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Review Article

Grape seeds: nutritional value, health advantages, and industrial applications

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Abstract: Grapes are one of the most widely cultivated fruits and have been used for winemaking since the ancient Greek and Roman civilizations. 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. The conjugated and colonic metabolites of grape seed proanthocyanidins are responsible for their advantageous health effects. Studies have reported that grape seeds exhibit a broad spectrum of pharmacological properties against oxidative stress. Their potential health benefits include anti-oxidant, anti-microbial, anti-obesity, anti-diabetic, anti-neurodegenerative, anti-osteoarthritis, anti-cancer, and cardio- and eye-protective properties. Consumers are using grape seeds as a dietary supplement as a result of their awareness of the health advantages associated with proanthocyanidins. This review article summarizes the previous studies of the phytochemical compounds, pharmacological properties, and industrial applications of grape seeds.

Keywords: grape seed extract; proanthocyanidins; nutritional values; applications

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1 Introduction

Grape seed extract (GSE) is a well-known source of powerful antioxidants and anti-inflammatory agents with a variety of therapeutic applications[1-4]. GSE has been demonstrated to have significant anti-inflammatory and antioxidant properties in various diseases, including cardiovascular and cerebrovascular diseases, liver and lung injury, obesity, and neurodegenerative diseases[5,6]. Grape polyphenolics are divided into two categories based on their structure and activity: flavonoids and non-flavonoids[7-9]. Grape seed contains protective and beneficial flavonoids, including proanthocyanidins, anthocyanins, procyanidins, and flavan-3-ols[10]. In addition to flavonoids, grape seeds contain numerous phenolic chemicals such as phenolic acids, carotenoids, stilbenes, tannins, and catechins[11]. Grape seed oil (8%–20%) contains various saturated and unsaturated fatty acids, including linolenic, linoleic, oleic, palmitic, arachidonic, and stearic acids[12,13]. Linoleic acid is the most prevalent fatty acid in grape seeds, accounting for 65%. Grape seed oil contains 85%–90% polyunsaturated fatty acids (PUFA), which are beneficial to human health[14].

Furthermore, grape seed contains several antioxidant vitamins, such as vitamins C and E (tocopherols and tocotrienols), considerably improving its antioxidant effects[15]. Grape seed oil has been demonstrated to have a high vitamin E concentration (average: 27 mg/(100 g) of oil), surpassing that of olive and soybean oils[14]. GSE antioxidants work directly by scavenging reactive oxygen species (ROS), preventing lipid oxidation, and chelating redox-active transition metals like copper and iron[16]. Previous research has shown that grape seed is more antioxidant-rich than other grape parts such as skin and leaves[17]. Grape seed's high antioxidant potential is due to its high catechin concentration, epicatechin, gallic acid, procyanidins, and proanthocyanidins[17]. The current review analyses the biological activities of this extract to provide fresh insights into preventative and potential therapeutic development opportunities.

2 Chemistry of grape seeds

Phenolic acids, flavonoids, anthocyanins, proanthocyanadines, and stilbenes are important bioactive substances found in grapes and their products that benefit human health[18,19]. Previous studies reported that GSE mainly contains 15 polyphenolic compounds, including 11 flavane-3-alcohols ((+)-catechin, epigallocatechin gallate, (−)-epicatechin, proanthocyanidins B1, proanthocyanidins B2, proanthocyanidins B3, proanthocyanidins B4, B1-3-*O*-gallate, B2-3-*O*-gallate, B2-3'-*O*-gallate, and gallate C1), three flavonols (kaempferol, myristin and quercetin), and phenolic acid (gallic acid)[20,21]. Sang *et al.*[22] extracted proanthocyanidin (5.023,9 g) from grape seeds by ultrasonication using ethanol at 25 °C using grape seeds as raw materials, ultrasonic-assisted extraction, and solvent extraction were used to extract proanthocyanidins. The

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effects of different solvents on the extraction rate of proanthocyanidins were experimentally explored, and the content of the obtained proanthocyanidins was determined by the hydrochloric acid-vanillin method. Comparing the two methods, it was concluded that at 25 °C, using ethanol as the solvent and using the ultrasonic-assisted extraction method, the extraction rate of proanthocyanidins is higher and the purity is also higher.

The oil content of grape seeds is traditionally extraction using mechanical methods or organic solvents[23]. In mechanical extraction, although the quality of product is superior, the extraction gives a lower yield. While organic solvent extraction gives a higher yield, it requires solvent recovery through distillation and the final product contains traces of residual solvent[23]. The supercritical method is regarded as a promising method that can produce a similar quantity and better quality of oil yield than mechanical and organic solvent extractions[23]. Cold-pressing is used to extract the oil from grape seeds without chemical treatment or heat[24]. Although cold pressing usually gives a lower yield than other conventional solvent extraction, it may retain more bioactive components and be safer because there are no solvent residues in the grape seed oil[25].

Various bioactive phenolic compound extracts in grapes are summarized in Fig. 1. The majority of phenolic components, including anthocyanins, flavonols, hydroxycinnamic acid derivatives, and proanthocyanidins, are concentrated in the berry's skin, with the seeds containing the least amount of resveratrol[26,27]. Furthermore, the seeds contain more flavan-3-ols and proanthocyanidins than the flesh, which includes just trace levels of anthocyanins and other phenolics.

The main phenolic compounds in grapes, flavonoid and resveratrol which belong to the stilbene group are potent antioxidants and have been suggested to have a role in protecting against cardiovascular diseases[28]. Condensed tannins named as proanthocyanadins were also reported to have cholesterol-lowering properties and reducing blood pressure[29]. Grapes are also rich in phytosterols and fatty acids[27] which may partially inhibit the intestinal absorption of both dietary and biliary endogenously produced cholesterol, lowering their circulating levels and exerting anti-atherogenic and cardio-protective effects[14].

Proanthocyanidins are polymeric flavan-3-ols with varying hydroxylation, esterification, and interflavan bonding (Fig. 2). The monomeric units are primarily (epi) afzelechin, (epi) catechin, and (epi) gallocatechin with varying degree(s) of polymerization (DP). Flavan-3-ol polymerization occurs through common B-type C4-C8/C4-C6 bonds and, less commonly, via A-type C2-*O*-C7/C2-*O*-C5 bonds. Additionally, proanthocyanidins may have gallic acid esters, glycosylation, or bonding to other flavonoids, such as anthocyanins[30]. The processing and preservation of foods may also induce polymerization, depolymerization, or oxidation of proanthocyanidins[31]. Thus, the stereochemistry, DP, and additional substitutions create significant diversity in proanthocyanidins distributed in food[32,33]. Grape seeds are particularly enriched in proanthocyanidins, containing 159 mg/g seed[20]. Grape seed proanthocyanidins (GSPs) are mainly B-type (epi) catechin polymers with a mean DP of ~16[34].

3 Bio-accessibility and bioavailability of grape bioactive molecules

It is widely acknowledged that grape bioactives need to be both bio-accessible and bioavailable, and they need to be present in adequate concentrations in foods, whether they are processed or raw, to have a biological effect. According to Mattioli *et al.*[35], bioavailability is defined as the fraction that reaches the systemic circulation in an amount sufficient to cause a reaction, while bio-accessibility is defined as the fraction released from the food matrix during gastrointestinal digestion. Food processing and food matrix may have an impact on bioavailability. For instance, phenolics have low bioavailability, limited water solubility, and are

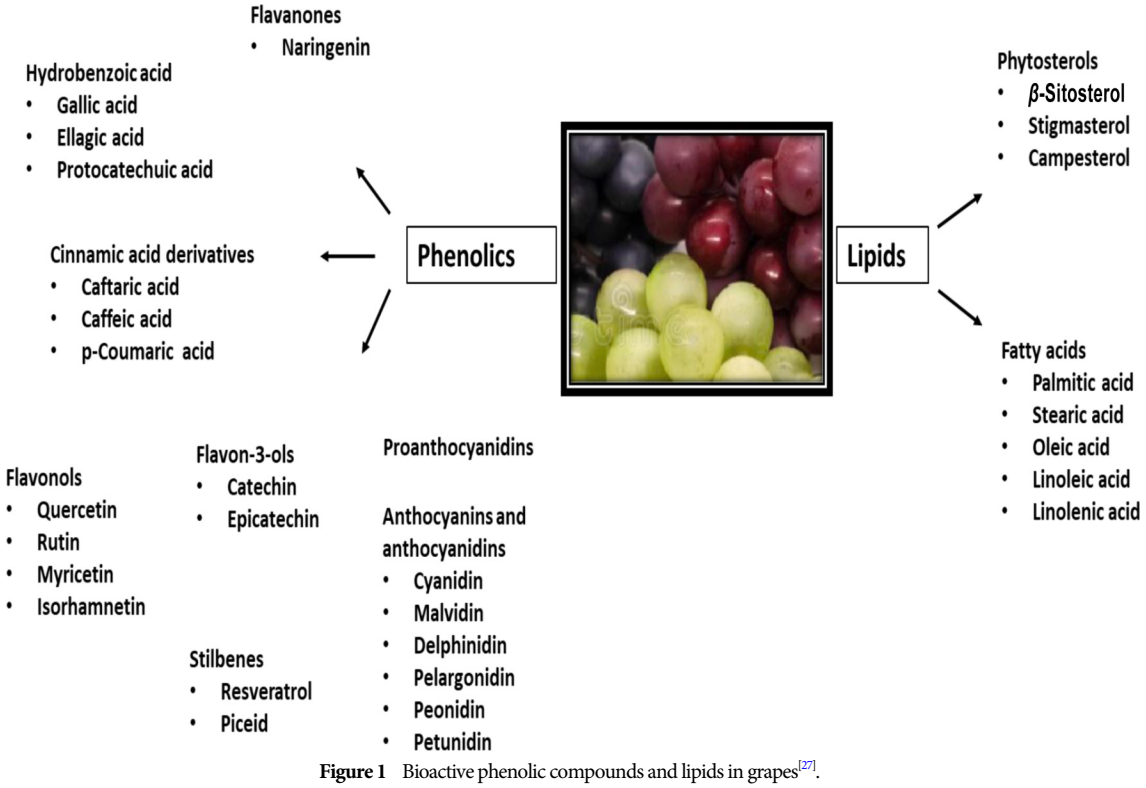

Figure 1 Bioactive phenolic compounds and lipids in grapes[27].

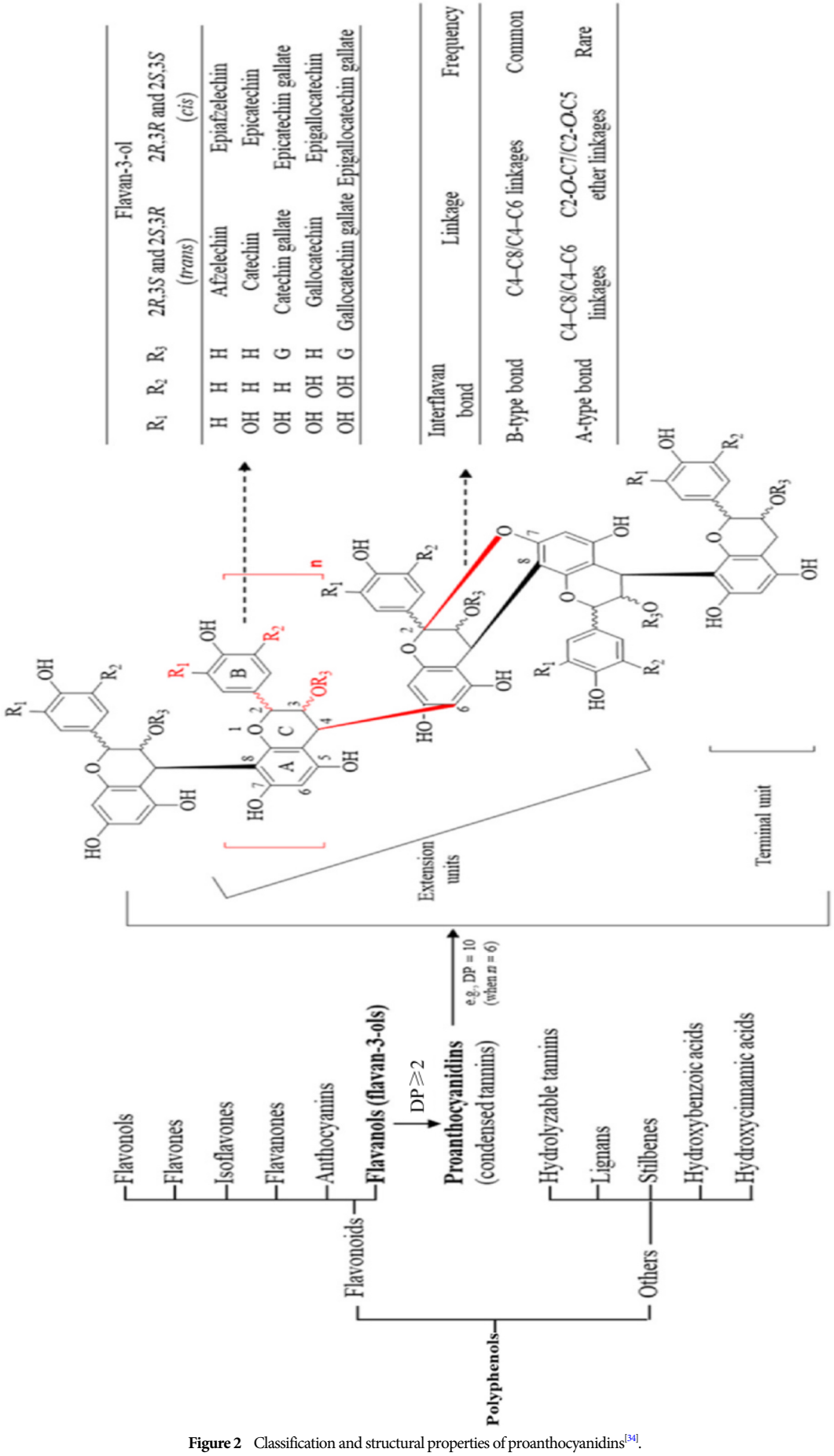

Figure 2 Classification and structural properties of proanthocyanidins[34].

susceptible to oxidation throughout food processing[36]. The food and pharmaceutical industries commonly use microencapsulation, which combines several techniques like freeze drying and spray drying, to overcome these restrictions when integrating GSE. These methods control how these bioactives are released, keep the contents from oxidizing and becoming more stable, and improve the overall quality of the meal[36]. The ability of phenolic chemicals to pass through the intestinal barrier and be released from the grape product during digestion determines their ultimate bioactivity.

