Review

Chemical Composition and Health Benefits of Grape and Grape Products

Didem Şöhretoğlu [1,*], Ayşenur Duru [1], and Öznur Bengisu Köylüoğlu [2]

[1] Department of Pharmacognosy, Faculty of Pharmacy, Hacettepe University, Sıhhiye, Ankara 06100, Turkey
[2] Faculty of Pharmacy, Hacettepe University, Sıhhiye, Ankara 06100, Turkey
* Correspondence: didems@hacettepe.edu.tr
Received: 2 February 2025; Revised: 19 March 2025; Accepted: 6 April 2025; Published: 28 April 2025

Abstract: Grape is a highly nutritious fruit that is widely consumed around the world. It is widely cultivated around the world. We provided knowledge on the phytochemical contents, biological impacts, and economic worth of grapes. Polyphenols are main constituents of grape and grape derivated products. They exhibited antioxidant, anti-inflammatory, and antihepatotoxic properties. The most prominent effect was the cardioprotective effect. The cardioprotective effect is shown by in vitro, in vivo studies as well as human studies.

Keywords: grape; Vitis; Vitaceae; polyphenol

1. Introduction

The genus *Vitis* L. (grape) comprises 68 species. This genus is different from the other Vitaceae plants by having petals that remain coalescent at the top and separated at the base, falling as a capGrape, the fruits of *Vitis vinifera* L. (Vitaceae) one of the most popular fruits of the world. Grapes are grown all around the world, especially Mediterranean type temperate climates. The cultivation of grapes began 6000–8000 years ago in around the Near East [1]. The cultivated grapes are mainly *Vitis vinifera* L. ssp. v*inifera* L. (European or wine grape), *V. vinifera* L. ssp. *slyvestris* Hegi (wild grape) and their hybrids and also *Vitis labrusca* L. [2]. Grapes can be eaten fresh as table grapes or used for making wine, jam, grape juice, grape seed extract, raisins, vinegar, and grape seed oil [3]. Commercially, *Vitis* species contain valuable raw materials for the production of wine, medicine and cosmetic industry.

Grapes contain simple phenolics, flavonoids, anthocyanins, tannins, stilbenes. *V. vinifera* fruits exhibit wide range of activity including cardioprotective, antioxidant, hepaprotective, antibacterial, etc. [4].

In this review, we aim to give information on the phytochemical composition, biological effects and commercial value of grape and grape derivated products.

2. History and Economic Value

Grape is produced in the regions between 20–52° north and 20–40° degrees south latitude in the world. Grape production is also seen in high altitude regions near the equator. The Caucasus and Mesopotamia are shown as the homeland of grapes. The Epic of Gilgamesh from the Mesopotamian period confirms this situation. It is the first written work in which the subject of wine is mentioned. Geological and archaeological research conducted in the 20th century shows that the grape was grown in many parts of the world 60 million years ago. It is thought that the cultivation and domestication of the grape took place in the geographical region between the Black Sea and Iran in 6000–5000 BC [5]. Grape seeds from the press residue from approximately 10 thousand years ago have been observed today. This shows how old grape winemaking is [5,6]. In the analysis of a jar found in Godin Hill in Iran in 3500 BC, a large amount of tartaric acid was detected, indicating that it contained wine. With the development of trade in Godin Hill between 3500–2900 BC, various goods spread to a wide area in the Near East. It is thought that the intercultural transfer of wine and winemaking occurred in this way [7].

There are also Egyptian hieroglyphs dating back to 2400 BC that mention winemaking. Wine was used as a cure for many years. Many scientists, such as Hippocrates, mentioned the medicinal properties of wine during those times [6].

The history of viticulture is intertwined with Anatolian civilizations. Different shapes of the grape plant have been encountered in rock paintings and sculptures from the Hittite civilization. These findings show that grapes and wine were offered to the gods as offerings in religious ceremonies between 1800–1550 BC. The Hittites also learned viticulture from other peoples who lived in Anatolia in earlier periods [5,6]. The Hittites were the first civilization in history to use agricultural laws by today's understanding in order to protect their vineyards and gardens [6].

The grape has great economic importance worldwide [8]. According to Food and Agriculture Organization of the United Nations (FAO) 2022 data, the top 10 in grape production are China, Italy, France, Spain, USA, Turkey, India, Chile, South Africa and Argentina. While China produced 12,600,000 tons of grapes in 2022, Argentina, ranked 10th, produced 1,936,803 million tons [9]. According to FAO data in 2022, Peru ranks first in the export value comparison with 526,857 tons of grape exports worth 1,292,376,000 USD [10]. The top 10 grape producers in 2017 were China, Italy, the USA, Spain, France, Turkey, India, Chile, South Africa, and Argentina [11].

According to the Food and Agriculture Organization of the United Nations, 75.866 square kilometres of the world is devoted to grapes. Approximately 71% of the world's grape production is used for wine, 27% as fresh fruit and 2% as dried fruit [12].

In 2016, the world produced 77.4 million tons of grapes from 7.1 million hectares of vineyards. In 1966, 52 million tons of grapes were produced from 9.5 million hectares. An increase in grape production was observed from 1966 to 2016 [1].

3. Chemistry

Many factors such as grape variety, soil and climate conditions, technical and cultural processes applied, and especially the degree of ripeness affect the content of the grape [13,14].

In general, the composition of grapes includes water, sugars, organic acids, phenolic compounds (Table 1), terpenes (Table 2), nitrogenous substances, vitamins, minerals and enzymes. Grapes contain between 65–85% water, depending on the variety. Since it contains a large amount of sugar in its composition, its caloric value is quite high. In addition, it is rich in minerals (such as calcium, potassium, sodium and iron) and is also considered an important source of some vitamins (vitamins A, B1, B2, B3 and C) [13].

Table 1. Some phenolic and polyphenolic compounds of grape and grape products.

Compound	Part of Plant	Reference
Flavan-3-ols		
Catechin	Seeds Fruits Grape Skin Wine Grape pomace	[15–17]
Catechin gallate	Grape skin Seeds	[15]
Epicatechin	Fruits Grape skin	[16,17]
Epicatechin gallate	Fruits Grape skin Seeds Grape juice Wine	[15,17]
Epigallocatechin	Fruits	[17]
Procyanidin B1	Wine Seeds	[15,18]
Procyanidin B2	Grape pomace Wine Seeds	[15,16,18]
Procyanidin B3	Wine	[18]
Procyanidin B4	Wine	[18]
Procyanidin C1	Wine	[18]
Anthocyanins and Anthocyanidins		
Cyanidin	Grape pomace Grape skins Seeds Wine	[15,18]
Cyanidin-3-glucoside	Wine Grape skin	[15,19]

