactive compounds, proanthocyanidins, antioxidant activity, antimicrobial activity, anti-inflammatory activity, anticancer activity.

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### I. INTRODUCTION

Grapes are one of the most widely cultivated fruits and have been used for winemaking since the ancient Greek and Roman civilizations. The root, vine, leaf and seed of grape tree can be used in medicinal applications. Grape seeds are rich in nutrients and proanthocyanidins, which have strong free radical scavenging properties, contributing to their high nutritional and therapeutic value. Grape seeds are a complex matrix containing 40% fiber, 16% oil, 11% proteins, and 7% complex phenols such as tannins [1]. Grape is one of the most cultivated fruit crops worldwide, with a global production of 80

million tons in 7.3 million hectares of vineyards in 2022. About 50 % of grapes are directed to wine and juice production. Grape pomace or marc is the major by-product of the wine and juice industry and accounts for 20 %-30 % of the harvested grape by weight [2, 3]. Grape pomace consists of skins, residual pulp, stems, and seeds. Grape seeds represent 38 %-52 % of grape pomace on a dry matter basis [4, 5]. In addition to flavonoids, grape seeds contain numerous phenolic chemicals such as phenolic acids, carotenoids, stilbenes, tannins, and catechins [6]. Grape pomace, as the primary by-product of winemaking, accounts for approximately 30 % of the total material weight [7], its yield is

corresponding to the trend of increasing wine production.

GSE extract and its biological activity have attracted more attention with respect to the reuse of grape seed resources [8]. Grape seed proanthocyanidin (GSPE), one of the most dispersed polyphenols, has free radical scavenging, antioxidative, and anti-inflammatory properties [9]. Grapevine seeds have high antioxidant potential; their beneficial effects include modulation of antioxidant enzyme expression, protection against oxidative damage in cells, anti-atherosclerotic and anti-inflammatory effects, and protection against certain types of cancer in both humans and animals [10]. Besides, the therapeutic components from grape pomace can be beneficial to the pharmaceutical and medicinal industry [11]. The polysaccharides such as pectin, cellulose, and lignin present in grape pomace are biopolymers that are compatible with food applications as emulsifiers, gelling agent, and carriers for encapsulating small bioactive compounds [12]. This review aims to investigate the Bioactive Compounds, Antioxidant Activity and Health Benefits of the Grapes.

## II. BIOACTIVE COMPOUNDS

Phytochemicals are minor organic substances naturally present in plants, and they can be classified based on different chemical configuration such as terpenoids, alkaloids, polyphenols and carotenoids [13, 14]. Grape pomace is characterized by the abundance of polyphenolic compounds, such as flavonoids, phenolic acids, and stilbenes [15]. Grape seeds comprise around 7% polyphenols (including tannins), 11% protein, 16% oil, and 40% fiber. They also contain various other substances, such as minerals and carbohydrates [16].

The polyphenolic components of GSE consist of monomeric and polymeric polyphenols. Monomeric polyphenols, which account for approximately 10% of the total polyphenols, include catechin and epicatechin. Meanwhile, the majority of GSE polyphenols are polymeric polyphenols, primarily proanthocyanidins, which constitute 75–85% of the total polyphenols.

Proanthocyanidins are polymers formed by monomeric polyphenols linked via C4-C6 or C4-C8 bonds [17, 18]. Phenolic acids are characterized by the presence of a carboxylic acid functional group and are classified into hydroxycinnamic acids and hydroxybenzoic acids. The former includes ferulic, chlorogenic, gallic, caffeic and sinapic acids, while the hydroxybenzoic acids contain protocatechuic, syringic and vanillic acids [15].

As the most prevalent phenolics in grape pomace, flavonoids can be extracted in all pomace components including seeds, skins and stem, such as anthocyanins and catechins. From the perspective of the structural configuration, flavonoids are composed by a 15-carbon skeleton (C6-C3-C6) including two aromatic rings, which supports various substitutions and chemical modifications, conferring their antioxidant capacity [19]. Stilbenes are another class of natural polyphenol compounds, mainly existing in grape skins [20]. Similar to other phenolics, stilbenes also exhibit crucial antioxidant and anticancer properties [21]. The main stilbene in grape pomace garnering much attention is resveratrol. Even after undergoing the traditional brewing process, the majority of the resveratrol are retained in the grape pomace [22].