It has been reported that polyphenols from berry fruits, such as grapes, have a higher bio-accessibility than other fruits due to their low content of non-digestible carbohydrates and protein, which is associated with efficient gastrointestinal delivery, thereby increasing their bioavailability[37]. A bio-accessibility study of grapes and products discovered that a higher proportion of skin and seed phenolics removed during juicing were highly bio-accessible[38]. It also stated that 100% grape juice and whole fruit consumption followed a similar pattern in phenolic distribution to consumers. The bioaccessibility of anthocyanins in grape juice (86%–135%) was compared to the whole grape (14%–39%), as were flavan-3-ols and phenolic acids in grape juice (48%–101%; 39%–85%) and whole grape (0%–3%; 9%–67%). As a result, consuming grapes/their products may have a positive impact on bio-accessibility and bioavailability, triggering a biological reaction. However, compounds like resveratrol and anthocyanins, which are frequently bioactive in grapes and have a major role in hypertension, have low bioavailability[35, 39].

In terms of uptake and distribution, oral absorption and bioavailability of proanthocyanidins have been well investigated in both humans and animals. The bioavailability of proanthocyanidins is influenced by their absorption, metabolism, and degradation[40]. These chemical structures and DP typically control their bioavailability[41]. When proanthocyanidins are consumed, they interact with oral mucosa and proline-rich proteins in the mouth to produce astringent reactions[42], allowing the remaining chemicals to pass through the intestinal barrier. According to studies using radiolabeled rats, some types of phenolic acids can pass through the intestinal barrier and travel through the vasculature to the liver, where they can potentially reach all organs in a matter of hours after consumption[43]. Low molecular weight forms—particularly monomeric and dimers of flavan-3-ols—have been demonstrated to be absorbed in the small intestine and broken down by phase-II enzymes, while polymeric forms are broken down by the colonic microbiota[44, 45]. Furthermore, upon digestion, the metabolized molecules may acquire new activities or lose their original features[46]. Additionally, it has been shown that phase-II metabolites are the primary substances that enter the systemic circulation and tissues 2 h after an acute proanthocyanidin administration[47, 48]. After ingestion, the circulatory levels of dimers and trimers equated to 0.35% and 0.01%, respectively, according to a study that used an oral GSE containing 20% and 30% of these substances[47]. According to Sierra *et al.*[47], this was caused by an excessive breakdown of dimers and trimers into monomeric catechins, which increased from 36% of the GSE by weight to 99% of circulating flavanols. The ability of Caco-2 human colonic cell lines cultured on filter membranes to absorb radiolabeled proanthocyanidins was examined by Deprez, Mila, Huneau, Tome, and Scalbert[49]. Researchers found that while larger oligomers (average DP = 7) were ten times less likely to be absorbed *in vivo*, lower molecular weight proanthocyanidin oligomers (average DP = 3) could be absorbed intact across a model of the gastrointestinal tract. Rats were given GSE, (+)-catechin, and procyanidin B3 meals by Donovan *et al.*[50]. There was no indication that the procyanidins were absorbed, even though conjugated metabolites of (+)-catechin were found in plasma and urine following the (+)-catechin and GSE meals.

4 Biological activities of grape seeds

4.1 Antioxidant activity

GSPE have a complex antioxidant action that includes chelation, inhibition of polyphenol oxidase, and free radical scavenging[51]. Rats have been used as the model for iron deposition in the dextran intraperitoneal injection approach[52]. Renal oxidative damage and dysfunction were brought on by the increased iron buildup in the renal cells. Following seven weeks of treatment, GSPE can improve the overall health of rats by lowering the amount of iron in the blood and kidney, boosting the antioxidant defense system, controlling kidney function and structure, and preventing renal apoptosis. The mechanism might have something to do with chelation and the antioxidative qualities[53]. Feng *et al.*[54] reported that high-dose GSE soft capsules (150 mg/day) increased superoxide dismutase (SOD) activity compared to pre-test levels ($P < 0.05$). Similarly, glutathione peroxidase (GSH-Px) activity increased significantly in the medium and high dose groups compared to before the test. The high-dose group showed increased GSH-Px activity than the control group ($P < 0.05$). MDA levels in the medium and high dose groups (100 and 150 mg) were significantly lower than before the test showing a substantial antioxidant effect from GSE capsules.

Oxidative stress contributes to and promotes a variety of reproductive disorders associated with granulocyte (GC) apoptosis. Some studies with follicular pig ovarian granulosa cells found that GC apoptosis played a key role in regulating ovarian follicular atresia, and ROS-induced GC apoptosis caused follicular atresia[55-57]. Grape seed proanthocyanidin B2 (GSPB2) was employed as an antioxidant to minimize oxidative stress and apoptosis in GCs treated with H_2O_2. The results demonstrated that GSPB2 may suppress H_2O_2-induced GC apoptosis and caspase-3 via up-regulating let-7a, indicating antioxidant activity[57]. The bioavailability of GSPE, specifically, their ability to pass through the intestinal barrier and their metabolism, determines their antioxidant activity[58]. According to Zhang *et al.*[57], GSPE demonstrated antioxidant activity during the *in vitro* studies and decreased the oxidative stress of proliferating cell nuclear antigen (PCNA) protein production in cardiac muscle, which in turn regulated the expression of associated genes. In ethanol-damaged human liver cancer cells (HepG2) and liver-damaged rats, Bak *et al.*[59] investigated the antioxidant and liver protective mechanisms of GSPE. The findings demonstrated that GSPE enhanced the activity and expressions of multiple antioxidant enzymes, including catalase, SOD, and glutathione (GSH) peroxidase *in vitro*, in addition to lowering ROS production and CYP2E1 expression. Tkacz *et al.*[60] employed high-performance liquid chromatography photodiode array (HPLC-PDA) and 2,2'-azinobis 3-ethylbenzthiazoline-6-sulphonate (ABTS) post-column derivations for the analysis, ferric reducing antioxidant power (FRAP), and Oxygen Radical Absorbance Capacity (ORAC) to measure the antioxidant activity of seeds. GSE was discovered to have strong antioxidant action[60].

Hernández-Jiménez *et al.*[17] discovered that grape seed has a higher antioxidant capacity than other grape parts such as skin, leaves, and wine. This high antioxidant capacity is attributed to grape seed's high catechin concentration, epicatechin, gallic acid, procyanidins, and proanthocyanidins.

4.2 Antidiabetic activity

Irandoost *et al.*[61] investigated the impact of grapeseed oil on insulin resistance and inflammation in 44 overweight or obese women between the ages of 20 and 50. After 8 weeks of treatment, inflammatory markers like tumor necrosis factor alpha (TNF-α) and a high-sensitivity C-reactive protein (hs-CRP) were reduced. Additionally, grape seed oil reduced ratings on the homeostatic model assessment of insulin resistance, or homeostatic model assessment for insulin resistance (HOMA-IR), suggesting an improvement in insulin resistance in obese females. In diabetic rats, Soğutlu *et al.*[62] investigated the effects of GSE on insulin, adiponectin, and resistin levels. The findings revealed that, compared to the rats in the diabetes category, the rats in the diabetes + GSE group had greater levels of adiponectin and insulin. There was no discernible difference in resistin concentration across the groups. In diabetic rats, GSE is likely to raise insulin levels while lowering adiponectin levels and having no effect on resistin levels[62]. A substantial ($P < 0.05$) decrease in serum glucose levels was seen in the group that consumed grape seed oil (GSO) ((124.80 ± 1.52) mg/dL) as compared to the other group in another investigation on the hepatic function of adult male rabbits[63]. Procyanidins in GSE have been shown to have insulin-mimetic qualities by promoting glucose absorption in insulin-sensitive cell lines and reducing hyperglycemia in diabetic rats given streptozotocin (STZ)[64]. Additionally, a study that involved diabetic rats fed GSO showed a substantial reduction in fasting blood sugar[65]. Considering the antioxidant effects and iron chelation properties of GSPE, Zhou *et al.*[66], Alomair *et al.*[67], and Li *et al.*[6] speculated that GSPE could alleviate oxidative damage in the pancreas caused by glycolipid toxicity.

4.3 Anticancer activity

GSPE had a favorable effect on liver cancer, lung cancer, esophageal cancer, tongue squamous cell carcinoma, breast cancer, and colon cancer. Wang *et al.*[68] treated HepG2 cells in nude mice with GSPE and discovered that 100 and 200 mg/kg of GSPE significantly inhibited HepG2 cell growth in nude mice without causing toxicity or autophagy, and induced phosphorylation of mitogen-activated protein kinase (MAPK) pathway-related proteins and telomere kinase (p-JNK). GSPE also regulated the protein kinase (p-ERK) and p38 mitogen-activated protein kinase (p38 MAPK) while decreasing the expression of survival. It was claimed that GSPE may have anti-liver cancer effects. Hamza *et al.*[69] developed a method that combines diethylnitrosamine (DEN) and 2-acetylaminofluorene (AAF, 2-AAF) to investigate the effect of GSE in the early stages of liver cancer. As expected, GSE dramatically reduced the establishment of pre-tumor foci in rats' livers. GSE's participation was ascribed to several inflammatory mechanisms, including reduced histone deacetylase (SIRTl) activity, cyclooxygenase 2 (COX-2), and inducible nitric oxide synthase (iNOS). Furthermore, GSE inhibited the activity of HepG2 cells by activating caspase-3 and Bax, resulting in early and late apoptosis. Furthermore, GSE promoted G2/M and G1/S cell cycle arrest, demonstrating anticancer activity.

Oncomirs are microRNAs (miRNA) linked to carcinogenesis and malignant transformation. They have emerged as promising molecular targets for anticancer treatment. Mao *et al.*[70] hypothesized that GSPE's antineoplastic actions were achieved by modulating oncomirs and their downstream targets. They discovered that GSPE dramatically reduced oncomirs miR-19a and miR-19b in several lung cancer cells. In addition, GSPE elevated mRNA and protein levels of insulin-like growth factor II receptor (IGF-2R) and phosphatase and tensin homolog (PTEN), which are expected targets of miRNA-19a and -19b. Furthermore, GSPE significantly boosted PTEN activity while decreasing AKT phosphorylation in A549 cells. Transfection of miR-19a and -19b mimics reversed the increase of *IGF2R* and *PTEN* gene expression, nullifying the anti-proliferative response induced by GSPE[70].

Lung carcinoma is one of the most common cancers, and it poses a major threat to human life and health. It has been observed that GSPE has a beneficial effect on the prevention and treatment of lung cancer, with no deleterious side effects on normal human cells. A549 cells were treated with a specific concentration of oligomeric GSPE. Oligomeric-GSPs (O-GSP) may improve the anti-tumor effect of *cis*-dichlorodiamineplatinum (II) (DDP) on A549 cells, showing its anti-lung cancer capabilities[71]. GSPE's mechanism of action on lung cancer cells consists primarily of three aspects: (1) tissue cell cycle inhibition of cell proliferation; (2) promotion of tumor cell death; and (3) reduction of metastasis and tumor cell spread (Fig. 3). O-GSP and DDP were employed in conjunction with A549 cells to down-regulate the expression levels of P-Rb, CyclinD1, and CDK4 proteins, resulting in cell cycle G0/G1 and S-phase suppression via the Cyclin D1-CDK4-Rb pathway. Furthermore, epidermal growth factor receptor (EGFR) expression may be inhibited to limit cell migratory force, while E-cadherin and N-cadherin could be upregulated and downregulated, respectively, to impede cancer cells' epithelial-mesenchymal transition. Additionally, EGFR expression may be inhibited to limit cell migratory force, while E-cadherin and N-cadherin could be upregulated and downregulated, respectively, to impede cancer cells' epithelial-mesenchymal transition. They could also increase the Bas:Bcl-2 ratio, activate caspases 3 and 9, and enhance the release of cytochrome enzyme C from mitochondria into the cytoplasm. Furthermore, the combination of O-GSP and DDP has the potential to diminish *GST-π* mRNA and tumor cell drug resistance. The inhibition of COX-2 resulted in the reduction of tumor occurrence and progression.

The anticancer mechanism of GSPE could be related to a signaling route. Inhibition studies of GSPE on human esophageal cancer cells (ECA109) have shown that GSPE activated caspase-3 and attenuated NF-κB signaling pathway, reducing the secretion of inflammatory cytokines, inducing apoptosis, and inhibiting the proliferation of ECA109 cells[72]. GSPE inhibited human tongue squamous cell carcinoma (Tca8113) cells by targeting the Akt/NF-κB signaling pathway. At non-toxic concentrations (25, 50 μg/mL), GSPE strongly suppressed matrix metalloproteinase-2 (MMP-2) and matrix metalloproteinase-9 (MMP-9) secretion from Tca8113 cells, reducing migration and invasion[73].