Table 1. *Cont.*

Compound	Part of Plant	Reference
Cyanidin-3,5-diglucoside	Seeds Grape skin	[15]
Malvidin-3-*O*-glucoside	Grape skin Seeds Wine	[15,19]
Malvidin 3,5-diglucoside	Grape skin Seeds	[15]
Delphinidin	Fruits	[17]
Delphinidin-3-*O*-glucoside	Grape skin Fruits Wine	[15,17,18]
Delphinidin 3,5-diglucoside	Seeds Grape skin	[15]
Delphinidin 3-(6″-acetyl)-glucoside	Seeds Grape skin	[15]
Delphinidin 3-(6″-caffeoil)-glucoside	Seeds Grape skin	[15]
Delphinidin 3-(6″-cumaroil)-glucoside	Seeds Grape skin	[15]
Pelargonidin	Fruits	[17]
Peonidin 3,5-diglucoside	Seeds Grape skin	[15]
Peonidin-3-*O*-glucoside	Grape skin Fruits Wine	[15,17,19]
Petunidin-3-*O*-glucoside	Seeds Grape skin Wine Fruits	[15,17,19]
Vitisin A	Wine	[20]
Vitisidin A	Wine	[20]
Vitisin B	Wine	[20]
Vitisidin B	Wine	[20]
Acetylvitisin A	Wine	[20]
Acetylvitisin B	Wine	[20]
Flavanones		
Naringenin	Grape skins Grape juice Wine	[18,21,22]
Hesperetin	Wine	[18]
Flavonols		
Rutin	Seeds Grape skin	[15]
Isorhamnetin	Seeds Grape skin	[15]
Myricetin	Seeds Grape skin Wine	[15,18]
Myricetin-3-*O*-glucuronide	Seeds Grape skin	[15]
Myricetin-3-*O*-glucoside	Seeds Grape skin	[15]
Quercetin	Seeds Fruits Wine	[15,17,19]
Quercetin-3-*O*-glucoside	Seeds Grape skin	[15]
Quercetin-3-*O*-glucuronide	Seeds Grape skin	[15]
Kaempferol	Grape skin Wine	[16,18]
Flavones		
Apigenin	Fruits Wine	[17,18]
Luteolin	Wine	[18]

Table 1. *Cont.*

Compound	Part of Plant	Reference
Stilbenoids		
Resveratrol	Wine Fruit Grape skin	[16,17,19]
Trans-Resveratrol	Grape skin Wine	[15,19]
Piceatannol	Wine	[18]

Table 2. Some terpenes of grape and grape products.

Compound	Part of Plant	Reference
Monoterpenes		
Linalool	Wine Fruit Grape skin Grape juice	[23–26]
Cis-Linalool oxide	Wine Grape juice	[23,25]
Trans-Linalool oxide	Wine	[23]
Linalool *E*-pyranic oxide Linalool *Z*-pyranic oxide	Fruit	[27]
Nerol	Wine Fruit Grape skin	[23,26,27]
Trans-8-Hydroxylinalool *Cis*-8-Hydroxylinalool	Grape skin	[26]
Nerol oxide	Fruit	[24]
Hydroxynerol	Grape skin	[26]
Geraniol	Wine Grape skin Fruit	[23,24,26]
α-Terpinene	Fruit	[24]
γ-Terpinene	Fruit	[24]
Terpinolene	Fruit	[24]
β-Citronellol	Grape juice Wine	[23,25]
Hotrienol	Wine Fruit Grape juice	[23,25,28]
α-Terpineol	Wine Grape skin Grape juice Fruit	[23,25,26,29]
Epoxylinalool-1/-2	Wine	[23]
2,6-dimetyl-3,7-octadiene-2,6-diol	Wine	[23]
Citronellol	Fruit Grape skin	[26,28]
Hydroxy-citronellol	Grape skin	[26]
Limonene	Fruit Wine	[30,31]
trans-citral (Geranial)	Fruit Wine	[31]
cis-citral (Neral)	Fruit Wine	[31]
γ-Isogeraniol	Fruit	[27]
trans-ocimenol	Fruit	[31]
cis-ocimenol	Fruit	[31]
Myrcenol	Fruit	[31]
Terpendiol I	Fruit	[27]
3-Carene	Wine	[31]

Table 2. *Cont.*

Compound	Part of Plant	Reference
Myrcenol	Fruit	[31]
Geranic acid	Fruit Wine	[31]
trans-Rose oxide *cis*-Rose oxide	Fruit Wine	[31]
Citronellyl acetate	Wine	[31]
Geranyl acetate	Wine Fruit	[31]
Neryl acetate	Wine Fruit	[31]
trans-Methyl geranoate	Fruit	[31]
Norisoprenoids		
Theaspirane A	Fruit	[30]
Theaspirane B	Fruit	[30]
β-Damascenone	Fruit Wine	[30,32]
α-ionone *β*-ionone	Fruit Wine	[31]
1,1,6-trimethyl-1,2-dihydronaphthalene	Fruit Wine	[32]
1-(2,3,6-trimethylphenyl)buta-1,3-diene	Fruit Wine	[32]
Actinidol A/B	Fruit	[28]
Vitispirane	Wine Fruit	[31]
Sesquiterpenes		
Selina-4(15),6-diene	Fruit	[30]
α-Muurolene	Fruit	[30]
γ-Muurolene	Fruit	[30]
α-Cadinene	Fruit	[30]
δ-Cadinene	Fruit	[30]
ω-Cadinene	Fruit	[30]
γ-Cadinene	Fruit	[30]
α-Calacorene	Fruit	[30]
1-epi-Cubenol	Fruit	[30]
Cubenol	Fruit	[30]
α-Copaene	Fruit	[30]
β-Copaene	Fruit	[30]
α-Ylangene	Fruit	[30]
β-Caryophyllene	Fruit	[30]
α-Guaiene	Fruit	[30]
Guaia-6,9-diene	Fruit	[30]
α-Humulene	Fruit	[30]
Zonarene	Fruit	[30]
epi-Zonarene	Fruit	[30]
β-Bourbonene	Fruit	[30]
Rotundone	Fruit Wine	[25]
Clovene	Fruit	[30]
δ-Selinene	Fruit	[30]
cis-Calamenene	Fruit	[30]
trans-Calamenene	Fruit	[30]
Germacrene D	Fruit	[31]
β-Farnesene	Fruit	[31]
α-Cadinol	Fruit	[31]
p-Cymene	Wine	[31]
Farnesol	Wine	[31]

Table 2. *Cont.*

Compound	Part of Plant	Reference
Triterpenes		
Sitosterol	Grape skin	[33]
β-Sitosterol-3-*O*-*β*- D-glucoside	Grape skin	[33]
Oleanolic acid	Grape skin	[33]

4. Bioactivity

Various parts/products of grapes were evaluated for their in vitro and in vivo activities in different test models given in below.

4.1. Antioxidant Effect

Antioxidant effect is involved in many activity mechanisms. This effect was attributed to either polyphenols or oils.

Grape, peel of grape and seed extracts scavenged different radical oxygen species higher than positive control and the latter exhibited the best effect among them in various studies [34–36]. Similarly, grape seed oil possesses a high antioxidant effect. Carignan, Sangiovese, Syrah, Muscat d'Alexandrie, Khamri, and Merlot seed oils scavenged 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical higher than that of positive control, butylated hydroxytoluene (BHT). Moreover, Carignan, Sangiovese, Syrah, Muscat d'Alexandrie, Khamri, Merlot, Razagui, Razaki and Marsaoui seed oils had higher metal chelating ability than BHT [37].