Condensed tannins have a complex chemical structure of flavanols. They may contain (epi)catechin, (epi)afzelechin, and (epi)gallocatechin units and they are named procyanidins, propelargonidins, and prodelphinidins respectively. Single linkages i.e., C4-C6 or C4-C8 bonds give rise to B type proanthocyanidins whereas A-type proanthocyanidins show additional C2-O-C7 or C2-O-C5 bonds. Grape proanthocyanidins are essentially of B-type, with C4-C8 linkages being much more abundant than C4-C6 bonds [23].

Proanthocyanidins as antinutrients inhibit digestive enzymes. Some *in vitro* studies indicate that smaller proanthocyanidin polymers and oligomers are consumed in limited amounts using models of the intestinal epithelium, although this uptake is largely constrained to cleaved monomer units [24]. Generally, proanthocyanidins are absorbed through passive diffusion [25]. Some of

the essential constituents present in GSE are shown in table 1.

TABLE I  
MAIN COMPOUNDS IN GSE [26]

| SL. No. | Compounds           | Chemical formula               |
|---------|---------------------|--------------------------------|
| 1       | Catechin            | $C_{15}H_{14}O_6 \cdot (H_2O)$ |
| 2       | Epicatechin         | $C_{15}H_{14}O_6$              |
| 3       | Epicatechin gallate | $C_{22}H_{18}O_{10}$           |
| 4       | Proanthocyanidin B1 | $C_{30}H_{26}O_{12}$           |
| 5       | Proanthocyanidin B2 | $C_{30}H_{26}O_{12}$           |
| 6       | Proanthocyanidin B3 | $C_{30}H_{26}O_{12}$           |
| 7       | Proanthocyanidin B4 | $C_{30}H_{26}O_{12}$           |
| 8       | Gallic acid         | $C_7H_6O_5$                    |

### III BIOLOGICAL ACTIVITY

#### 1) ANTIOXIDANT ACTIVITY

GSE, a natural antioxidant, derives its antioxidant properties primarily from its high content of polyphenolic compounds. These compounds effectively inhibit lipid oxidation and prevent food spoilage through multiple mechanisms [27]. Lipid oxidation is a complex free radical chain reaction comprising three main stages: initiation, propagation, and termination. During the initiation stage, free radicals are generated through environmental exposure or endogenous oxidative reactions. The antioxidant capacity of GSE polyphenols, particularly flavonoids like catechin, epicatechin, and their polymers (proanthocyanidins), is fundamentally linked to their molecular structure. The key feature is the o-dihydroxy (catechol) group on the B-ring, which acts as an excellent hydrogen donor. In the propagation stage, these phenolic hydroxyl groups can donate a hydrogen atom ( $H\cdot$ ) to a lipid peroxy radical ( $ROO\cdot$ ), a primary carrier of the oxidation chain, thus terminating the radical and forming a stable lipid hydroperoxide ( $ROOH$ ) [28]. Proanthocyanidins (GSPE) in grape seeds possess a comprehensive antioxidant mechanism, including free radical scavenging, chelation and inhibition of polyphenol oxidase [29]. Antioxidants in grape seeds play a critical role in neutralizing free radicals and reducing oxidative stress [30, 31]. For instance, black grape seeds generally exhibit higher antioxidant potential due to their elevated anthocyanin content compared to green grape seeds [32, 33]. This is consistent

with findings that darker-coloured seeds tend to have stronger radical scavenging capabilities and ferric-reducing antioxidant power [34].

#### 2) ANTIBACTERIAL ACTIVITY

The antibacterial activity of grape seeds is attributed to bioactive compounds such as proanthocyanidins, which disrupt microbial cell membranes. Iranian varieties, including black and green seeds, show promise due to their unique polyphenolic profiles [35, 36, 37, 38]. One of the best medical practices at the moment is antimicrobial therapy. Antimicrobial medicines are essential for invasive surgery as a prophylactic measure against infectious illnesses, and their use has reduced mortality in certain patient populations [39]. Antibiotics of over a hundred varieties are currently administered in therapeutic settings. Antibiotics have been found to be an effective treatment for a wide range of illnesses; however, the discovery and spread of drug resistance has presented a new challenge for healthcare facilities [40]. Antibiotic resistance has increased, and the failure to recognize all resistance mechanisms has slowed the development of new antibiotics. It is evident that the management of antibiotic resistance requires an appropriate substitute. It has been discovered that plants manufacture a wide range of chemicals to defend themselves against infections. Phytochemicals have been viewed as promising sources of novel antibacterial medicines in this context.