GSE (0.05–100 μg/mL) inhibited human breast cancer cell (MCF-7) activity and induced apoptosis[74]. GSE in non-connected MCF-7 cells stimulated gap junction-mediated intercellular communication (GJIC). GJIC was transitory but greatly increased. A real-time polymerase chain reaction revealed a considerable increase in connexin-43 (*cx43*) mRNA expression on the membrane. This result confirmed the idea that GSE's proliferation

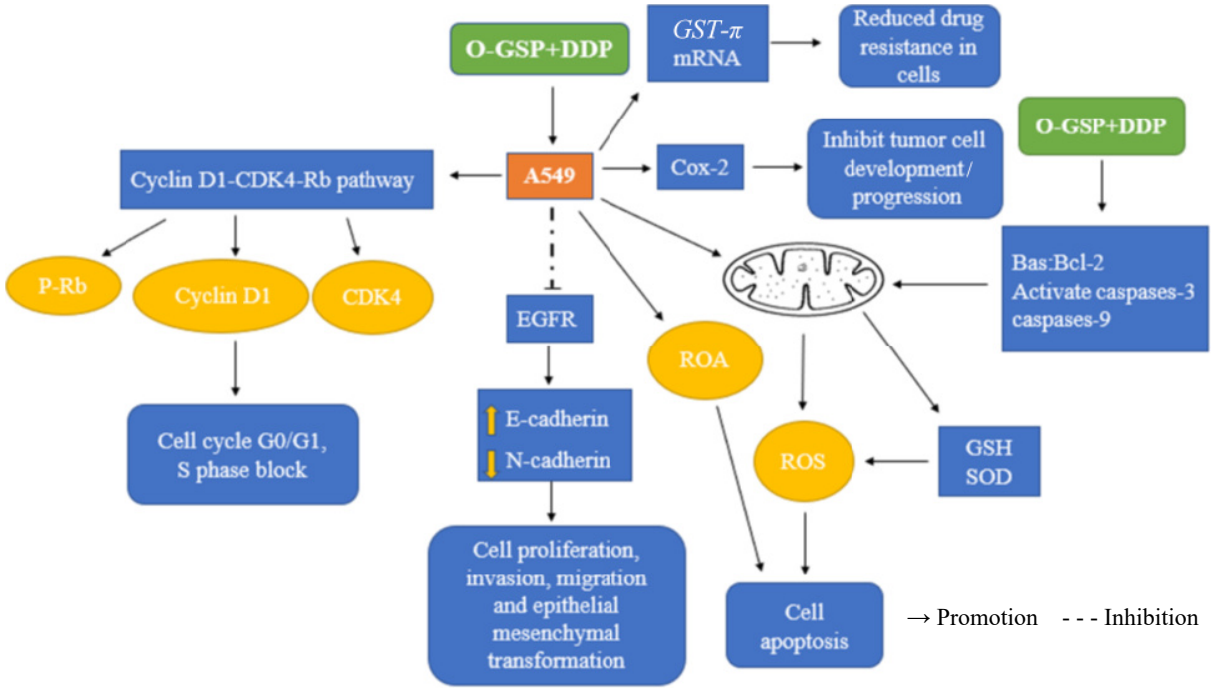

Figure 3 Mechanism of action of GSPE on lung cancer cells[71].

suppression and proapoptotic actions on MCF-7 were mediated by Cx43 protein relocalization and gene upregulation[75]. Similarly, GSPE dramatically affected the shape of colon cancer cells (SW480 and SW620), inhibiting cell proliferation by disrupting the cell cycle and triggering apoptosis. This mechanism relied heavily on the Akt signaling route and the antioxidant signaling pathway represented by FoxM1. When oligomeric procanthocyanidins (OPCs) were combined with chemotherapeutic agents, the expression and activity of several key ABC transporters in cell lines were significantly reduced, potentially preventing cancer patients from developing resistance to targeted therapy[76-78].

Cancer formation is influenced by disruptions in the normal regulation of cell-cycle progression and division. Several proteins are known to control the timing of events during the cell cycle. Cyclins and cyclin-dependent kinases (CDKs) are key regulatory switches in the cell cycle. GSE and many of its constituents (chiefly epigallocatechin-3-gallate (EGCG) and resveratrol) have been demonstrated to exert their antiproliferative effects on leukemia[79], ovary[80], lung[81], head and neck[82], prostate[83,84], breast[85-87]. It is worth mentioning that, as previously stated, natural GSE and tea extract have a far stronger antiproliferative effect than isolated chemicals or synthetic mixtures[88].

GSE treatment significantly reduced the expression levels of CDK2, CDK4, and CDK6[89]. Similarly, GSE treatment caused a significant decrease in cyclins D1, D2, and E, as well as an increase in the expression of negative cell cycle regulators (Cdki, such as p21 and p27), resulting in dramatic inhibition of cell growth and subsequent cell cycle arrest in G1, S, or G2/M phase[90]. The antiproliferative impact of GSE involves numerous molecular targets, including up-regulation of Rb phosphorylation and down-regulation of E2F via modulation of the EGFR-ERK1/2 pathway[82]. Ultimately, these signals converge and activate cyclins, which bind to Cdki and cause cell cycle progression to S phase. CDK activity is necessary for cancer progression, and their functions are strictly controlled by Cdki. The increased expression of Cdki, together with decreased expression of cyclins (specifically Cyclin-1)[91], and CDKs on GSE-treated cancer cells, suggests that GSE may be effective as a chemotherapeutic drug for the treatment of a variety of tumors. These effects are expected to include GSE-mediated suppression of the PI3K/Akt pathway, down-regulation of the EGFR[92], and interference with NF-κB activity (Fig. 4).

4.4 Cardiovascular activity

One of the main issues brought on by the contemporary, unhealthy lifestyle—which is the leading cause of death worldwide—is cardiovascular disorders (CVD). In general, CVD refers to a condition where changes in heart and blood vessel function can result in heart attacks, cardiac arrest, chest pain, and other related symptoms. A healthy lifestyle is essential for preventing CVD. A healthy diet high in fresh fruits and vegetables, frequent exercise, etc., lowers the risk of CVD. The risk factors for the development of atherosclerosis and CVD include diabetes mellitus, high blood pressure, and dyslipidemias. These conditions can be reduced by altering one's lifestyle[93]. Atherosclerotic plaque is created when lipoprotein is deposited in the artery's intimal layer. Furthermore, modifications in the plasma lipid profile cause hydroxyperoxide to develop and phospholipids, oxysterol, and other lipids to lyse[6]. Particles of oxidized low-density lipoprotein (Ox-LDL) are essential to the pathophysiology of atherosclerosis. When endothelial cells are exposed to Ox-LDL, monocytes migrate to the subendothelial layers, where they develop into macrophages and produce growth factors. Furthermore, exposure to Ox-LDL triggers angiotensin II-like effects, platelet aggregation, and the proliferation of smooth muscle cells and fibroblasts[94]. Accordingly, the pathophysiology of CVD is significantly influenced by the free radical scavenger[6,95]. Numerous animal and human studies have demonstrated the promising outcomes of GSE's cholesterol-lowering qualities; nevertheless, some researchers disagree about how these attributes affect lipid profiles[96].

Research and data indicate that certain fruits and vegetables, such as grapes, have cardioprotective properties (Table 1). Consuming foods high in polyphenols can also lower the risk of

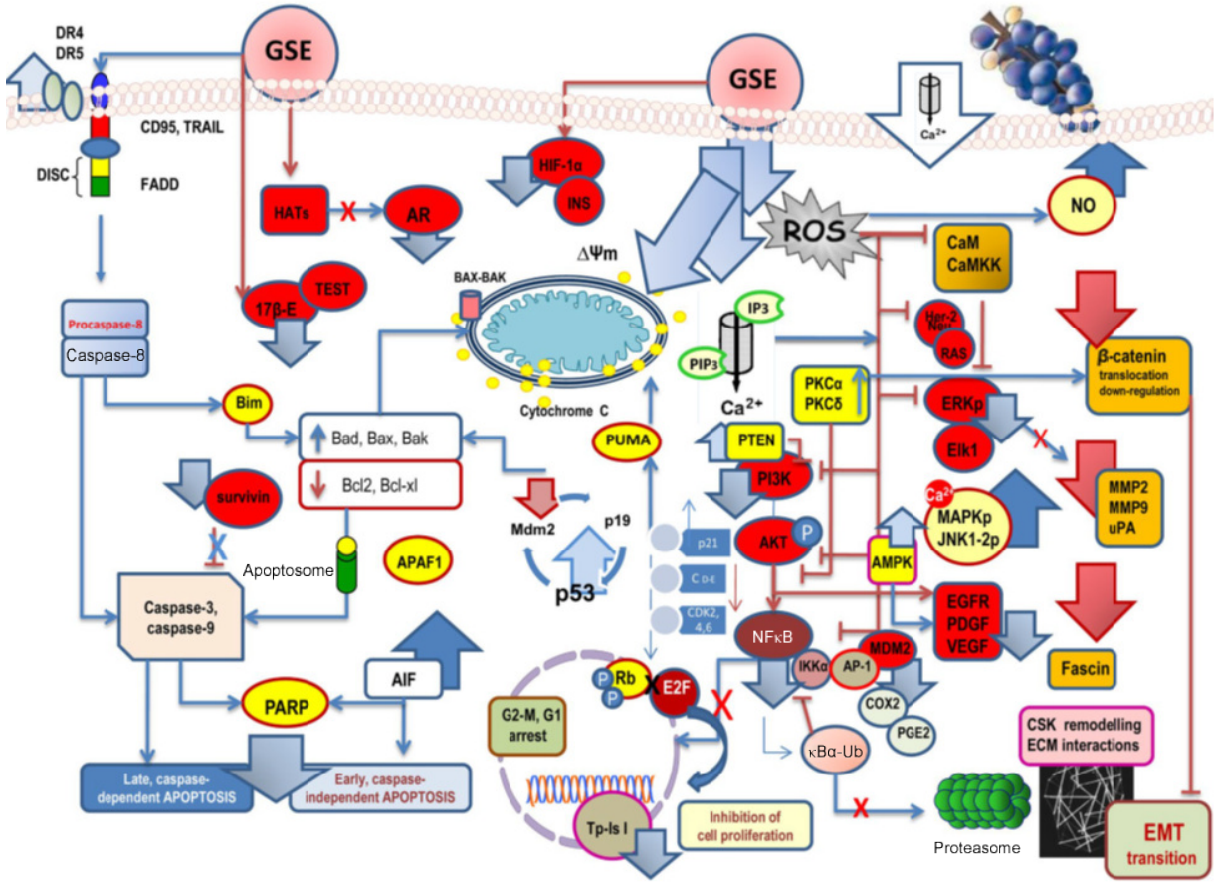

Figure 4 Molecular mechanisms of GSE interactions. GSE interacts with many cellular biochemical and genetic pathways, through which cell proliferation, cytoskeleton rearrangement, apoptosis, and cell differentiation are modulated. A pivotal key step is supported by the increase in ROS formation induced in cancer cells by GSE through the selective regulation of the redox balance[81]. DISC, death-inducing signaling complex; FADD, Fas associated death domain; transmembrane death receptors, DR4, DR5; TRAIL, tumor necrosis factor-related apoptosis-inducing ligand; INS, insulin; PARP, poly-ADP-ribose polymerase; FOXO1, forkhead box O1; HATs, histone androgen acetyltransferase; AIF, apoptosis Inducing factor; APAF, apoptotic protease activating factor 1; HIF-α, hypoxia-inducible factor 1-alpha; TEST, testosterone; AR, Androgen receptor; IP3, Inositol-3-phospgate; PIP3, phosphatydyl-Inositol-3-phosphate; CaM, calmodulin; CaMKK, calmodulin kinase; PKC, protein kinase C; PUMA, p53 upregulated modulator of apoptosis; IK-b, inhibitor of kappa B (comprising the subunits IKKα, β, γ); MDM2, mouse double minute 2 homolog; AP-1, activator protein 1; NO, nitric oxide; uPA, urokinase-type plasminogen activator; MMP2-9, matrix metalloproteinases; Tp-Is 1, topoisomerase-I; PGE2, prostaglandin E2; Elk-1, ETS domain-containing protein; C, cyclin; Ub, ubiquitination complex; CSK, cytoskeleton; ECM, extra-cellular matrix; EMT, epithelial-mesenchymal transition.

Table 1 Various studies on the role of GSE in cardiovascular disorder

Methods	Benefits	References
Carotid B-mode ultrasound	Inhibits the progression of plaque in CIMT	[100]
Antioxidant properties, Endothelial function (cultured endothelial cells are used), anti-platelet effects (used a coronary artery platelet aggregation model)	Inhibits the oxidation of LDL, improving endothelial function, inhibition of platelet aggregation, reducing inflammation, lowering blood pressure and prevent cell senescence by activating novel proteins	[97]
Anti-platelet action of extracts was compared with action of well characterized antioxidative and anti-platelet commercial monomeric polyphenol-resveratrol	Protects against myocardial injury, myocardial ischaemia–reperfusion, reduction in platelet adhesion, aggregation and generation of superoxide anion	[105]
Anti-thrombotic effect of proanthocyanidin was assessed by a shear-induced thrombosis test *in vitro* and by a laser induced thrombosis test in the mouse carotid artery, *in vivo*	Inhibits the thrombus formation	[104]
Measurement of inhibitory effects on pancreatic lipase and lipoprotein lipase activities and on lipolysis of 3T3-L1 adipocytes was assayed using GSE	Minimize the accumulation of fat in adipose tissue and dietary fat absorption by inhibiting fat-metabolizing enzymes; pancreatic lipase and lipoprotein lipase	[103]

cardiovascular disease. Numerous epidemiological studies have been conducted, indicating that consuming grapes high in polyphenols may reduce the risk of cardiovascular death. GSE inhibits or limits the oxidation of low-density lipoprotein (LDL), lowers blood pressure, reduces inflammation, inhibits platelet aggregation, and activates certain proteins that delay cell senescence, among other mechanisms by which it prevents atherosclerosis[97]. The *in vitro* and *in vivo* studies show a relationship between the antioxidant phenolics' presence and the decrease of Ox-LDL particles. Additionally, eating a diet high in phenolic antioxidant-rich foods lowered the incidence of heart disease[98]. There is a direct correlation between the prevention of CVD and the ability of the (poly)phenols found in GSE to prevent radical oxidation of the PUFA of LDL, which frequently happens

through oxidative modification of the apoprotein toward an atherogenic form[99]. An investigation into GSE's anti-atherogenic properties was conducted. 287 patients with abnormal plaque carotid intima-media thickness (CIMT) or asymptomatic carotid plaques were included in this study. It was found throughout this investigation that GSE reduces the amount of carotid plaque in patients and slows the growth of mean maximum CIMT. Accordingly, it was determined that the proanthocyanidin-loaded GSE had atherogenic effects[100].