The seedless black grape (pulp and skin) suppressed systemic oxidative and inflammatory stress in CCl_4intoxicated rats. It reduced radical oxygen species (ROS), nitric oxide (NO) and 2,2′-azino-bis (3-ethylbenzothiazoline)-6-sulfonic acid (ABTS) radical thiobarbituric acid reactive substances (TBARS) levels, as well as myeloperoxidase (MPO) activity as related to the CCl_4 group. Furthermore, the levels of total antioxidant capacity, reduced glutathione (GSH), as well as the activity of superoxide dismutase and glutathione peroxidase were increased associated with ROS/NF-κB (Nuclear Factor kappa-B) signalling pathways [38].

In the study examining the antioxidant effects of wines obtained from different *V. vinifera* varieties, the wine with the highest total phenol (1968.27 ± 1.50 mg/L), hydroxy-cinnamoyl tartaric acid (352.52 ± 0.66 mg/L) and flavonol (209.04 ± 1.05 mg/L) contents were examined. The highest DPPH radical scavenging effect of wine (EC50 = 49.24 ± 0.26mL/g) was observed [39].

In a study examining the effects of red wine polyphenols on heart health, rats fed a fructose-rich diet were given an aqueous solution of red wine polyphenolic extract (10mL/kg) and a solution containing the same amount of red wine polyphenolic extract and 10% ethanol. Superoxide anion production increased in the aorta and heart tissues of rats due to fructose consumption. As a result, a significant decrease was observed in superoxide radical levels in the group consuming aqueous solution of red wine polyphenolic extract and the group consuming a solution that contained the same amount of red wine polyphenolic extract and 10% ethanol compared to the control groups (10% (*v*/*v*) ethanol-water consuming group and water-only consuming group) [40].

The DPPH, ABTS, CUPRAC (Cupric Reducing Antioxidant Capacity) and FRAP radical scavenging activities of extracts obtained from wine (alcohol-free wine, alcohol-free wine aqueous extract and alcohol-free wine ethylacetate extract) and grape skin decoction, oil obtained from the seed and grape skin soxhlet extract were examined and wine extracts were found to be higher than other extracts [41].

4.2. Anticancer Effect

Saponifiable-fraction of black and green grapes seeds exhibited cytotoxicity by inducing apoptosis and reducing inflammation more than 5-fluorouracil in MCF-7 cells. Treatment with each extract 150 mg/kg for 7 days reduced tumor size in peritoneal Ehrlich ascites carcinoma inoculated mice. The treatment reduced hepatic injury due to carcinoma in comparison 5-fluorouracil. Moreover, the authors indicated that the anticancer effect may related to fatty acids. The extracts exhibited cytotoxic and apoptotic effects associated with induction of oxidative stress in cancer cells. They also alleviated cell migration by reducing the level of CD44+ cells in cancer cells and inhibiting of Matrix metalloproteinases protein-9 (MMP-9) and cathepsin B activities [42]. The non-saponifiable-fraction of grape seeds exhibited cytotoxicity and induced apoptosis in Huh7 hepatocellular carcinoma cells related to oxidant status and inflammation [43].

The seedless black grape extracts exhibited cytotoxicity and apoptotic effects in HepG2 and Huh7 hepatocellular carcinoma cells. These extracts also reduced tumor size in vivo [44]. Grape seed proanthocyanidin extract reversed drug resistance through down-regulation of the expression of MPR1 (multidrug resistance-

associated protein 1), MDR1 (Multidrug resistance protein 1) and LRP (Lung resistance-related protein) by inhibiting the PI3K/Akt pathway in adriamycin resistant acute myeloid leukemia cells (HL-60) [45]. Red wine inhibits proliferation of A549 lung cancer cells and blocks clonogenic survival at low concentrations (0.02%). This effect is associated with inhibition of basal and epidermal growth factor (EGF) -stimulated Akt (Protein kinase B) and Erk (Extracellular signal-regulated kinase) signals and enhancement of total and phosphorylated levels of p53. White wine mediates similar effects at higher concentrations (0.5–2%). Anti-proliferative effects of wine were not mediated by the associated contents of ethanol or the polyphenol resveratrol and were independent of glucose transport into cancer cells [46]. Ethanol at low concentrations (12.5 mM to 25 mM) has been shown to increase the proliferation of breast cancer (MCF-7) and esophageal cancer (KYSE-510) cell lines. Specifically, red wine concentrations ranging from 6.25 mM to 100 mM resulted in growth inhibition, with complete inhibition of MCF-7 cell growth observed at a concentration of 25 mM. Furthermore, the effects of red wine were also studied on human lung carcinoma cells (A-549) and human colon cancer cell lines, including SW-480 and RKO. Growth inhibition was noted for all these cell lines in a dose-dependent manner. Research examined both perennial and low-year wines, revealing that perennial wines were more effective at inhibiting cancer cell growth. An increase in the transcription of RNA polymerase III-dependent genes is associated with cell proliferation, cell transformation, and tumorigenesis. It was found that ethanol enhances the transcription of these genes, whereas red wine significantly reduces their transcription [47]. However, these wine concentrations are extremely high and do not appear to be biologically achievable.

4.3. Anti-Inflammatory Effect

The ethanolic extract of *V. vinifera* (Muscat variety) seeds was found to downregulate inflammatory markers such as TNF-α (Tumor necrosis factor-α), NF-κB, p65, IKK-β, IL-1β (Interleukin-1β), and IL-6 (Interleukin-6) in the livers of rats with Type II diabetes [48]. Similarly, the extract from seedless fruits of *V. vinifera* reduced pro-inflammatory markers, including TNF-α, IL-1β, and IL-8, and also decreased levels of NF-κB, iNOS (nitric oxide synthase), and COX-2 (cyclooxygenase-2) in rats [38]. Effect of a methanol/ethanol (8:2) extract of grape pomace investigated in inflammatory bowel disease model in Caco-2 cells. It reduced the intestinal expression and release of IL-6, monocyte chemoattractant protein MCP-1 (Monocyte Chemoattractant Protein-1), and MMP-9 and MMP-2. Furthermore, it downregulated the gene expression of several pro-inflammatory markers, including IL-1β, TNF-α, macrophage colony-stimulating factor, C-X-C motif ligand (CXCL)-10, intercellular adhesion molecule (ICAM)-1, vascular cell adhesion molecule (VCAM)-1, and COX-2 mediated by the inhibition of NF-κB activity and reduced intracellular ROS levels [49]. Additionally, the ethanolic extract of grape pomace demonstrated a dose-dependent reduction in carrageenan-induced paw edema. Notably, a dosage of 40 mg/kg of the extract exhibited an anti-inflammatory effect comparable to the positive control, indomethacin, by reducing the pro-inflammatory cytokines IL-6 and IL-1β, as well as the COX-2 and myeloperoxidase enzymes [50].

Black grape seed hydroalcoholic extract (50, 100, and 200 mg/kg) and black grape seed oil (2, 4, and 8 mL/kg) were administered orally to rats, two hours before the induction of colitis and continued for an additional four days. This treatment resulted in a dose-dependent reduction in colon weight, ulcer index, and total colitis index when compared to the control group. These findings suggest that both black grape seed oil and the hydroalcoholic extract have protective and preventive effects in an acute model of experimental ulcerative colitis [51].