#### 3) ANTIMICROBIAL ACTIVITY

As rich sources of proanthocyanidins, grape seeds are regarded as novel microbial agents. The high number of hydroxyl groups in proanthocyanidins inhibits bacterial adhesion and coaggregation, reducing biofilm formation and decreasing inflammation. Tannins possess metal ions complexation properties [41], especially iron and zinc, which are essential mineral micronutrients for most microorganisms [42]. A-type proanthocyanidins contain an interflavan linkage, which is steadier than B-type linkages [43], and thus correlate most robustly with reduced bacterial virulence [44]. Defatted grape

seed extracts could completely inhibit Gram-positive (*Bacillus cereus*, *Bacillus coagulans*, *Bacillus subtilis*) and Gram-negative (*Pseudomonas aeruginosa*, *Escherichia coli*) bacteria at 850–1000 and 1250–1500 ppm respectively [45]. Grape seed extract further demonstrated antimicrobial activity against *E. coli*, *P. aeruginosa*, *Micrococcus luteus*, *S. aureus*, *Aspergillus niger*, and *Fusarium oxysporum* with an inhibition growth zone diameter ranging from 15 to 20 mm [46]. Studies have shown that phenolic compounds influence microbial growth and reproduction, although the specific mechanisms remain unclear. The structural diversity of these compounds allows various interactions with microorganisms, resulting in varying antimicrobial effects [47].

#### 4) ANTI-INFLAMMATORY ACTIVITY

Inflammation is a defensive response of living tissue with vascular system against damage factors. In the rat model of ulcerative colitis (UC), grape seed polyphenols (GSP) exhibited protective effect on UC induced by dextran sodium sulfate (DSS) by alleviating inflammation and apoptosis [48]. The activation of signal transduction and transcriptional activator (STAT3) might be involved in the acceleration of inflammation by promoting the production of inflammatory cytokines, and the inhibition of STAT3 activity may be essential to reduce colonic inflammation [49]. In addition, it was found that GSP could downregulate the mRNA expression of inflammatory cytokines (IL-6, IL-1 $\beta$  and TNF- $\alpha$ ) and the phosphorylation of signal transduction and transcriptional activator (STAT3), improving the apoptosis of intestinal epithelial cells (IECs) [49]. GSE extract may be developed as a potential new therapeutic and preventive agent for inflammatory reactions and diseases. It has been demonstrated that GSPs extract exhibited potent anti-inflammatory activity, which was indicated by transcriptional inhibition of COX-2 and inflammatory cytokines expression in macrophages. These effects were mediated by the blockade of MAPKs and NF- $\kappa$ B signaling transduction pathways. In this context, GSE may be an ideal natural product with strong anti-

inflammatory activity [50]. GSPE exhibited positive effects on liver cancer, lung cancer, esophageal cancer, tongue squamous cell carcinoma, breast cancer and colon cancer.

#### 5) ANTI-CANCER ACTIVITY

Grape seed proanthocyanidins can prevent the formation of H<sub>2</sub>O<sub>2</sub>, protein oxidation, lipid peroxidation, and DNA damage in cells, along with scavenging superoxide anions and hydroxyl radicals, and enhancing the antioxidant defense compounds glutathione peroxidase, superoxide dismutase, catalase, and glutathione [51]. Proanthocyanidins can bind directly with signaling molecules involved in many cellular processes and regulate their activity. Proanthocyanidins produce both cytotoxic and proapoptotic effects by regulating MAPK and NF- $\kappa$ B-targeted gene expression and antimetastatic impacts by inhibiting genes for cell migration [52]. Additionally, lipid nanocarriers containing 25% grape seed oil and 2% laurel leaf oil reached 98% antioxidant activity, evidencing their potential to reduce delivery system toxicity and significantly improve various cellular events and mechanisms; i.e., antioxidant activity, cell cycle arrest and apoptosis induction, and antioxidant enzyme modulation [53].

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