It was also shown that antioxidants found in red GSE can deactivate superoxide anions and prevent lipid peroxidation. Red GSE provides significant cardio-protection against reperfusion-induced harm by free radicals following ischemia[101]. Some preclinical *in vivo* investigations found that winery residues inhibit LDL oxidation, and 15% grape pomace in a cholesterol diet (0.3%) can reduce rat liver and serum cholesterol levels by half while increasing high-density lipoproteins (HDL) by 26%[102]. Thus, GSE can lessen the risk of CVD by blocking LDL oxidation, enhancing endothelial function, decreasing platelet aggregation, reducing inflammation, lowering blood pressure, and preventing cell senescence by activating new proteins[97]. GSE can also be used to reduce fat accumulation in adipose tissue and dietary fat absorption by blocking fat-metabolizing enzymes such as pancreatic lipase and lipoprotein lipase[103]. According to Sano *et al.*[104], oral and intravenous treatment of procyanidins derived from grape seeds effectively reduces thrombus development in mouse models. It has also been proven that GSE protects against myocardial damage and ischemia-reperfusion, reduces platelet adhesion and aggregation, and generates superoxide anion in rats[105]. GSO has high linoleic acid content; it is confirmed that its intake may result in lipid profile refining. Also, high amounts of tocotrienols and vitamin E derivatives may inhibit HMG-COA reductase and improve lipid profiles[106]. Shiri-Shahsava *et al.*[65] study showed that following this notion, we found a significant reduction in TG plausibly by phenolic acid in the GSO group. Also, procyanidins indirectly increase the nitrogen oxide lifetime by inhibiting the production of superoxide, its major physiological scavenger, and directly inhibiting angiotensin-converting enzyme[107].

In a double-blind, placebo-controlled, randomized, parallel-group intervention study, the effect of a specific GSE, rich in polyphenolic compounds (300 mg/day) versus placebo, was evaluated in subjects with pre- and stage I hypertension. Data showed that the consumption of the polyphenol extract did not significantly decrease ambulatory blood pressure[108].

Thiruchenduran *et al.*[109], using Wistar rats fed with a high-cholesterol diet, found that GSPs acted against CVD promoters, in particular the ones induced by the diet, partially restoring those changes. In another study, using animals as well, the authors observed an improvement on the blood pressure and in hypertriglyceridemia, what is probably related with the oxidative stress[110].

In a randomized, double-blind, placebo controlled study; analogous extracts were given to 40 hypercholesteraemic subjects, during 8 weeks. The results showed a significant reduction in LDL-c and in total cholesterol (T-c) levels for the GSPs group. However, this group was additionally supplemented with niacin-bound chromium, what suggests that other factors acting in synergy may enhance the nutritional benefits[111]. In another randomized double-blind placebo-controlled clinical trial, the effect of red GSPs extract consumption by 52 mildly hyperlipidemic subjects was evaluated. During 2 months, two different groups received either 200 mg/day of the seed extract or placebo. The results showed a reduction of T-c, LDL-c and Ox-LDL particles, decreasing the risk of atherosclerosis and CVD in those individuals[112].

4.5 Antimicrobial activity

Grape seeds have proven potential as novel microbial agents due to their high polyphenol content. Defatted GSEs were found to have antibacterial properties against *Bacillus cereus*, *Bacillus subtilis*, *Staphylococcus aureus*, *Bacillus coagulans*, *Escherichia coli*, and *Pseudomonas aeruginosa*[113]. It was also discovered that these extracts completely inhibited both Gram-positive and Gram-negative bacteria at doses of 850–1,000 and 1,250–1,500 ppm, respectively. According to Anastasiadi *et al.*[114], GSE has a minimum inhibitory concentration of 0.26 against *Listeria monocytogenes*, suggesting that it could be used as a low-cost source of natural antilisterial combinations. Many bacteria, including *S. aureus*, *Psedomonas aeruginosa*, and *Enterococcus faecalis*, exhibit antimicrobial activity in response to resveratrol[115]. When resveratrol is given topically to healthy skin, it causes an increase in cathelicidin. Cathelicidin inhibits the growth of *S. aureus* and stimulates the production of antimicrobial peptides[116]. Resveratrol has been found to have antibacterial characteristics, specifically the generation of oxidative damage to bacterial membranes without affecting host cells, especially in *E. coli*. These findings shed light on how resveratrol could be utilized to supplement conventional treatments when antibiotics fail or prove ineffective[117]. According to Paulo *et al.*[118], GSE's antibacterial effects are due to changes in cell shape and DNA content.

Helicobacter pylori is a pathogenic bacteria identified as a potential risk factor for gastritis, gastric ulcers, and gastric cancer. During stomach colonization, *H. pylori* triggers a strong inflammatory response and subsequent oxidative stress, which are associated with tissue damage[119]. Silvan *et al.*[120] showed that GSE and its fractions demonstrate antibacterial activity against all strains of *H. pylori* used in the study. The fraction enriched in high molecular weight polymeric procyanidins (PPC) showed the highest antimicrobial activity. We have previously described similar behavior in a GSE rich in procyanidins, where their structure facilitates the interaction between hydroxyl groups and the bacterial membrane[121]. This interaction would increase with the greater availability of hydroxyl groups related to the higher DP of the procyanidin chains. The chemical characterization of the GSE showed that the extract consists mainly of PPC. The concentration of this polymeric fraction (PPC) up to 96% (PPC-rich fraction) led to an increase in the anti-inflammatory and antimicrobial capacity of the extract[122].

4.6 Neuroprotective activity

Alzheimer's disease (AD) is characterized by increased amyloid beta (Aβ) levels, hyperphosphorylation, and tau protein aggregation in the brain[123, 124]. Impaired protein homeostasis (proteostasis) leads to Aβ aggregation and the formation of neuritic plaques, a hallmark of AD[125, 126]. Proteostasis governs protein synthesis, folding, and degradation, ensuring proper cellular metabolic activity[126]. Accumulation of insoluble Aβ in the brain causes peptides to aggregate and form amyloid fibrils, impairing synaptic architecture and functioning. In addition to tau aggregation, different alterations occur in the brains of AD patients. Acetylcholine, for example, is lower in the brain, which increases inflammation[13]. Tau aggregation induces

neuroinflammation in the AD brain. Tau aggregation has been demonstrated to cause hyperactivation of astrocytes and microglia, leading to astrocytosis and microgliosis, which are closely related to inflammation[127]. In contrast, inflammation and oxidative stress, particularly mitochondrial-associated oxidative stress, are important in the development of AD[127, 128]. Thus, because GSE includes various antioxidant compounds, such as vitamin C, vitamin E, procyanidins, and proanthocyanidins, it is likely to have an inhibitory effect on AD onset and progression[129].

GSE treatment reduces MDA levels while increasing GSH and SOD concentrations. This extract can also prevent the loss of Akt and ERK activity in the hippocampus and cerebral cortex[130], implying that GSE can improve hippocampal synaptic plasticity generated by oxidative stress and repair cognitive deficits in AD. Furthermore, grape seed procyanidins may disrupt the lipid peroxidation chain and protect neurons by stimulating Akt phosphorylation[131]. Mantena and Katiyar[132] found that they can reduce oxidative stress by activating signaling pathways such as Nrf2, NF-κB, and MAPK. Furthermore, GSE may reduce mitochondrial-associated oxidative stress. This extract has been shown to inhibit mitochondrial permeability transition pore (mPTP) opening by increasing phosphorylated glycogen synthase kinase 3β (p-GSK-3β) binding to adenine nucleotide translocator (ANT), resulting in a decrease in the formation of the complex ANT-cyclophilin D (CypD)[133]. GSE also protects neuroinflammation by preventing acetylcholine levels from dropping in the Alzheimer's brain[13].

Grape seed also has neuroprotective properties because it modulates Sirtuin 1 (SIRT1) and cAMP response element-binding protein (CREB). GSE-derived procyanidins have been shown to alter ERK phosphorylation, promote CREB-mediated gene expression, and influence SIRT1/CREB signaling (Fig. 4)[123]. SIRT1 protein, found in the cytoplasm and nucleus of mammalian cells, can operate as an anti-aging protein. Furthermore, the CREB protein, a transcription regulator in neurons, is essential for neurogenesis and cognitive ability. The SIRT1/CREB signaling pathway is impaired in the AD brain[123].

Impaired proteostasis is closely linked to the pathogenesis of Parkinson's disease. Alpha-synuclein aggregation is crucial in causing mitochondrial dysfunction in Parkinson's disease by changing mitochondrial dynamics through Drp1 mislocalization[134]. Furthermore, aggregation of this protein causes a variety of additional dysfunctions, including synaptic dysfunction, axonal transport disruption, and calcium homeostasis impairment, all of which contribute to Parkinson's symptoms[135]. Remarkably, GSE improves brain proteostasis while decreasing alpha-synuclein aggregation[136]. Grape phenols have been demonstrated to diminish alpha-synuclein aggregation in the frontal cortex and the production of neuroinflammatory markers such as ionized calcium-binding adaptor molecule 1 (IBA1) and CD54, resulting in relief of non-motor symptoms[136]. GSE has also been shown to reduce ROS, inflammation, and apoptosis in the substantia nigra of the midbrain, as well as protect dopaminergic neurons from 6-hydroxydopamine (6-OHDA) and improve motor capabilities (Fig. 5)[4].

4.7 Anti-inflammation activity

Inflammation is a protective reaction of living tissue with a circulatory system to damaging factors. Grape seed polyphenols (GSP) in the rat model of ulcerative colitis (UC) alleviated inflammation and apoptosis, protecting against UC produced by dextran sodium sulfate (DSS)[2]. The activation of signal transduction and transcriptional activator (STAT3) may contribute to the acceleration of inflammation by increasing the production of inflammatory cytokines, and inhibiting STAT3 activity may be required to reduce colonic inflammation[137]. GSP has been shown to reduce the expression of inflammatory cytokines (iterleukin-6 (IL-6), iterleukin 1 beta (IL-1β), and

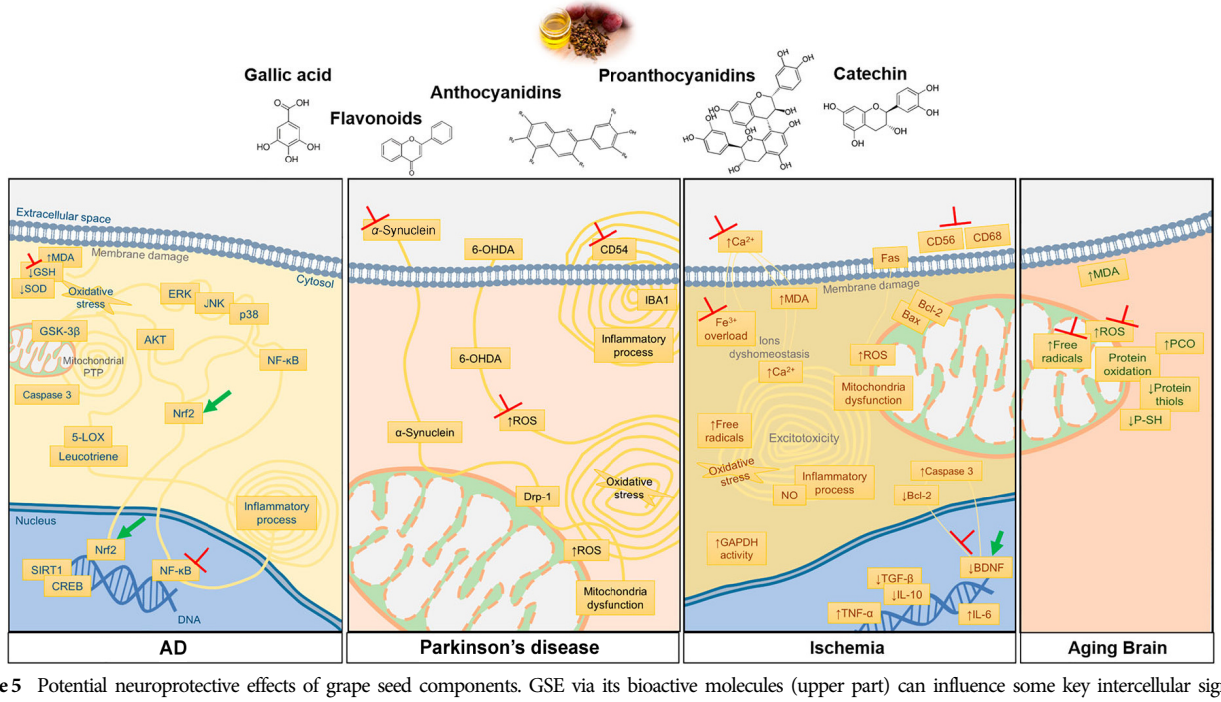

Figure 5 Potential neuroprotective effects of grape seed components. GSE via its bioactive molecules (upper part) can influence some key intercellular signaling pathways, which contribute to the pathogenesis of AD, Parkinson's disease, ischemia, and aging brain (down section). GSE enhances the anti-oxidative status, which slows down Alzheimer's processes by removing dysfunctional mitochondria and inflammatory responses. They also reduce inflammation, oxidative stress, ion overloads, and mitochondrial dysfunction, which influence the processes of Parkinson's disease, ischemia, and aging brain. Green arrows represent upregulation, and blocked lines (red) symbolize down-regulation[124].