It has been observed that Cabernet Franc, Cabernet Sauvignon and Sauvignon Blanc wine types showed anti-inflammatory activity by reducing the levels of nitric oxide, TNF-α and IL-1β, the amount of which increases with lipopolysaccharide, in RAW 264.7 cells [52]. In another study, wine extracts (alcohol-free wine, alcohol-free wine aqueous extract and alcohol-free wine ethylacetate extract) inhibited the lipoxygenase enzyme in a concentration-dependent manner and showed 30–50% and 100% inhibition at the tested concentrations (10 and 100 μg/mL), respectively [41]. Solvent-solvent partitioning was performed on alcohol-free wines obtained through various separation methods from different types of wines, including white wines such as Robola of Kefalonia, Tsaousi, Kakotrigis, Muscat of Kefalonia, and White Thiako, as well as red wines like Petrokoritho, Vertzami, Avgoustiatis, Red Thiako, and Mavrodaphne of Kefalonia. Several subfractions were obtained from these wines. The antioxidant, anti-inflammatory, and antiplatelet activities of the subfractions were subsequently examined. All extracts demonstrated antioxidant, anti-inflammatory, and antiplatelet properties; however, the extract with the highest phenolic content exhibited the most significant activity. For assessing antioxidant activity, the DPPH radical scavenging effect and the ability to inhibit lipoxygenase activity were measured. Antiplatelet activity was evaluated by examining the inhibition of platelet-activating factor (PAF), Adenosine diphosphate (ADP), tartrate-resistant acid phosphatase (TRAP), collagen, and arachidonic acid. For the anti-inflammatory activity, it was noted that the extracts significantly reduced the increased secretion of TNF-α and IL-1β, which result from the

inflammatory response induced in peripheral blood mononuclear cells from healthy volunteers. This study indicated that both white and red wines contain biologically active microconstituents that help combat oxidative stress, inflammation, and thrombosis. Therefore, a wine's protective effect is not related to its color, but rather to its specific microconstituent profile [53]. Wine extract rich in polyphenols (extract obtained with the C18 cartridge of Port Barrel Reserve wine) reduced the increase in lipopolysaccharide-induced ROS levels in human colon CDD-18Co fibroblast cells. NF-κB, IL-6 and TNF-α gene expression, which increased with the application of lipopolysaccharide, decreased with the application of wine extract. Cell adhesion molecules have been observed to be upregulated in inflammatory bowel diseases. By downregulating these molecules, the development of inflammatory bowel disease can be prevented. For this purpose, ICAM-1, VCAM-1 and PECAM-1 (Platelet endothelial cell adhesion molecule-1) gene expression increased with the application of lipopolysaccharide. Pretreatment with wine extract resulted in a decrease in the expression increase of these genes [54].

4.4. Antihepatotoxic Effect

The ethanolic extract of red grape seeds has been shown to attenuate paracetamol-induced hepatotoxicity in rats. After administering the extract for six weeks, there was a reduction in serum cholesterol, triglycerides, low-density lipoprotein (LDL-C), and very low-density lipoprotein (VLDL-C), along with a significant increase in levels of high-density lipoprotein (HDL-C). The extract provided notable hepatoprotection by decreasing the activities of liver enzymes, improving kidney parameters, and reducing lipid peroxidation. Additionally, the extract enhanced the activity levels of endogenous antioxidants, including GSH, SOD, and CAT, bringing them close to normal levels [55].

Grape seed oil also possesses protective effects on CCl_4 induced acute liver injury in γ-irradiated rats by antioxidant, anti-inflammatory and anti-apoptotic activities. The induced activities of SOD, CAT, GSH-Px (glutathione peroxidase), GST (glutathione transferase). It reduced alleviated ALT (alanine aminotransferase), AST (aspartate aminotransferase), IL-6 and TNF-α levels associated withdown-regulation of the CYP2E1 (Cytochrome P450 2E1), iNOS, Caspase-3 and NF-κB expression, up-regulation of the trace elements concentration levels and activation of SIRT1 (silent information regulator protein-1) gene expression are responsible for the improvement of the antioxidant and anti-inflammatory status in the hepatic tissues. [56]

4.5. Antidiabetic Activity

The administration of a water extract from *V. vinifera* (Muscat variety) seeds over 28 days demonstrated an antidiabetic effect in rats with streptozotocin-induced diabetes. This treatment resulted in a reduction of fasting blood glucose, glycated haemoglobin (HbA1c), lipid profile, and serum insulin levels, bringing them closer to normal levels. Additionally, it caused less pancreatic damage. The extract-treated rats showed higher levels of insulin, GLUT-2, SOD, CAT, and glutathione peroxidase, while levels of TNF-α, IκB, and caspase-3 were lower in their pancreas [57]. A dried grape skin was extracted with water. The concentrated water extract was applied to a cationic ion-exchange resin column and eluted using ethanol, a mixture of ethanol and water, and finally water. The water portion was discarded, while the other fractions, which were rich in polyphenols, were administered to rats over a period of 19 days. This treatment demonstrated hypoglycemic effects in normal mice and antihyperglycemic effects in alloxan-induced diabetic mice. The authors suggested that these effects occur independently of increased insulin release but are related to enhanced insulin sensitivity, which is associated with increased Akt phosphorylation and higher levels of insulin receptors and GLUT-4 in skeletal muscle [58].

4.6. Antimicrobial Effect

Antimicrobial effects of seeds of grape reported in various studies. A methanolic extract of grape seeds inhibited biofilm formation of methicillin-resistant *Staphylococcus aureus and Staphylococcus haemolyticus* [59]. Moreover, seed extracts of some endemic Turkish grape varieties including Hasandede, Emir and Kalecik karası exhibited antimicrobial effects against *Escherichia coli*, *Klebsiella pneumoniae*, *Mycobacterium smegmatis*, *Proteus vulgaris*, *Pseudomonas aeruginosa*, *Pseudomonas fluorescens*, *Salmonella enteritidis*, *Salmonella typhimurium*, *Staphylococcus aureus* ve *Yersinia enterocolitica*. The effect was attributed to flavan-3-ols in the extract [60]. Furthermore, seed oil of Tamjanika, a Balkan native grape variety of *V. vinifera* exhibited antifungal activity against *Trichophyton mentagrophytes*, *Trichophyton rubrum*, *Trichophyton verrucosum*, *Microsporum gypseum* and *Microsporum canis* [61].

4.7. Miscellenous Effects

The ethanolic extract of *V. vinifera* seeds has been shown to promote wound healing in an excision wound model using albino rats. After the wounds occurred, a treatment of 2 mg of the extract per wound or the positive control, Mebo®®, was applied twice daily for 14 days. The results indicated that the extract improved wound closure rates, increased levels of TGF-β (Transforming Growth Factor-β) and VEGF, and decreased levels of TNF-α and IL-1β when compared to the Mebo®®-treated group [36].

Primitivo and Negroamaro polyphenolic extracts, inhibited monocyte adhesion to stimulated endothelial cells at 1 μg/mL. The extracts down-regulated the expression of adhesion molecules, including ICAM-1, VCAM-1, E-Selectin, as well as MCP-1 and M-CSF (macrophage colony-stimulating factor), at mRNA and protein levels. In addition, these treatments reduced NF-κB, AP-1 (activator protein-1) activation and intracellular ROS levels in lipopolysaccharide-stimulated HUVEC cells. Thus, they exhibited anti-atherosclerotic effect [62].