TNF-α) and phosphorylate STAT3, leading to improved apoptosis in intestinal epithelial cells[2].

Induction of lipopolysaccharide (LPS) led to increased secretion of inflammatory markers by macrophages, including NO, iNOS, and pro-inflammatory cytokines (TNF-α, IL-1β, IL-6)[138]. High levels of these inflammatory cytokines have been linked to pathophysiology and chronic inflammation[139]. Harbeoui *et al.*[140] found that GSE strongly inhibited TNF-α and IL-6 in mononuclear macrophages from leukemia cells in mice (RAW 264.7). LPS reduced inflammation in murine macrophage RAW 264.7 cells by stimulating iNOS and NO inducible isomers. This was linked to the NF-κB cascade and down-regulation of MAPKs[140].

GSE extract could be used as a novel therapeutic and preventative treatment for inflammatory reactions and illnesses. GSP extract has been shown to have a significant anti-inflammatory effect, as evidenced by transcriptional suppression of COX-2 and inflammatory cytokine production in macrophages. The effects were mediated by the blockage of MAPKs and NF-κB signaling pathways. In this situation, GSE could be an excellent natural product with potent anti-inflammatory properties[141].

GSPE has been shown to protect against hepatic IR injury in mice with fatty liver ischemia/reperfusion (IR) injury. The GSPE group had significantly lower serum (alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels ($P < 0.05$), reduced macrophage infiltration and apoptotic cells, and decreased expression of inflammatory factor mRNA. The process may be due to reduced oxidative stress and inflammation during liver reperfusion, and increased p-p38 expression[142].

4.8 Toxicological studies

Several toxicological studies have been conducted to determine the safety profile of GSEs containing proanthocyanidin. Yamakoshi *et al.*[143] investigated the safety of GSE in Fischer 344 rats and discovered that the no-observed-adverse-effect level in their subchronic toxicity research was 2% of the diet, corresponding to a dietary intake of 1.4 and 1.5 g/(kg·day) in males and females, respectively. In acute oral toxicity experiments in rats, GSE was found to be well tolerated and non-toxic, with a lethal dose 50 (LD_{50}) of 5,000 mg/kg for a single oral dose administered via stomach intubation. Furthermore, a 6-month chronic toxicity study on female B6C3F1 mice revealed that administering GSE at doses of 100, 250, or 500 mg/(kg·day) is safe, with no treatment-related mortality and no significant changes in body weight or physical appearance[144].

In another 90-day oral toxicity study, administration of water-extracted GSE containing less than 5.5% catechin monomers to 4 groups of rats (20 rats per sex per group) at dosages of 0, 0.5%, 1.0%, or 2.0% resulted in no clinical symptoms of toxicity or weight loss[145]. Also, Bentivegna and Whitney[146] revealed that a diet containing 2.5% GSE produced no apparent adverse effects in rats, including no ocular abnormalities or histological results indicating toxicity, thereby validating GSE's safety and tolerance in experimental animal models. Furthermore, the acute oral toxicity of GSE was assessed in a litmus test using female Wistar rats. When GSE was delivered orally via stomach intubation, the LD_{50} exceeded 5,000 mg/kg. Furthermore, no toxicological effects were reported in rats 14 days after dosage, and no gross lesions were found after necropsy[147].

Comparably adult male ICR (CD-I) mice given 100 mg/kg bodyweight GSE by gavage for 7–10 days were found to have multiorgan protection against drug- and chemical-induced toxicity, with no significant changes in serum creatine kinase and ALT activity, blood urea nitrogen level, DNA fragmentation, or organ histopathology compared to the saline control groups[148]. Furthermore, when GSPE was injected once dermally for 24 h into the clipped, unbroken skin of five male and five female albino rats, the LD_{50} was greater than 2,000 mg/kg body weight. During the study, no fatalities, weight changes, or gross necropsies were recorded[149].

4.9 Industrial applications

4.9.1 *Application in food*

Lipid peroxidation is a key cause of food product deterioration during processing and storage. Antioxidants have been added to food goods to extend their shelf life. Because of their carcinogenic and poisonous effects, synthetic antioxidants such as tertiary butylhydroquinone (TBHQ), butylated hydroxyanisole (BHA), and butylated hydroxytoluene (BHT) have been barred from usage in food items. As a result, in recent years, there has been a surge in interest in natural antioxidants, particularly those derived from fruits.

Grape seeds can also be used to preserve food goods. For example, GSEs have been utilized as a food additive in Japan[143]. Jayaprakasha *et al.*[150] found that GSEs effectively reduced potassium ferricyanide at 500 μg/L concentrations. In addition, GSEs demonstrated 65%–90% antioxidant activity at 100 ppm. GSEs have been tested for their antioxidative properties in meat products[151,152]. Ahn *et al.*[151] found that adding GSEs increased oxidative stability and reduced hexanal concentrations in cooked ground beef by 97% after three days of refrigerated storage compared to the control without antioxidants. Lau and King[152] found similar improvements in oxidative stability in turkey patties. Furthermore, Lau and King[152] showed that adding GSEs at 1.0% and 2.0% to turkey patties reduced thiobarbituric acid reactive substances (TBARS) readings by approximately tenfold compared to the control.

GSEs applied to turkey patties were likewise found to have a wine aroma and a slightly bitter aftertaste[152]. In a study that investigated the effect of four different concentrations of GSEs (i.e., 0.0, 0.4, 0.8, and 1.6 g/kg) on cooked turkey breast meat, Mielnik *et al.*[153] found that adding GSEs before cooking significantly improved the lipid stability of turkey breast meat during cooking and chill storage. Mielnik *et al.*[153] also showed that the effectiveness of GSE in preventing oxidation increased as the antioxidant concentration increased from 0.4 g/kg to 1.6 g/kg. As a result, it is proposed that GSEs can be an extremely effective antioxidant in reducing lipid oxidation of cooked turkey meat during cool storage. Likewise, Brannan[154] found that adding GSEs to ground chicken during refrigerated storage reduced lipid oxidation indicators and sensory scores for key features.

Brannan and Mah[155] found that 0.1% GSE was efficient at inhibiting the production of primary (e.g., hexanal and lipid hydroperoxides) and secondary oxidation products (e.g., TBARS) in both raw and cooked beef systems during refrigerated and frozen storage. GSEs' *in vivo* antioxidant action is thought to involve the suppression of nitrositive stress, activation of enzymatic nitric oxide synthesis[156], and oxygen radical scavenging[149]. Temperature and time-hating conditions can impact the antioxidant activity of GSEs. Kim *et al.*[157] found that heat treatment significantly increased the concentrations of caffeine and gallocatechin gallate in GSEs, indicating that heating

could be used to improve the antioxidant activity of GSEs. Grape seeds' polyphenols have antibacterial activity; therefore, they could be included in meals to limit the growth of foodborne pathogens such *L. monocytogenes*[114]. Kim *et al.*[158] found that replacing some of the pork fat with pre-emulsified grape seed oil could improve meat emulsion processing. Kokabian *et al.*[159] discovered that the best milk fat replacement concentration of GSO for creating low-fat yoghurt was 1.5%, which also had the highest overall acceptance.

4.9.2 *Application in cosmetics*

GSEs are often used in cosmetic product compositions as an anti-aging ingredient. This is because GSEs are high in proanthocyanidins, which have potent free radical scavenging activities[160]. Various products on the market contain GSE as a key ingredient. These goods include tablets, capsules, lotions, creams, and so on. A study was conducted to explore the anti-aging and redox state-regulating effects of GSE and cranberry concentrate (CBC). The study found that proanthocyanidin-rich GSE and CBC extracts have a promising role in anti-aging and redox state control[161]. Other active constituents of GSE include phenolic acids, phytosterols, flavonoids, tocopherols, carotenoids, tocopherols, and tocotrienols, which have significant antioxidant activity and can help with skin health[162].

Nowadays, aquaculture is a field in great development and needs to become more sustainable day by day, facing out the aquaculture paradox (fishing ocean fish to produce fish meal for reared fish). Quagliardi *et al.*[163] review showed that agricultural wastes, as grape by-products (grape seed and grape pomace), are a valid source for a new high-quality and resilient aquaculture. Grape by-products demonstrate to be precious phytonutrients that could be added to fish feed to implement growing performance and fish health during rearing conditions.

5 Conclusion and future perspectives

Research has demonstrated that grapes and their derivatives are abundant in naturally occurring bioactive compounds that provide a range of pharmacological attributes, such as anti-inflammatory, anti-tumor, neuroprotective, lipid-lowering, bacteriostatic, and hypotensive effects. Still, numerous distinct components that are pure grape seed have been identified. However, several studies have suggested that grape seeds might exhibit one or more of the biological functions outlined above. Further investigation was therefore needed to verify that GSE, as a multi-component molecule, possessed biological features such as lipid-lowering, bacteriostatic, neuroprotective, antioxidant, anti-inflammatory, and anticancer effects. This review demonstrates the GSE's significant protective and therapeutic benefits, however, it should be highlighted that the current findings are based on animal and laboratory studies, and additional clinical trials and human-based studies are required. The authors advocate conducting clinical trials with GSE to enhance patients' regular treatments to understand the therapeutic effects. Furthermore, the effects of grape seed on certain neurological illnesses, such as bipolar, remain uncertain. Future research should look at grape seed's preventive and therapeutic benefits on other disorders.

Conflicts of interest

The authors declare that there are no conflicts of interest in this work. Fatma M. El-Demerdash is the editorial board member, but she is not involved in the peer-review or decision of this article.

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References

[1] Barbe, A., Ramé, C., Mellouk, N., et al. Effects of grape seed extract and proanthocyanidin B2 on *in vitro* proliferation, viability, steroidogenesis, oxidative stress, and cell signaling in human granulosa cells. *International Journal of Molecular Sciences*, **2019**, 20: 4215. https://doi.org/10.3390/ijms20174215

[2] Wang, Y., Wang, Y., Shen, W., et al. Grape seed polyphenols ameliorated dextran sulfate sodium-induced colitis via suppression of inflammation and apoptosis. *Pharmacology*, **2020**, 105: 9–18. https://doi.org/10.1159/000501897

[3] Lian, Q., Nie, Y., Zhang, X., et al. Effects of grape seed proanthocyanidin on Alzheimer's disease *in vitro* and *in vivo*. *Experimental and Therapeutic Medicine*, **2016**, 12: 1681–1692. https://doi.org/10.3892/etm.2016.3530

[4] Ben Youssef, S., Brisson, G., Doucet-Beaupré, H., et al. Neuroprotective benefits of grape seed and skin extract in a mouse model of Parkinson's disease. *Nutritional Neuroscience*, **2021**, 24: 197–211. https://doi.org/10.1080/1028415X.2019.1616435

[5] Chu, L., Zhang, S., Wu, W., et al. Grape seed proanthocyanidin extract alleviates inflammation in experimental colitis mice by inhibiting NF-κB signaling pathway. *Environmental Toxicology*, **2024**, 39: 2572–2582. https://doi.org/10.1002/tox.24129

[6] Li, H., Zhang, H., Wang, T., et al. Grape seed proanthocyanidins protect pancreatic β cells against ferroptosis via the Nrf2 pathway in type 2 diabetes. *Biological Trace Element Research*, **2024**, 202: 5531–5544. https://doi.org/10.1007/s12011-024-04093-9

[7] Wang, J., Pfleger, C. M., Friedman, L., et al. Potential application of grape derived polyphenols in huntington's disease. *Translational Neuroscience*, **2010**: 195–100. https://doi.org/10.2478/v10134-010-0022-y

[8] Xia, E. Q., Deng, G. F., Guo, Y. J., et al. Biological activities of polyphenols from grapes. *International Journal of Molecular Science*, **2010,** 11: 622–646. https://doi.org/10.3390/ijms11020622

[9] Sochorova, L., Prusova, B., Cebova, M., et al. Health effects of grape seed and skin extracts and their influence on biochemical markers. *Molecules*, **2020**, 14: 5311. https://doi.org/10.3390/molecules25225311

[10] Garrido-Bañuelos, G., Buica, A., Schückel, J., et al. Investigating the relationship between grape cell wall polysaccharide composition and the extractability of phenolic compounds into Shiraz wines. Part I: vintage and ripeness effects. *Food Chemistry*, **2019**, 25: 36–46. https://doi.org/10.1016/j.foodchem.2018.10.134

[11] de Souza, R. C., Machado, B. A. S., Barreto, G. A., et al. Effect of Experimental Parameters on the Extraction of Grape Seed Oil Obtained by Low Pressure and Supercritical Fluid Extraction. *Molecules*, **2020**, 25: 1634. https://doi.org/10.3390/molecules25071634

[12] Rombaut, N., Savoire, R., Thomasset, B., et al. Optimization of oil yield and oil total phenolic content during grape seed cold screw pressing. *Industrial Crops and Products*, **2015**, 63: 26–33. https://doi.org/10.1016/j.indcrop.2014.10.001

[13] Berahmand, F., Anoush, G., Hosseini, M. J., et al. Grape seed oil as a natural therapy in male rats with Alzheimer's diseases. *Advanced Pharmaceutical Bulletin*, **2020**, 10: 430–436. https://doi.org/10.34172/apb.2020.052

[14] Garavaglia, J., Markoski, M. M., Oliveira, A., et al. Grape seed oil compounds: biological and chemical actions for health. *Nutrition and Metabolic Insights*, **2016**, 9: 59–64. https://doi.org/10.4137/NMI.S32910

[15] Alkhedaide, A., Alshehri, Z. S., Sabry, A., et al. Protective effect of grape seed extract against cadmium-induced testicular dysfunction.