Pretreatment with grape seed oil at a dosage of 4 mL/kg/day was given for 14 days. After this period, ischemia was induced by isoproterenol The grape seed oil was found to reduce ventricular conduction, mitigate the cardiotoxic effects of isoproterenol in the ventricular myocardium, and lower the levels of pro-inflammatory cytokines. Additionally, the oil prevented the increase in heart rate and the reduction in RR interval caused by isoproterenol, which may contribute to its cardioprotective effects in acute myocardial ischemia [63].

4.8. Clinical Trials

A meta-analysis of 37 randomized controlled studies found a significant increase in total antioxidant capacity from the use of grape products. However, there was no significant effect on SOD and oxygen radical absorbance capacity (ORAC). While higher doses of grape products lead to increased SOD and ORAC levels, prolonged use specifically raised ORAC levels. Overall, the application of grape products in healthy volunteers significantly influenced total antioxidant capacity, SOD, and ORAC levels [64].

In a meta-analysis including 24 randomized controlled studies, the use of grape products (grape extract, grape juice, grape powder, grape seed extract, grape seed oil, raisins, and whole grapes) significantly reduced C-reactive protein (CRP) levels. However, it was observed that they had no significant effects on serum TNF-α, IL-6, total antioxidant capacity and malondialdehyde. Subgroup analysis showed that grape juice and grape seed extract had a significant CRP-lowering effect in randomized controlled studies conducted on participants who were administered high doses of grape products and fell into the normal or obese body mass index categories. In subgroup analyzes for TNF-α levels, a significant lowering effect of grape products on TNF-α levels was observed when grape seed extract was used, when high doses of grape products were used, or when administered to overweight and obese subjects [65].

A meta-analysis of 29 randomized controlled trials examined the effects of grape and grape product supplements on glycemic responses. The study found that these supplements significantly reduced the homeostatic model assessment of insulin resistance. However, there was no impact on fasting insulin levels or hemoglobin A1C percentages. Interestingly, the use of grape and grape product supplements, particularly grape juice, resulted in an increase in fasting blood sugar compared to the control group. The authors suggested that this effect might be related to the sugar content in grape juice [66].

In a meta-analysis including 48 randomized controlled studies, it was observed that consumption of grape products reduced total cholesterol, low-density lipoprotein and triglyceride concentrations. However, the use of grape products had no effect on high-density lipoprotein. Supplementation of grape products has been observed to reduce triglyceride levels in patients with hyperlipidemia, diabetes, and metabolic syndrome. At low doses and intervention periods of less than 8 weeks, triglyceride-lowering effects were observed for grape seed extract and whole grape extract forms, but not for raisins and grape juice. Supplements in the forms of whole grape extract, grape juice, and grape seed extract significantly reduced low-density lipoprotein levels, especially in hyperlipidemic patients [67].

In another meta-analysis examining 30 randomized controlled studies, it was observed that grape products significantly reduced systolic blood pressure compared to the control group. According to subgroup analyses, consumption of raisins and grape powder caused a decrease in systolic blood pressure, while such an effect was not observed with grape juice consumption. An increase in VCAM-1 has been observed. No significant effects were observed on diastolic blood pressure, endothelial function, heart rate, pulse rate and soluble intercellular adhesion molecule-1 (sICAM-1) as a result of consumption of grape products. However, the authors rated the reliability of the majority of included studies (25 out of 30) as low or moderate [68].

An open, prospective, cross-over, randomised, and controlled cross-sectional clinical trial showed that moderate red wine consumption decreases serum oxidation parameters and reduces the propensity of LDL to

undergo lipid peroxidation, whereas both red wine it increases HDL-cholesterol. However, drinking red wine lowers the production of endothelial adhesion molecules and monocytes, which, when they interact with endothelial receptors, enable monocytes to penetrate the endothelium wall and postpone the early stages of atherosclerosis. On the other hand, red wine consumption reduces the expression of monocyte and endothelial adhesion molecules, which after interaction with endothelial receptors allows the monocytes to pass through the endothelial wall, delaying the early processes of atherosclerosis [69]. A meta-analysis that included 48 animal studies and 37 human studies evaluated the impact of red wine polyphenols, which consist of a complex and varied array of molecules, including flavonoids like (+)-catechin, quercetin, anthocyanins, and stilbenes, on vascular health. The human studies found that the consumption of red wine resulted in a reduction in systolic blood pressure by an average of −2.6 mmHg. However, there were no significant effects observed on diastolic blood pressure or overall vascular function. When pure resveratrol was administered alone, a greater reduction in systolic blood pressure was recorded, averaging −3.7 mmHg. Nonetheless, these beneficial effects are not as pronounced as those seen in animal models [70].

A meta-analysis of ninety-one randomized controlled trials revealed that drinking red wine improved lipid profiles, intestinal microbiota, thrombosis, immune function and inflammation, and antioxidant status, while having no effect on body weight or glucose metabolism. While there were no changes in blood pressure, weight gain, or blood sugar levels, five of the seven studies that were examined showed positive benefits of wine consumption in terms of indicators of oxidative stress, inflammation, and nephropathy as well as a little decrease in the risk of cardiovascular disease. According to the evaluated cohort studies, moderate consumption of red wine may offer protection against atrial fibrillation [71].

Several studies were shown that light and moderate daily wine consumption decreased whereas high consumption increased colorectal, breast and prostate cancer development risk [72–74].

In a meta-analysis examining 9 studies, it was observed that products derived from grapes did not significantly change serum AST and ALT concentrations, but a significant decrease in serum alkaline phosphatase (ALP) levels was observed. Subgroup analyzes are meaningful only in studies where the effect on ALP was also evaluated in healthy participants. ALT concentration of grape products showed a significant decrease in the subgroup of healthy volunteers [75].

5. Conclusions and Prospective

Grapes and their various products have been consumed for many years. They possess a range of physiological effects due to the presence of compound groups such as flavonoids, tannins, anthocyanins, and phenolic acids. While these compounds are primarily known for their antioxidant properties, they also exhibit a variety of beneficial effects, including anticancer, antidiabetic, hepatoprotective, and anti-inflammatory properties, as well as promoting wound healing. These effects can be observed in the application of different parts of the grape or extracts derived from them. Recent studies have also focused on the biological effects of by-products (grape pomace) obtained in the production of wine from grapes. Especially cardioprotective effects of not only wine but also other grape products proved by many studies including clinical trials. Wine, an important product obtained from grapes, has attracted the attention of researchers. In particular, the cardiovascular protective effect of wine was suggested by the French Paradox, and over time, various studies have been conducted on this effect of wine. Although wine contains important phenolic compound groups, its effects on wine consumption and health are a matter of debate among researchers due to the alcohol it contains. It seems that seed extracts or seed oils are safer options.

Author Contributions: D.S.: Conceptualization, investigation, Writing—Original Draft; A.D.: investigation, Writing—Original Draft; Ö.B.K.: investigation. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

ABTS	2,2-azino-bis(3-etilbenzotiazolin)-6-sulfonic acid
ADP	Adenosine diphosphate
Akt	Protein kinase B
ALP	Alkaline phosphatase

ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AP-1	Activator protein-1
CAT	Catalase
COX-2	Cyclooxygenase-2
CRP	C-reactive protein
CUPRAC	CUPric Reducing Antioxidant Capacity
CXCL-10	C-X-C motif ligand-10
CYP2E1	Cytochrome P450 2E1
DPPH	1,1-diphenyl-2-picrylhydrazyl
Erk	Extracellular signal-regulated kinase
EGF	Epidermal Growth Factor
FAO	Food and Agriculture Organization of the United Nations
FRAP	Ferric reducing antioxidant power
GLUT-2	Glucose transporter-2
GLUT-4	Glucose transporter-4
GSH	Glutathione
GSH-Px	Glutathione peroxidase
GST	Glutathione transferase
HDL-C	High-density lipoprotein
ICAM-1	Intercellular adhesion molecule-1
IL-1β	Interleukin-1β
IL-6	Interleukin-6
IL-8	Interleukin-8
iNOS	Nitric oxide synthase
LDL-C	Low-density lipoprotein
LRP	Lung resistance-related protein
MCP-1	Monocyte Chemoattractant Protein-1
M-CSF	Macrophage colony-stimulating factor
MPO	Myeloperoxidase
MMP	Matrix metalloproteinases protein
MDR1	Multidrug resistance protein 1
MPR1	Multidrug resistance-associated protein 1,
NF-kB	Nuclear Factor kappa B
NO	Nitric oxide
ORAC	Oxygen radical absorbance capacity
PAF	Platelet-activating factor
PECAM-1	Platelet endothelial cell adhesion molecule
PI3K	Phosphatidylinositol 3-kinase
RNA	Ribonucleic acid
ROS	Radical oxygen species
sICAM-1	Soluble intercellular adhesion molecule-1
SIRT-1	Silent information regulator protein-1
SOD	Superoxide dismutase
TBARS	Thiobarbituric acid reactive substances
TGF-β	Transforming Growth Factor-β
TNF-α	Tumor Necrosis Factor-α
TRAP	Tartrate-resistant acid phosphatase
VCAM-1	Vascular cell adhesion molecule-1
VLDL-C	Very low-density lipoprotein

References

1. Alston, J.M.; Sambucci, O. Grapes in the World Economy. In *Grape Genom*, 1st ed.; Cantu, D., Walker, M.A., Eds.; Springer Nature: Cham, Switzerland, 2019. pp. 1–24.
2. Barbalho, S.M.; Bueno Ottoboni, A.M.M.; Fiorini, A.M.R.; et al. Grape juice or wine: Which is the best option? *Crit. Rev. Food Sci. Nutr.* **2020**, *60*, 3876–3889.
3. Fortes, A.M.; Pais, M.S. Grape (*Vitis* species). In *Nutritional Composition of Fruit Cultivars*; Simmonds, M.S.J., Preedy, V.R., Eds.; Academic Press: London, UK, 2016; pp. 257–286.
4. Zhou, D.D.; Li, J.; Xiong, R.G.; et al. Bioactive Compounds, Health Benefits and Food Applications of Grape. *Foods* **2022**, *11*, 2755.
5. Sağlam, H.; Çalkan Sağlam, Ö. Türkiye Bağcılığına Tarihsel Bir Bakış; Asma Genetik Kaynaklarının Önemi. *SJAFS* **2018**, *32*, 601–606.
6. Çalkan Sağlam, Ö.; Sağlam, H. İnsanlık Tarihinde Üzümün Önemi. *J. Agric.* **2018**, *1*, 1–10.
7. McGovern, P.E.; Fleming, S.J.; Katz, S.H. (Eds.) *The Origins and Ancient History of Wine: Food and Nutrition in History and Antropology*, 1st ed.; Routledge: London, UK, 1996.

8. Maliogka, V.I.; Martelli, G.P.; Fuchs, M.; et al. Control of viruses infecting grapevine. In *Advances in Virus Research*, 1st ed.; Loebenstein, G., Katis, N. I., Eds.; Academic Press; London, UK, 2015; Volume 91, pp. 175–227.
9. Food and Agriculture Organization of the United Nations. Top 10 Country Production of Grapes-2022. Available online: https://www.fao.org/faostat/en/#rankings/countries_by_commodity (accessed on 10 February 2024).
10. Food and Agriculture Organization of the United Nations. Top 10 Country, Export Quantity of Grapes-2022. Available online: https://www.fao.org/faostat/en/#rankings/countries_by_commodity_exports (accessed on 10 February 2024).
11. Food and Agriculture Organization of the United Nations. Top 10 Country Production of Grapes-2017. Available online: https://www.fao.org/faostat/en/#rankings/countries_by_commodity (accessed on 10 February 2024).
12. Khan, N.; Fahad, S.; Naushad, M.; et al. Grape production critical review in the world. *SSRN* **2020**, *3595842*.
13. Cabaroğlu, T.; Yilmaztekin, M. *Üzümün Bileşimi ve Insan Sağlığı Üzerine Etkisi*; Buldan Sempozyumu: Denizli, Turkey, 2006.
14. Sahu, A.; Singh, D.; Shukla, R. Bioactive Compounds and Reported Pharmacological Activities of *Vitis vinifera* L. An Overview. *WJPR* **2023**, *12*, 27–38.
15. Sabra, A.; Netticadan, T.; Wijekoon, C. Grape bioactive molecules, and the potential health benefits in reducing the risk of heart diseases. *Food Chem. X* **2021**, *12*, 100149.
16. Spinei, M.; Oroian, M. The Potential of Grape Pomace Varieties as a Dietary Source of Pectic Substances. *Foods* **2021**, *10*, 867.
17. Wijekoon, C.; Netticadan, T.; Siow, Y.L.; et al. Potential Associations among Bioactive Molecules, Antioxidant Activity and Resveratrol Production in *Vitis vinifera* Fruits of North America. *Molecules* **2022**, *27*, 336.
18. Visioli, F.; Panaite, S.A.; Tomé-Carneiro, J. Wine's Phenolic Compounds and Health: A Pythagorean View. *Molecules* **2020**, *25*, 4105.
19. Xia, E.Q.; Deng, G.F.; Guo, Y.J.; et al. Biological activities of polyphenols from grapes. *Int. J. Mol. Sci.* **2010**, *11*, 622–646.
20. Bakker, J.; Timberlake, C.F. Isolation, Identification, and Characterization of New Color-Stable Anthocyanins Occurring in Some Red Wines. *J. Agric. Food Chem.* **1997**, *45*, 35–43.
21. Perestrelo, R.; Lu, Y.; Santos, S.A.O.; et al. Phenolic profile of Sercial and Tinta Negra *Vitis vinifera* L. grape skins by HPLC–DAD–ESI-MSn: Novel phenolic compounds in *Vitis vinifera* L. grape. *Food Chem.* **2012**, *135*, 94–104.
22. Creaser, C.S.; Koupai-Abyazani, M.R.; Stephenson, G.R. Gas chromatographic–mass spectrometric characterization of flavanones in citrus and grape juices. *Analyst* **1992**, *117*, 1105–1109.
23. Baron, M.; Prusova, B.; Tomaskova, L.; et al. Terpene content of wine from the aromatic grape variety 'Irsai Oliver' (*Vitis vinifera* L.) depends on maceration time. *Open Life Sci.* **2017**, *12*, 42–50.
24. Luo, J.; Brotchie, J.; Pang, M.; et al. Free terpene evolution during the berry maturation of five *Vitis vinifera* L. cultivars. *Food Chem.* **2019**, *299*, 125101.
25. Kostrz, M.; Satora, P. Formation of terpenes in grapes and wines. *Folia Pomer. Univ. Technol. Stetin. Agric. Aliment. Pisc. Zootech.* **2018**, *340*, 31–38.
26. Mateo, J.J.; Jiménez, M. Monoterpenes in grape juice and wines. *J. Chromatogr. A* **2000**, *881*, 557–567.
27. Coelho, E.; Rocha, S.M.; Barros, A.S.; et al. Screening of variety- and pre-fermentation-related volatile compounds during ripening of white grapes to define their evolution profile. *Anal. Chim. Acta.* **2007**, *597*, 257–264.
28. D'Onofrio, C.; Matarese, F.; Cuzzola, A. Study of the terpene profile at harvest and during berry development of *Vitis vinifera* L. aromatic varieties Aleatico, Brachetto, Malvasia di Candia aromatica and Moscato bianco. *J. Sci. Food Agric.* **2017**, *97*, 2898–2907.
29. Fenoll, J.; Manso, A.; Hellín, P.; et al. Changes in the aromatic composition of the *Vitis vinifera* grape Muscat Hamburg during ripening. *Food Chem.* **2009**, *114*, 420–428.
30. Zhang, P.; Fuentes, S.; Siebert, T.; et al. Terpene evolution during the development of *Vitis vinifera* L. cv. Shiraz grapes. *Food Chem.* **2016**, *204*, 463–474.
31. Marais, J. Terpenes in the aroma of grapes and wines: A review. *SAJEV* **1983**, *4*, 49–58.
32. Darriet, P.; Thibon, C.; Dubourdieu, D.; et al. Aroma and aroma precursors in grape berry. In *The Biochemistry of the Grape Berry*; Bentham Science: Sharjah, United Arab Emirates, 2012; Volume 26, pp 111–136.
33. Orbán, N.; Kozák, I.O.; Drávucz, M.; et al. LC-MS method development to evaluate major triterpenes in skins and cuticular waxes of grape berries. *IJFST* **2009**, *44*, 869–873.
34. Chidambara Murthy, K.N.; Singh, R.P.; Jayaprakasha, G.K. Antioxidant Activities of Grape (*Vitis vinifera*) Pomace Extracts. *J. Agric. Food Chem.* **2002**, *50*, 5909–5914.
35. Tsantila, E.M.; Esslinger, N.; Christou, M.; et al. Antioxidant and Anticancer Activity of *Vitis vinifera* Extracts in Breast Cell Lines. *Life* **2024**, *14*, 228.
36. Al-Warhi, T.; Zahran, E.M.; Selim, S.; et al. Antioxidant and Wound Healing Potential of *Vitis vinifera* Seeds Supported by Phytochemical Characterization and Docking Studies. *Antioxidants* **2022**, *11*, 881.