Molecular Medicine Reports, **2016**, 13: 3101–3109. https://doi.org/10.3892/mmr.2016.4928

[16] Kim, Y., Choi, Y., Ham, H., et al. Protective effects of oligomeric and polymeric procyanidin fractions from defatted grape seeds on tert-butyl hydroperoxide-induced oxidative damage in HepG2 cells. *Food Chemistry*, **2013**, 137: 136–141. https://doi.org/10.1016/j.foodchem.2012.10.006

[17] Hernández-Jiménez, A., Gómez-Plaza, E., Martínez-Cutillas, A., et al. Grape skin and seed proanthocyanidins from Monastrell x Syrah grapes. *Journal of Agriculture and Food Chemistry*, **2009**, 25: 10798–10803. https://doi.org/10.1021/jf903465p

[18] Nassiri-Asl, M., Hosseinzadeh, H. Review of the pharmacological effects of *Vitis vinifera* (Grape) and its bioactive constituents: an update. *Phytotherapy Research*, **2016**, 30: 1392–1403. https://doi.org/10.1002/ptr.5644

[19] Yang, J., Xiao, Y. Grape phytochemicals and associated health benefits. *Crticail Reviews in Food Science and Nutrition*, **2013**, 53: 1202–1225. https://doi.org/10.1080/10408398.2012.692408

[20] Rodríguez-Pérez, C., García-Villanova, B., Guerra-Hernández, E., et al. Grape seeds proanthocyanidins: an overview of *in vivo* bioactivity in animal models. *Nutrients*, **2019**, 11: 2435. https://doi.org/10.3390/nu11102435

[21] Zhao, Y., Lou, H. X. Chemical constituents & biological activities of grape. *Drugs & Clinic*, **2001**, 5: 185–190.

[22] Sang, Y. L., Li, X. C., Wang, X. Y., et al. Extraction and content determination of proanthocyanidin in grape seed. *Journal of Chifeng University* (*Natural Science edition*), **2018**, 34: 40–42. https://doi.org/10.13398/j.cnki.issn1673-260x.2018.09.013

[23] Duba, K. S., Fiori, L. Supercritical CO_2 extraction of grape seed oil: effect of process parameters on theextraction kinetics. *The Journal of Supercritical Fluids*, **2015**, 98: 33–43. https://doi.org/10.1016/j.supflu.2014.12.021

[24] Ma , Z. F., Zhang, H. Phytochemical constituents, health benefits, and industrial applications of grape seeds: a mini-review. *Antioxidants*, **2017**, 6: 71. https://doi.org/10.3390/antiox6030071

[25] Shinagawa, F. B., Santana, F. C. D., Torres, L. R. O., et al. Grape seed oil: a potential functional food? *Journal of Food Science and Technology*, **2015**, 35: 399–406.

[26] Rebello, L., Lago-Vanzela, E., Barcia, M., et al. Phenolic composition of the berry parts of hybrid grape cultivar BRS Violeta (BRS Rubea × IAC 1398–21) using HPLC–DAD–ESI-MS/MS. *Food Research Intenationalr*, **2013**, 54: 354–366.

[27] Sabra, A., Netticadan, T., Wijekoon, C. Grape bioactive molecules, and the potential health benefits in reducing the risk of heart diseases. *Food Chemistry: X*, **2021**, 12: 100149. https://doi.org/10.1016/j.fochx.2021.100149

[28] Raj, P., Zieroth, S., Netticadan, T. An overview of the efficacy of resveratrol in the management of ischemic heart disease. *Annals of the New York Academy of Sciences*, **2015**, 1348: 55–67. https://doi.org/10.1111/nyas.12828

[29] Kumar, A., Mosa, K. A., Ji, L., et al. Metabolomics-assisted biotechnological interventions for developing plant-based functional foods and nutraceuticals. *Crticali Reviews in Food Science and Nutrition*, **2018**, 58: 1791–1807. https://doi.org/10.1080/10408398.2017.1285752

[30] Rauf, A., Imran, M., Abu-Izneid, T., et al. Proanthocyanidins: a comprehensive review. *Biomedical and Pharmacology Journal*, **2019**, 116: 108999. https://doi.org/10.1016/j.biopha.2019.108999

[31] Liu, X., Le Bourvellec, C., Guyot, S., et al. Reactivity of flavanols: their fate in physical food processing and recent advances in their analysis by depolymerization. *Comprhenseve Reviews in Food Science and Food Safety*, **2021**, 20: 4841–4880. https://doi.org/10.1111/1541-4337.12797

[32] Pei, R., Liu, X., Bolling, B. W. Flavonoids and gut health. *Current Opinion Biotechnology*, **2020**, 61: 153–159. https://doi.org/10.1016/j.copbio.2019.12.018

[33] Qin, Z., Liu, H. M., Ma, Y. X., et al. Developments in extraction, purification, and structural elucidation of proanthocyanidins. in: Studies in Natural Products Chemistry. Edited by Rahman A-u. Elsevier; **2021**, pp. 347–391.

[34] Liu, C., Bolling, B. W. Dietary proanthocyanidins for improving gut immune health. *Current Opinion in Food Science*, **2024**, 56: 101133. https://doi.org/10.1016/j.cofs.2024.101133

[35] Mattioli, R., Francioso, A., Mosca, L., et al. Anthocyanins: a comprehensive review of their chemical properties and health effects on cardiovascular and neurodegenerative diseases. *Molecules*, **2020**, 25: 3809. https://doi.org/10.3390/molecules25173809

[36] Sagis, L. M. Microencapsulation and microspheres for food applications. Academic Press, **2015**, pp. P235–P251.

[37] Olivas-Aguirre, F. J., Mendoza, S., Alvarez-Parrilla, E., et al. First-Pass metabolism of polyphenols from selected berries: a high-throughput bioanalytical approach. *Antioxidants* (*Basel*), **2020**, 9: 311. https://doi.org/10.3390/antiox9040311

[38] Mohamedshah, Z., Chadwick-Corbin, S., Wightman, J., et al. Comparative assessment of phenolic bioaccessibility from 100% grape juice and whole grapes. *Food & Function*, **2020**, 11: 6433–6445.

[39] Rasines-Perea, Z., Ky, I., Cros, G., et al. Grape pomace: antioxidant activity, potential effect against hypertension and metabolites characterization after intake. *Diseases*, **2018**, 6: 60.

[40] D'Archivio, M., Filesi, C., Di Benedetto, R., et al. Polyphenols, dietary sources and bioavailability. *Annali dell'Istituto Superiore di Sanità*, **2007**, 43: 348–361.

[41] Choy, Y. Y.,Waterhouse, A. L. Proanthocyanidin metabolism, a mini review. *Nutrition and Aging*, **2014**, 2: 111–116. https://doi.org/10.3233/NUA-140038

[42] Payne, C., Bowyer, P. K., Herderich, M., et al. Interaction of astringent grape seed procyanidins with oral epithelial cells. *Food Chemistry*, **2009**, 115: 551–557. https://doi.org/10.1016/j.foodchem.2008.12.061

[43] Gonthier, M. P., Donovan, J. L., Texier, O., et al. Metabolism of dietary procyanidins in rats. *Free Radical Biology and Medicine*, **2003**, 35: 837–844. https://doi.org/10.1016/S0891-5849(03)00394-0

[44] Aura, A. M. Microbial metabolism of dietary phenolic compounds in the colon. *Phytochemistry Reviews*, **2008**, 7: 407–429. https://doi.org/10.1007/s11101-008-9095-3

[45] Monagas, M., Urpi-Sarda, M., Sánchez-Patán, F., et al. Insights into the metabolism and microbial biotransformation of dietary flavan-3-ols and the bioactivity of their metabolites. *Food & Function*, **2010**, 1: 233–253.

[46] Margalef, M., Guerreroa, L., Pons, Z., et al. A dose–response study of the bioavailability of grape seed proanthocyanidin in rat and lipid-lowering effects of generated metabolites in HepG2 cells. *Food Research Interaction*, **2014**, 64: 500–507. https://doi.org/10.1016/j.foodres.2014.07.019

[47] Serra, A., Macià, A., Romero, M. P., et al. Bioavailability of procyanidin dimers and trimers and matrix food effects in *in vitro* and *in vivo* models. *British Journal of Nutrition*, **2010**, 103: 944–952. https://doi.org/10.1017/S0007114509992741

[48] Serra, A., Macià, A., Rubió, L., et al. Distribution of procyanidins and their metabolites in rat plasma and tissues in relation to ingestion of procyanidin-enriched or procyanidin-rich cocoa creams. *European Journal of Nutrition*, **2013**, 52: 1029–1038. https://doi.org/10.1007/s00394-012-0409-2

[49] Deprez, S., Mila, I., Huneau, J. F., et al. Transport of proanthocyanidin dimer, trimer, and polymer across monolayers of human intestinal epithelial Caco-2 cells. *Antioxidants & Redox Signaling*, **2001**, 3: 957–967.

[50] Donovan, J. L., Manach, C., Rios, L., et al. Procyanidins are not bioavailable in rats fed a single meal containing a grape seed extract or the procyanidin dimer B3. *British Journal of Nutrition*, **2002**, 87: 299–306. https://doi.org/10.1079/BJN2001517

[51] Ariga, T. The antioxidative function, preventive action on disease and utilization of proanthocyanidins. *Biofactors*, **2004**, 21: 197–201. https://doi.org/10.1002/biof.552210140

[52] Galleano, M., Puntarulo, S. Hepatic chemiluminescence and lipid peroxidation in mild iron overload. *Toxicology*, **1992**, 76: 27–38. https://doi.org/10.1016/0300-483X(92)90015-7

[53] Yun, S., Chu, D., He, X., et al. Protective effects of grape seed proanthocyanidins against iron overload-induced renal oxidative damage in rats. *Journal of Trace Elements in Medicine and Biology*, **2020**, 57: 126407. https://doi.org/10.1016/j.jtemb.2019.126407

[54] Feng, D. J., Xu, G. F., Zhao, Y. Population test of antioxidant capacity of grape seed extract in different doses. *Food & Medicine*, **2012**, 14: 32–34.

[55] Lu, J., Wang, Z., Cao, J., et al. A novel and compact review on the role of oxidative stress in female reproduction. *Reproductive Biology and Endocrinology*, **2018**, 16: 80. https://doi.org/10.1186/s12958-018-0391-5

[56] Matsui, T., Manabe, N., Goto, Y., et al. Expression and activity of Apaf1 and caspase-9 in granulosa cells during follicular atresia in pig ovaries. *Reproduction-Cambridge*, **2003**, 126: 113–120. https://doi.org/10.1530/rep.0.1260113

[57] Zhang, J. Q., Wang, X. W., Chen, J. F., et al Grape seed procyanidin B2 protects porcine ovarian granulosa cells against oxidative stress-induced apoptosis by upregulating let-7a expression. *Oxidative Medicine and Cellular Longevity*, **2019**: 6512**.** https://doi.org/10.1155/2019/1076512

[58] Scalbert, A., Mila, I., Albrecht, A. M., et al. Proanthocyanidins and human health: systemic effects and local effects in the gut. *Biofactors*, **2000**, 13: 115–120. https://doi.org/10.1002/biof.5520130119

[59] Bak, M. J., Truong, V. L., Ko, S. Y., et al. Antioxidant and hepatoprotective effects of procyanidins from wild grape (*Vitis amurensis*) seeds in ethanol-induced cells and rats. *International Journal of Molecular Science*, **2016**, 17: 758. https://doi.org/10.3390/ijms17050758

[60] Tkacz, K., Wojdyło, A., Nowicka, P., et al. Characterization *in vitro* potency of biological active fractions of seeds, skins and flesh from selected *Vitis vinifera* L. cultivars and interspecific hybrids. *Journal of Function Foods*, **2019**, 56: 353–363. https://doi.org/10.1016/j.jff.2019.03.029

[61] Irandoost, P., Ebrahimi-Mameghani, M., Pirouzpanah, S. Does grape seed oil improve inflammation and insulin resistance in overweight or obese women? *International Journal of Food Science and Nutrition*, **2013**, 64 : 706–710.