37. Harbeoui, H.; Bettaieb Rebey, I.; Ouerghemmi, I.; et al. Biochemical characterization and antioxidant activity of grape (*Vitis vinifera* L.) seed oils from nine Tunisian varieties. *J. Food Biochem.* **2018**, *42*, e12595.
38. Habashy, N.H.; Kodous, A.S.; Abu-Serie, M.M. Targeting ROS/NF-κB signaling pathway by the seedless black *Vitis vinifera* polyphenols in CCl_4-intoxicated kidney, lung, brain, and spleen in rats. *Sci. Rep.* **2021**, *11*, 16575.
39. Radovanović, A.N.; Jovančićević, B.S.; Radovanović, B.C.; et al. Antioxidant and antimicrobial potentials of Serbian red wines produced from international *Vitis vinifera* grape varieties. *J. Sci. Food Agric.* **2012**, *92*, 2154–2161.
40. Al-Awwadi, N.A.; Bornet, A.; Azay, J.; et al. Red Wine Polyphenols Alone or in Association with Ethanol Prevent Hypertension, Cardiac Hypertrophy, and Production of Reactive Oxygen Species in the Insulin-Resistant Fructose-Fed Rat. *J. Agric. Food Chem.* **2004**, *52*, 5593–5597.
41. Mollica, A.; Scioli, G.; Della Valle, A.; et al. Phenolic Analysis and In Vitro Biological Activity of Red Wine, Pomace and Grape Seeds Oil Derived from *Vitis vinifera* L. cv. Montepulciano d'Abruzzo. *Antioxidants* **2021**, *10*, 1704.
42. Shaban, N.Z.; El-Faham, A.A.; Abu-Serie, M.M.; et al. Targeting apoptosis in MCF-7 and Ehrlich ascites carcinoma cells by saponifiable fractions from green and black *Vitis vinifera* seed oil. *Biomed. Pharmacother.* **2023**, *157*, 114017.
43. Shaban, N.Z.; El-Faham, A.A.; Abu-Serie, M.M.; et al. The black *Vitis vinifera* seed oil saponifiable fraction ameliorates hepatocellular carcinoma in vitro and in vivo via modulating apoptosis and ROS/NF-κB signaling. *Biomed. Pharmacother.* **2024**, *171*, 116215.
44. Shaban, N.Z.; Hegazy, W.A.; Abu-Serie, M.M.; et al. Seedless black *Vitis vinifera* polyphenols suppress hepatocellular carcinoma in vitro and in vivo by targeting apoptosis, cancer stem cells, and proliferation. *Biomed. Pharmacother.* **2024**, *175*, 116638.
45. Lin, K.N.; Jiang, Y.L.; Zhang, S.G.; et al. Grape seed proanthocyanidin extract reverses multidrug resistance in HL-60/ADR cells via inhibition of the PI3K/Akt signaling pathway. *Biomed. Pharmacother.* **2020**, *125*, 109885.
46. Barron, C.C.; Moore, J.; Tsakiridis, T.; et al. Inhibition of human lung cancer cell proliferation and survival by wine. *Cancer Cell Int.* **2014**, *14*, 6.
47. Chen, S.; Yi, Y.; Xia, T.; et al. The influences of red wine in phenotypes of human cancer cells. *Gene* **2019**, *702*, 194–204.
48. Giribabu, N.; Karim, K.; Kilari, E.K.; et al. Anti-Inflammatory, Antiapoptotic and Proproliferative Effects of *Vitis vinifera* Seed Ethanolic Extract in the Liver of Streptozotocin-Nicotinamide-Induced Type 2 Diabetes in Male Rats. *Can. J. Diabetes* **2018**, *42*, 138–149.
49. Calabriso, N.; Massaro, M.; Scoditti, E.; et al. Grape Pomace Extract Attenuates Inflammatory Response in Intestinal Epithelial and Endothelial Cells: Potential Health-Promoting Properties in Bowel Inflammation. *Nutrients* **2022**, *14*, 1175.
50. Nery-Flores, S.D.; Castro-López, C.M.; Martínez-Hernández, L.; et al. Grape Pomace Polyphenols Reduce Acute Inflammatory Response Induced by Carrageenan in a Murine Model. *Chem. Biodivers.* **2024**, *21*, e202302065.
51. Niknami, E.; Sajjadi, S.E.; Talebi, A.; et al. Protective Effect of *Vitis vinifera* (Black Grape) Seed Extract and Oil on Acetic Acid-Induced Colitis in Rats. *Int. J. Prev. Med.* **2020**, *11*, 102.
52. Bezerra, I.L.; Caillot, A.R.C.; Palhares, L.C.G.F.; et al. Structural characterization of polysaccharides from Cabernet Franc, Cabernet Sauvignon and Sauvignon Blanc wines: Anti-inflammatory activity in LPS stimulated RAW 264.7 cells. *Carbohydr. Polym.* **2018**, *186*, 91–99.
53. Fragopoulou, E.; Petsini, F.; Choleva, M.; et al. Evaluation of Anti-Inflammatory, Anti-Platelet and Anti-Oxidant Activity of Wine Extracts Prepared from Ten Different Grape Varieties. *Molecules* **2020**, *25*, 5054.
54. Angel-Morales, G.; Noratto, G.; Mertens-Talcott, S. Red wine polyphenolics reduce the expression of inflammation markers in human colon-derived CCD-18Co myofibroblast cells: Potential role of microRNA-126. *Food Funct.* **2012**, *3*, 745–752.
55. Madi Almajwal, A.; Farouk Elsadek, M. Lipid-lowering and hepatoprotective effects of *Vitis vinifera* dried seeds on paracetamol-induced hepatotoxicity in rats. *Nutr. Res. Pract.* **2015**, *9*, 37–42.
56. Ismail, A.F.M.; Salem, A.A.M.; Eassawy, M.M.T. Hepatoprotective effect of grape seed oil against carbon tetrachloride induced oxidative stress in liver of γ-irradiated rat. *J. Photochem. Photobiol. B Biol.* **2016**, *160*, 1–10.
57. Adam, S.H.; Giribabu, N.; Kassim, N.; et al. Protective effect of aqueous seed extract of *Vitis vinifera* against oxidative stress, inflammation and apoptosis in the pancreas of adult male rats with diabetes mellitus. *Biomed. Pharmacother.* **2016**, *81*, 439–452.
58. Soares de Moura, R.; da Costa, G.F.; Moreira, A.S.B.; et al. *Vitis vinifera* L. grape skin extract activates the insulin-signalling cascade and reduces hyperglycaemia in alloxan-induced diabetic mice. *J. Pharm. Pharmacol.* **2012**, *64*, 268–276.
59. Al-Mousawi, A.H.; Al-kaabi, S.J.; Albaghdadi, A.J.H.; et al. Effect of Black Grape Seed Extract (*Vitis vinifera*) on Biofilm Formation of Methicillin-Resistant *Staphylococcus aureus* and *Staphylococcus haemolyticus*. *Curr. Microbiol.* **2020**, *77*, 238–245.
60. Jayaprakasha, G.K.; Selvi, T.; Sakariah, K.K. Antibacterial and antioxidant activities of grape (*Vitis vinifera*) seed extracts. *Food Res. Int.* **2003**, *36*, 117–122.
61. Đorđevski, N.; Stojković, D.; Živković, J.; et al. Tamjanika, a Balkan native variety of *Vitis vinifera* L.: Chemical characterization, antibacterial, and anti-dermatomycosis potential of seed oil. *Food Sci. Nutr.* **2022**, *10*, 1312–1319.