[62] Soğutlu, İ., Mert, N., Mert, H., et al. The effects of grape seed extract on insulin, adiponectin and resistin levels in diabetic rats. *Turkish Journal of Agriculture and Food Science Technology*, **2021**, 9: 709–713. https://doi.org/10.24925/turjaf.v9i4.709-713.4023

[63] Khudiar, K., Aldabaj, A. M. A. Effect of grape seed oil on hepatic function in adult male rabbits treated with sodium fluoride. (*Part-II*) *Advances in Animal Veternity Sciences*, **2015**, 3: 550–558. https://doi.org/10.14737/journal.aavs/2015/3.10.550.558

[64] Suwannaphet, W., Meeprom, A., Yibchok-Anun, S., et al. Preventive effect of grape seed extract against high-fructose diet-induced insulin resistance and oxidative stress in rats. *Food and Chemical Toxicology*, **2010**, 48: 1853–1857. https://doi.org/10.1016/j.fct.2010.04.021

[65] Shiri-Shahsavar, M. R., Alijani, S., Parsamanesh, N., et al. The effect of grape-seed oil on diabetes-related hyperglycemia, dyslipidemia, and inflammation in streptozotocin-induced diabetic rats. *Obesity Medicine*, **2023**, 37: 100476. https://doi.org/10.1016/j.obmed.2022.100476

[66] Zhou, H., Yin, C., Zhang, Z., et al. Proanthocyanidin promotes functional recovery of spinal cord injury via inhibiting ferroptosis. *Journal of Chemical Neuroanatomy*, **2020**, 107: 101807. https://doi.org/10.1016/j.jchemneu.2020.101807

[67] Alomair, M. K., Alobaid, A. A., Almajed, M. A. A., et al. Grape seed extract and urolithiasis: protection against oxidative stress and inflammation. *Pharmacognosy Magazine*, **2023**, 19: 117–127. https://doi.org/10.1177/09731296221145069

[68] Wang, L., Huang, W., Zhan, J. Grape seed proanthocyanidins induce autophagy and modulate survivin in HepG2 cells and inhibit xenograft tumor growth *in vivo*. *Nutrients*, **2019**, 11: 2983. https://doi.org/10.3390/nu11122983

[69] Hamza, A. A., Heeba, G. H., Elwy, H. M., et al. Molecular characterization of the grape seeds extract's effect against chemically induced liver cancer: *in vivo* and *in vitro* analyses. *Scientific Reports*, **2018**, 8: 1–16. https://doi.org/10.1038/s41598-018-19492-x

[70] Mao, J. T., Xue, B., Smoake, J., et al. MicroRNA-19a/b mediates grape seed procyanidin extract-induced anti-neoplastic effects against lung cancer. *Journal of Nutrition and Biochemistry*, **2016**, 34: 118–125. https://doi.org/10.1016/j.jnutbio.2016.05.003

[71] Chen, Y., Wen, J., Deng, Z., et al. Effective utilization of food wastes: bioactivity of grape seed extraction and its application in food industry. *Journal of Functional Food*, **2020**, 73: 104113. https://doi.org/10.1016/j.jff.2020.104113

[72] Guo, F., Hu, Y., Niu, Q., et al. Grape seed proanthocyanidin extract inhibits human esophageal squamous cancerous cell line eca109 via the NF-κB signaling pathway. *Mediators of Inflammation*, **2018**: 3972. https://doi.org/10.1155/2018/3403972.

[73] Yang, N., Gao, J., Cheng, X., et al. Grape seed proanthocyanidins inhibit the proliferation, migration and invasion of tongue squamous cell carcinoma cells through suppressing the protein kinase B/nuclear factor-κB signaling pathway. *International Journal of Molecular Medicine*, **2017**, 40: 1881–1888. https://doi.org/10.3892/ijmm.2017.3162

[74] Leone, A., Longo, C., Gerardi, C., et al. Pro-apoptotic effect of grape seed extract on MCF-7 involves transient increase of gap junction intercellular communication and Cx43 up-regulation: a mechanism of chemoprevention. *International Journal of Molecular Science*, **2019**, 20: 3244. https://doi.org/10.3390/ijms20133244

[75] Chasampalioti, M., Green, A. R., Ellis, I. O., et al. Connexin 43 is an independent predictor of patient outcome in breast cancer patients. *Breast Cancer Research and Treatment*, **2019**, 174: 93–102. https://doi.org/10.1007/s10549-018-5063-9

[76] Perez-Ortiz, J. M., Alguacil, L. F., Salas, E., et al. Antiproliferative and cytotoxic effects of grape pomace and grape seed extracts on colorectal cancer cell lines. *Food Science and Nutrition*, **2019**, 7: 2948–2957. https://doi.org/10.1002/fsn3.1150u

[77] Ravindranathan, P., Pasham, D., Goel, A. Oligomeric proanthocyanidins (OPCs) from grape seed extract suppress the activity of ABC transporters in overcoming chemoresistance in colorectal cancer cells. *Carcinogenesis*, **2019**, 40: 412–421. https://doi.org/10.1093/carcin/bgy184

[78] Shi, H. H., Lü, C. C.,Zhu, Y. F. A preliminary study on the inhibitory effect of grape seed procyanidins on colon cancer cells. *Chinese Journal of Cell Biology*, **2019**, 41: 1523–1533.

[79] Kang, J. H., Park, Y. H., Choi, S. W., et al. Resveratrol derivatives potently induce apoptosis in human promyelocytic leukemia cells. *Experimental & Molecular Medicine*, **2003**, 35: 467–474.

[80] Tyagi, A., Singh, R. P., Agarwal, C., et al. Resveratrol causes Cdc2-tyr15 phosphorylation via ATM/ATR-Chk1/2-Cdc25C pathway as a central mechanism for S phase arrest in human ovarian carcinoma Ovcar-3 cells. *Carcinogenesis*, **2005**, 26: 1978–1987. https://doi.org/10.1093/carcin/bgi165

[81] Dinicola, S., Cucina, A., Antonacci, D., et al. Anticancer effects of grape seed extract on human cancers: a review. *Journal of Carcinogenesis and Mutagenesis*, **2014**, S8: 005. https://doi.org/10.4172/2157-2518.S8-005

[82] Prasad, R, Katiyar, S. K. Bioactive phytochemical proanthocyanidins inhibit growth of head and neck squamous cell carcinoma cells by targeting multiple signaling molecules. *PLoS One*, **2012**, 7: e46404. https://doi.org/10.1371/journal.pone.0046404

[83] Dinicola, S., Cucina, A., Pasqualato, A., et al. Antiproliferative and

apoptotic effects triggered by grape seed extract (GSE) versus epigallocatechin and procyanidins on colon cancer cell lines. *International Journal of Molecular Science*, **2012**, 13: 651–664. https://doi.org/10.3390/ijms13010651

[84] Raina, K., Singh, R. P., Agarwal, R., et al. Oral grape seed extract inhibits prostate tumor growth and progression in TRAMP mice. *Cancer Research*, **2007**, 67: 5976–5982. https://doi.org/10.1158/0008-5472.CAN-07-0295

[85] Dinicola, S., Pasqualato, A., Cucina, A., et al. Grape seed extract suppresses MDA-MB231 breast cancer cell migration and invasion. *Eurpean Journal of Nutrition*, **2013**, 104: 824–832.

[86] Marel, A. K., Lizard, G., Izard, J. C., et al. Inhibitory effects of trans-resveratrol analogs molecules on the proliferation and the cell cycle progression of human colon tumoral cells. *Molecular Nutrition and Food Research*, **2008**, 52: 538–548. https://doi.org/10.1002/mnfr.200700185

[87] Kaur, M., Mandair, R., Agarwal, R., et al. Grape seed extract induces cell cycle arrest and apoptosis in human colon carcinoma cells. *Nutrition and Cancer*, **2008**, 60: 2–11. https://doi.org/10.1080/01635580802381295

[88] Morré, D. J., Morré, D. M., Sun, H., et al. Tea catechin synergies in inhibition of cancer cell proliferation and of a cancer specific cell surface oxidase (ECTO-NOX). *Pharmacological Toxicology*, **2003**, 92: 234–241. https://doi.org/10.1034/j.1600-0773.2003.920506.x

[89] Meeran, S. M., Katiyar, S. K. Cell cycle control as a basis for cancer chemoprevention through dietary agents. *Frontiers Bioscience*, **2008**, 13: 2191–2202. https://doi.org/10.2741/2834

[90] Laurent, C., Besançon, P., Auger, C., et al. Grape seed extract affects proliferation and differentiation of human intestinal Caco-2 cells. *Journal of Agriculture and Food Chemistry*, **2004**, 52: 3301–3308. https://doi.org/10.1021/jf035231e

[91] Lim, Y. C., Lee, S. H., Song, M. H., et al. Growth inhibition and apoptosis by (−)-epicatechin gallate are mediated by cyclin D1 suppression in head and neck squamous carcinoma cells. *European Journal of Cancer*, **2006**, 42: 3260–3266. https://doi.org/10.1016/j.ejca.2006.07.014

[92] Sun, Q., Prasad, R., Rosenthal, E., et al. Grape seed proanthocyanidins inhibit the invasive potential of head and neck cutaneous squamous cell carcinoma cells by targeting EGFR expression and epithelialto-mesenchymal transition. *BMC Complement Alternative Medicine*, **2011**, 11: 134. https://doi.org/10.1186/1472-6882-11-134

[93] Masana, L., Ros, E., Sudano, I., et al. Is there a role for lifestyle changes in cardiovascular prevention? what, when and how. *Atherosclerosis Supplements*, **2017**, 26: 2–15. https://doi.org/10.1016/S1567-5688(17)30020-X

[94] Mitra, S., Goyal, T., Mehta, J. L. Oxidized LDL, LOX-1 and atherosclerosis. *Cardiovascular Drugs Therapy*, **2011**, 25: 419–429. https://doi.org/10.1007/s10557-011-6341-5

[95] Lopez Farre´, A., Casado, S. Heart failure, redox alterations, and endothelial dysfunction. *Hypertension*, **2001**, 38: 1400–1405. https://doi.org/10.1161/hy1201.099612

[96] Caimari, A., Del Bas, J. M., Crescenti, A., et al. Low doses of grape seed procyanidins reduce adiposity and improve the plasma lipid profile in hamsters. *International Journal of Obesity*, **2013**, 37: 576–583. https://doi.org/10.1038/ijo.2012.75

[97] Dohadwala, M. M., Vita, J. A. Grapes and cardiovascular disease. *The Journal of Nutrition*, **2009**, 139: 1788S–1793S. https://doi.org/10.3945/jn.109.107474

[98] Kinsella, J. E., Frankel, E., German, B. et al. Possible mechanism for the protective role of the antioxidant in wine and plant foods. *Food Technology*, **1993**, 47: 85–89.

[99] Rimm, E. B., Stampfer, M. J., Asherio, A., et al. Vitamin E consumption and the risk of coronary heart disease in men. *The New England Journal of Medicine*, **1993**, 328: 1450–1456. https://doi.org/10.1056/NEJM199305203282004

[100] Cao, A., Wang, J., Cao, H., et al. Beneficial clinical effects of grape seed proanthocyanidin extract on the progression of carotid atherosclerotic plaques. *Journal of Geriatric Cardiology*, **2015**, 12: 417–423.

[101] Bagchi, D., Sen, C. K., Ray, S. D., et al. Molecular mechanisms of cardioprotection by a novel grape seed proanthocyanidin extract. *Mutation Research*, **2003**, 523/524: 87–97. https://doi.org/10.1016/S0027-5107(02)00324-X

[102] Bobek, P. Dietary tomato and grape pomace in rats: effect on lipids in serum and liver, and on antioxidant status. *British Journal of Biomedical Science*, **1999**, 56: 109–113.

[103] Moreno, D. A., Ilic, N., Poulev, A., et al. Inhibitory effects of grape seed extract on lipases. *Nutrition*, **2003**, 19: 876–879. https://doi.org/10.1016/S0899-9007(03)00167-9

[104] Sano, T., Oda, E., Yamashita, T., et al. Anti-thrombotic effect of proanthocyanidin, a purified ingredient of grape seed. *Thrombosis Research*, **2005**, 115: 115–121. https://doi.org/10.1016/j.thromres.2004.07.015

[105] Olas, B., Wachowicz, B., Tomczak, A., et al. Comparative antiplatelet and antioxidant properties of polyphenol-rich extracts from: berries of *Aronia melanocarpa*, seeds of grape and bark of *Yucca schidigera in vitro*. *Platelets*, **2008**, 19: 70–77. https://doi.org/10.1080/09537100701708506

[106] Choi, Y., Lee, J. Antioxidant and antiproliferative properties of a tocotrienol-rich fraction from grape seeds. *Food Chemistry*, **2009**, 114: 1386–1390. https://doi.org/10.1016/j.foodchem.2008.11.018

[107] Belcaro, G., Ledda, A., Hu, S., et al. Grape seed procyanidins in pre- and mild hypertension: a registry study. *Evidence Based Complementary and Alternative Medicine*, **2013**, 2013: 313142.

[108] Ras, R. T., Zock, P. L., Zebregs, Y. E., et al. Effect of polyphenol-rich grape seed extract on ambulatory blood pressure in subjects with pre- and stage I hypertension. *British Journal of Nutrition*, **2013**, 110: 2234–2241. https://doi.org/10.1017/S000711451300161X

[109] Thiruchenduran, M., Vijayan, N. A., Sawaminathan, J. K., et al. Protective effect of grape seed proanthocyanidins against cholesterol cholic acid diet-induced hypercholesterolemia in rats. *Cardiovascular Pathology*, **2011**, 20: 361–368. https://doi.org/10.1016/j.carpath.2010.09.002

[110] Pons, Z., Guerrero, L., Margalef, M., et al. Effect of low molecular grape seed proanthocyanidins on blood pressure and lipid homeostasis in cafeteria diet-fed rats. *Journal of Physiology and Biochemistry*, **2014**, 70: 629–637. https://doi.org/10.1007/s13105-014-0329-0

[111] Leifert, W. R., Abeywardena, M. Y. Cardioprotective actions of grape polyphenols. *Nutrition Research*, **2008**, 28: 729–737. https://doi.org/10.1016/j.nutres.2008.08.007

[112] Razavi, S. M., Gholamin, S., Eskandari, A., et al. Red grape seed extract improves lipid profiles and decreases oxidized low-density lipoprotein in patients with mild hyperlipidemia. *Journal of Medicinal Food*, **2013**, 16: 255–258. https://doi.org/10.1089/jmf.2012.2408

[113] Vikas, T. M., Gulshan, K., Nalwa, C. A review on antioxidant, anti-tumor and other qualitative properties of grape seed extract. *Advanced Crop Science and Techology*, **2022**, 10: 541.