62. Calabriso, N.; Scoditti, E.; Massaro, M.; et al. Multiple anti-inflammatory and anti-atherosclerotic properties of red wine polyphenolic extracts: Differential role of hydroxycinnamic acids, flavonols and stilbenes on endothelial inflammatory gene expression. *Eur. J. Nutr.* **2016**, *55*, 477–489.
63. Bocsan, I.C.; Pop, R.M.; Sabin, O.; et al. Comparative Protective Effect of *Nigella sativa* Oil and *Vitis vinifera* Seed Oil in an Experimental Model of Isoproterenol-Induced Acute Myocardial Ischemia in Rats. *Molecules* **2021**, *26*, 3221.
64. Sarkhosh-Khorasani, S.; Sangsefidi, Z.S.; Hosseinzadeh, M. The effect of grape products containing polyphenols on oxidative stress: A systematic review and meta-analysis of randomized clinical trials. *Nutr. J.* **2021**, *20*, 25.
65. Ghalishourani, S.S.; Farzollahpour, F.; Shirinbakhshmasoleh, M.; et al. Effects of grape products on inflammation and oxidative stress: A systematic review and meta-analysis of randomized controlled trials. *Phytother. Res.* **2021**, *35*, 4898–4912.
66. Moodi, V.; Abedi, S.; Esmaeilpour, M.; et al. The effect of grapes/grape products on glycemic response: A systematic review and meta-analysis of randomized controlled trials. *Phytother. Res.* **2021**, *35*, 5053–5067.
67. Ghaedi, E.; Moradi, S.; Aslani, Z.; et al. Effects of grape products on blood lipids: A systematic review and dose–response meta-analysis of randomized controlled trials. *Food Funct.* **2019**, *10*, 6399–6416.
68. Ashoori, M.; Soltani, S.; Kolahdouz-Mohammadi, R.; et al. The effect of whole grape products on blood pressure and vascular function: A systematic review and meta-analysis of randomized controlled trials. *Nutr. Metab. Cardiovasc. Dis.* **2023**, *33*, 1836–1848.
69. Estruch, R. Wine and cardiovascular disease. *Int. Food Res.* **2000**, *33*, 219–226.
70. Weaver, S.R.; Rendeiro, C.; McGettrick, H.M.; et al. Fine wine or sour grapes? A systematic review and meta-analysis of the impact of red wine polyphenols on vascular health. *Eur. J. Nutr.* **2021**, *60*, 1–28.
71. Lombardo, M.; Feraco, A.; Camajani, E.; et al. Health Effects of Red Wine Consumption: A Narrative Review of an Issue That Still Deserves Debate. *Nutrients* **2023**, *15*, 1921.
72. Kim, Y.; Je, Y.; Giovannucci, E.L. Association between Alcohol Consumption and Survival in Colorectal Cancer: A Meta-analysis. *Cancer Epidemiol. Biomark. Prev.* **2019**, *28*, 1891–1901.
73. Chen, J.-Y.; Zhu, H.-C.; Guo, Q.; et al. Dose-dependent associations between wine drinking and breast cancer risk-meta-analysis findings. *Asian Pac. J. Cancer Prev.* **2016**, *17*, 1221–1233.
74. Vartolomei, M.D.; Kimura, S.; Ferro, M.; et al. The impact of moderate wine consumption on the risk of developing prostate cancer. *Clin. Epidemiol.* **2018**, *10*, 431–444.
75. Alhajlah, S. Effect of grape-derived products on the serum levels of enzymes mainly produced by the liver: A systematic review and meta-analysis of parallel randomized controlled trials. *Phytother. Res.* **2024**, *38*, 3583–3593.