[114] Anastasiadi, M., Chorianopoulos, N. G., Nychas, G. J. E., et al. Antilisterial activities of polyphenol-rich extracts of grapes and vinification by products. *Jouranal of Agriculture and Food Chemistry*, **2009**, 57: 457–463. https://doi.org/10.1021/jf8024979

[115] Chan, M. M. Y. Antimicrobial effect of resveratrol on dermatophytes and bacterial pathogens of the skin. *Biochemistry and Pharmacology*, **2002**, 63: 99–104. https://doi.org/10.1016/S0006-2952(01)00886-3

[116] Park, K., Elias, P. M., Hupe, M., et al. Resveratrol stimulates sphingosine-1-phosphate signaling of cathelicidin production. *Journal of Investigative Dermatology*, **2013**, 133: 1942–1949. https://doi.org/10.1038/jid.2013.133

[117] Subramanian, M., Goswami, M., Chakraborty, S., et al. Resveratrol induced inhibition of *Escherichia coli* proceeds via membrane oxidation and independent of diffusible reactive oxygen species

generation. *Redox Bio-Nutrients*, **2014**, 2: 865–872. https://doi.org/10.1016/j.redox.2014.06.007

[118] Paulo, L., Ferreira, S., Gallardo, E., et al. Antimicrobial activity and effects of resveratrol on human pathogenic bacteria. *World Journal of Microbiology, Biology and Biotechnology*, **2010**, 26: 1533–1538.

[119] Ríos, J. L., Recio, M. C. Medicinal plants and antimicrobial activity. *Journal of Ethnopharmacology*, **2005**, 100: 80–84. https://doi.org/10.1016/j.jep.2005.04.025

[120] Silvan, J. M., Gutierrez-Docio, A., Guerrero-Hurtado, E., et al. Pre-Treatment with grape seed extract reduces inflammatory response and oxidative stress induced by *Helicobacter pylori* infection in human gastric epithelial cells. *Antioxidants*, **2021**, 10: 943. https://doi.org/10.3390/antiox10060943

[121] Silvan, J. M., Gutiérrez-Docio, A., Moreno-Fernandez, S., et al. Procyanidinrich extract from grape seeds as a putative tool against *Helicobacter pylori*. *Foods*, **2020**, 9: 1370. https://doi.org/10.3390/foods9101370

[122] Bitzer, Z. T., Glisan, S. L., Dorenkott, M. R., et al. Cocoa procyanidins with different degrees of polymerization possess distinct activities in models of colonic inflammation. *Journal of Nutrition and Biochemistry*, **2015**, 26: 827–831. https://doi.org/10.1016/j.jnutbio.2015.02.007

[123] Zhao, S., Zhang, L., Yang, C., et al. Procyanidins and Alzheimer's disease. *Molecular Neurobiology*, **2019**, 56: 5556–5567. https://doi.org/10.1007/s12035-019-1469-6

[124] Mahdipour, R., Ebrahimzadeh-Bideskan, A., Hosseini, M., et al. The benefits of grape seed extract in neurological disorders and brain aging. *Nutritional Neuroscience*, **2022**, 1954. https://doi.org/10.1080/1028415X.2022.2051954

[125] Loureiro, J. A., Andrade, S., Duarte, A., et al. Resveratrol and grape extract-loaded solid lipid nanoparticles for the treatment of Alzheimer's disease. *Molecules*, **2017**, 13: 277. https://doi.org/10.3390/molecules22020277

[126] Guerrero-Muñoz, M. J., Castillo-Carranza, D. L., Kayed, R. Therapeutic approaches against common structural features of toxic oligomers shared by multiple amyloidogenic proteins. *Biochemical Pharmacology*, **2014**, 88: 468–478. https://doi.org/10.1016/j.bcp.2013.12.023

[127] Saito, T., Saido, T. C. Neuroinflammation in mouse models of Alzheimer's disease. *Clinical Expirement and Neuroimmunology*, **2018**, 9: 211–218. https://doi.org/10.1111/cen3.12475

[128] Crack, P. J., Cimdins, K., Ali, U., et al. Lack of glutathione peroxidase-1 exacerbates a beta mediated neurotoxicity in cortical neurons. *Journal of Neural Transmission* (*Vienna*), **2006**, 113: 645–657. https://doi.org/10.1007/s00702-005-0352-y

[129] Shahba, S., Mehrzad, J., Malvandi, A. M. Neuroimmune disruptions from naturally occurring levels of mycotoxins. *Environmental Science and Pollution Research Interactions*, **2021**, 28: 32156–32176. https://doi.org/10.1007/s11356-021-14146-4

[130] Gao, W. L., Li, X. H., Dun, X. P., et al. Grape seed proanthocyanidin extract ameliorates streptozotocin-induced cognitive and synaptic plasticity deficits by inhibiting oxidative stress and preserving AKT and ERK activities. *Current Medical Science*, **2020**, 40: 434–443. https://doi.org/10.1007/s11596-020-2197-x

[131] Dong C. Protective effect of proanthocyanidins in cadmium induced neurotoxicity in mice. *Drug Research* (*Stuttg*), **2015**, 65: 555–560. https://doi.org/10.1055/s-0034-1395544

[132] Mantena, S. K., Katiyar, S. K. Grape seed proanthocyanidins inhibit UV-radiation-induced oxidative stress and activation of MAPK and NF-κB signaling in human epidermal keratinocytes. *Free Radical and Biological Medicine*, **2006**, 40: 1603–1614. https://doi.org/10.1016/j.freeradbiomed.2005.12.032

[133] Sun, Q., Jia, N., Li, X., et al. Grape seed proanthocyanidins ameliorate neuronal oxidative damage by inhibiting GSK-3β-dependent mitochondrial permeability transition pore opening in an experimental model of sporadic Alzheimer's disease. *Aging* (*Albany NY*), **2019**, 24: 4107–4124. https://doi.org/10.18632/aging.102041

[134] Ordonez, D. G., Lee, M. K., Feany, M. B. α-Synuclein induces mitochondrial dysfunction through spectrin and the actin cytoskeleton. *Neuron*, **2018**, 97: 108–124. https://doi.org/10.1016/j.neuron.2017.11.036

[135] Paillusson, S., Gomez-Suaga P., Stoica, R., et al. α-Synuclein binds to the ER-mitochondria tethering protein VAPB to disrupt Ca^{2+} homeostasis and mitochondrial ATP production. *Acta Neuropathology*, **2017**, 134: 129–149. https://doi.org/10.1007/s00401-017-1704-z

[136] Tikhonova, M. A., Tikhonova, N. G., Tenditnik, M. V., et al. Effects of grape polyphenols on the life span and neuroinflammatory alterations related to neurodegenerative Parkinson disease-like disturbances in mice. *Molecules*, **2020**, 16: 5339. https://doi.org/10.3390/molecules25225339

[137] Nguyen, A. V., Wu, Y. Y.,Lin, E. Y. STAT3 and sphingosine-1-phosphate in inflammation-associated colorectal cancer. *World journal of gastroenterology: WJG*, **2014**, 20: 10279. https://doi.org/10.3748/wjg.v20.i30.10279

[138] Lee, A. K., Sung, S. H., Kim, Y. C., et al. Inhibition of lipopolysaccharide inducible nitric oxide synthase, TNF-α and COX-2 expression by sauchinone effects on I-κBα phosphorylation, C/EBP and AP-1 activation. *British Journal of Pharmacology*, **2003**, 139: 11–20. https://doi.org/10.1038/sj.bjp.0705231

[139] Medzhitov, R. Inflammation 2010: New adventures of an old flame. *Cell*, **2010**, 140: 771–776. https://doi.org/10.1016/j.cell.2010.03.006

[140] Harbeoui, H., Hichami, A., Wannes, W. A., et al. Anti-inflammatory effect of grape (*Vitis vinifera* L.) seed extract through the downregulation of NF-κB and MAPK pathways in LPS-induced RAW264.7 macrophages. *South Africa Journal of Botany*, **2019**, 125: 1–8. https://doi.org/10.1016/j.sajb.2019.06.026

[141] Chu, H., Tang, Q., Huang, H., et al. Grape-seed proanthocyanidins inhibit the lipopolysaccharide-induced inflammatory mediator expression in RAW264.7 macrophages by suppressing MAPK and NF-κB signal pathways. *Envirnmental Toxicology Pharmacology*, **2016**, 41: 159–166. https://doi.org/10.1016/j.etap.2015.11.018

[142] Li, S. W., Liu, Z. Z., Liu, C. X., et al. Protective effect of grape seed proanthocyanidins in mouse fatty liver models suffering ischemia-reperfusion injury. *Journal of Shandong University* (*Medical Edition*), **2015**, 53: 41–46. https://doi.org/10.6040/j.issn.16717554.0.2014.716

[143] Yamakoshi, J.; Saito, M.; Kataoka, S., et al. Safety evaluation of proanthocyanidin-rich extract from grape seeds. *Food Chemistry and Toxicology*, **2002**, 40: 599–607. https://doi.org/10.1016/S0278-6915(02)00006-6

[144] Ray, S., Bagchi, D., Lim, P. M., et al. Acute and long-term safety evaluation of a novel IH636 grape seed proanthocyanidin extract. *Research Communications in Molecular Pathology and Pharmacology*, **2001**, 109: 165–197.

[145] Wren, A. F., Cleary, M., Frantz, C., et al. 90-day oral toxicity study of a grape seed extract (IH636) in rats. *Journal of Agriculture Food Chemistry*, **2002**, 50: 2180–2192.

[146] Bentivegna, S. S., Whitney, K. M. Subchronic 3-month oral toxicity study of grape seed and grape skin extracts. *Food Chemistry and Toxicology*, **2002**, 40: 1731–1743.

[147] Lluis, L., Munoz, M., Nogues, M. R., et al. Toxicology evaluation of a procyanidinrich extract from grape skins and seeds. *Food Chemistry and Toxicology*, **2011**, 49: 1450–1454.

[148] Bagchi, D., Ray, S. D., Patel, D., et al. Protection against drug- and chemical induced multiorgan toxicity by a novel lH636 grape seed proanthocyanidin extract. *Drusg Under Expirmental and Clinical Research*, **2001**, 27: 3–15.

[149] Bagchi, D., Bagchi, M., Stohs, S. J., et al. Free radicalsand grape seed proanthocyanidin extract: importance in human health and disease prevention. *Toxicology*, **2000**, 148: 187–197. https://doi.org/10.1016/S0300-483X(00)00210-9

[150] Jayaprakasha, G. K.; Singh, R. P.; Sakariah, K. K. Antioxidant

activity of grape seed (*Vitis vinifera*) extracts on peroxidation models *in vitro*. *Food Chemistry*, **2001**, 73: 285–290. https://doi.org/10.1016/S0308-8146(00)00298-3

[151] Ahn, J., Grün, I. U., Fernando, L. N. Antioxidant properties of natural plant extracts containing polyphenolic compounds in cooked ground beef. *Journal of Food Science*, **2002**, 67: 1364–1369. https://doi.org/10.1111/j.1365-2621.2002.tb10290.x

[152] Lau, D. W., King, A. J. Pre- and post-mortem use of grape seed extract in dark poultry meat to inhibit development of thiobarbituric acid reactive substances. *Journal of Agriculture and Food Chemistry*, **2003**, 51: 1602–1607. https://doi.org/10.1021/jf020740m

[153] Mielnik, M. B., Olsen, E., Vogt, G., et al. Grape seed extract as antioxidant in cooked, cold stored turkey meat. *Food Science and Technology*, **2006**, 39: 191–198.

[154] Brannan, R. G. Effect of grape seed extract on descriptive sensory analysis of ground chicken during refrigerated storage. *Meat Science*, **2009**, 81: 589–595. https://doi.org/10.1016/j.meatsci.2008.10.014

[155] Brannan, R. G., Mah, E. Grape seed extract inhibits lipid oxidation in muscle from different species during refrigerated and frozen storage and oxidation catalyzed by peroxynitrite and iron/ascorbate in a pyrogallol red model system. *Meat Science*, **2007**, 77: 540–546. https://doi.org/10.1016/j.meatsci.2007.05.001

[156] Roychowdhury, S., Wolf, G., Keilhoff, G., et al. Protection of primary glial cells by grape seed proanthocyanidin extract against nitrosative/oxidative stress. *Nitric Oxide*, **2001**, 5: 137–149. https://doi.org/10.1006/niox.2001.0335

[157] Kim, S. Y., Jeong, S. M., Park, W. P., et al. Effect of heating conditions of grape seeds on the antioxidant activity of grape seed extracts. *Food Chemistry*, **2006**, 97: 472–479. https://doi.org/10.1016/j.foodchem.2005.05.027

[158] Kim, T. K., Yong, H. I., Jung, S., et al. Effects of replacing pork fat with grape seed oil and gelatine/alginate for meat emulsions. *Meat Science*, **2020**, 163: 108079. https://doi.org/10.1016/j.meatsci.2020.108079

[159] Kokabian, A., Daraei Garmakhany, A., Jafarzadeh, S., et al. Incorporation of omega-3 fatty acid-rich grape seed oil in yoghurt: response surface optimization of physicochemical, textural, and sensory attributes during refrigerated storage. *Food science and Nutrition*, **2020**, 9: 331–344.

[160] Allemann, I. B., Baumann, L. Antioxidants used in skin care formulations. *Skin Therapy Letter*, **2008**, 13: 5–9.

[161] Costa, A., Pegas, P. E. S., Assumpcao, E. C., et al. Assessment of clinical effects and safety of an oral supplement based on marine protein, vitamin C, grape seed extract, zinc & tomato extract in the improvement of visible signs of skin aging in men. *Clinical, Cosmetic and Investigational Dermatology*, **2015**, 8: 319–328

[162] Devi, S., Singh, R. Antioxidant and anti-hypercholesterolemic potential of *Vitis vinifera* leaves. *Pharmacognosy Journal*, **2017**, 9: 565–572. https://doi.org/10.5530/pj.2017.4.90

[163] Quagliardi, M., Frapiccini, E., Marini, M., et al. Use of grape by-products in aquaculture: new frontiers for a circular economy application. *Heliyon*, **2024**, 10: e27443. https://doi.org/10.1016/j.heliyon.2024.e27443