

A recent review on the traditional use, phytochemical constituents, and pharmacological activity of *Vitis vinifera* L. (Vitaceae)

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ABSTRACT

Vitis vinifera link (Vitaceae) has been traditionally employed for the treatment of pain conditions, including abdominal and dental pain, as well as for its antibacterial and anti-inflammatory properties. This review aims to compile and analyze existing data regarding the traditional applications, phytochemical constituents, and pharmacological activities of *V. vinifera*. A comprehensive literature search was conducted in the Scopus and ScienceDirect databases, resulting in the selection of 93 relevant publications from the period 2017 to 2024. Among the identified bioactive constituents, proanthocyanidins and phenolic compounds have been recognized as major contributors to the plant's pharmacological effects, which include anti-inflammatory, antioxidant, neuroprotective (particularly in cognitive disorders), and anticancer activities. The analgesic and antibacterial effects of *V. vinifera* have been substantiated through both *in vitro* and *in vivo* experimental models, primarily attributed to its phenolic content. Furthermore, the development of techniques that promote the strategic production of specific grape compounds is proposed as an alternative practice to mitigate the impacts of climate change on the chemical composition of grapevines.

1. INTRODUCTION

Vitis vinifera L. (Vitaceae), native to Western Asia and Southern Europe, accounts for approximately 90% of all known grapevine species [1]. The species comprises around 900 cultivated varieties adapted to a broad range of climatic zones, including tropical, subtropical, and temperate regions [2]. Due to its diverse biological activities, *V. vinifera* has been extensively studied across various plant organs [2-7], developmental stages [8], and even vineyard pruning residues [9]. Research on newly cultivated varieties has further led to the identification of novel bioactive compounds exhibiting antioxidant, antimicrobial, anticancer, and anti-aging properties [4].

Recent studies have demonstrated that fortification of *V. vinifera* seeds with compounds such as chitosan and gelatin significantly enhances their total polyphenol content [10]. Among the principal bioactive

constituents identified in *V. vinifera*, flavonols are particularly notable for their antioxidant potential [11]. These compounds are characterized by an aromatic phenol ring substituted with one or more hydroxyl groups [12], structural features that are strongly associated with their biological activity [13]. The biosynthesis and concentration of these secondary metabolites are influenced by environmental factors such as soil composition, and the application of elicitor substances has been shown to elevate phenolic content and corresponding antioxidant activity compared to untreated crops [14]. In addition, post-harvest processing technologies significantly affect the levels and stability of these compounds [15].

The term "antioxidant" refers to molecules capable of neutralizing reactive oxygen species (ROS) produced during normal metabolic processes, which, when accumulated, can disrupt cellular redox homeostasis [16]. During aging, oxidative stress leads to the modification of biomolecules, including proteins, lipids, carbohydrates, and nucleic acids. Natural antioxidants, such as those derived from *V. vinifera*, can mitigate these deleterious effects [12]. These compounds have garnered attention as potential alternatives to synthetic antioxidants, such as butylated hydroxyanisole, which have been shown to

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inhibit enzymes such as metalloproteinase-2, implicated in collagen degradation [11,17,18]. The polyphenolic content of *V. vinifera* is typically analyzed using spectrophotometric and chromatographic techniques [19], and antioxidant activity is commonly assessed through assays such as 2,2-diphenyl-1-picrylhydrazyl (DPPH), 2,2'-azinobis-3-ethylbenzothiazoline-6-sulfonic acid (ABTS^{o+}), and the phosphomolybdenum reduction method [2,12].

Common names for *V. vinifera* vary by region. In Spain, it is referred to as *parra*, *parreña*, *parrón*, *vid*, *vinagrera*, *viña*, *uva*, *cepa*, or *uva isabela*; in France, as *cépage*; and in Italy, as *vitigno*. Several synonyms exist in botanical nomenclature, including *Cissus vinifera* (L.) Kuntze [20], *V. vinifera* subsp. *sativa* Hegi [21], *V. vinifera* subsp. *sylvestris* Hegi [22], and *Vitis sylvestris* C.C. Gmel [23]. Taxonomically, *V. vinifera* is classified within the kingdom Plantae, division Tracheophyta, class Magnoliopsida, order Rhamnales, family Vitaceae, genus *Vitis*, and species *V. vinifera*. It is a climbing or semi-woody perennial that can reach up to 15 m in height. The plant typically produces fruit in clusters ranging from 15 to 300 grape berries. Leaves are simple, alternate, distichous at a 180° angle, sheathed at the base, and bear two stipules that abscise early. Seeds are ovoid and taper apically. The flowers are small (approximately 2 mm), green, and pentamerous. Fruits are ovoid berries with diameters ranging from 5 to 25 mm, containing two cavities within the pericarp [24].

This systematic review aims to consolidate recent scientific evidence regarding the ethnomedicinal applications, phytochemical composition, and pharmacological activities of *V. vinifera* L., providing a comprehensive understanding of its therapeutic potential.

2. MATERIALS AND METHODS

The research articles were compiled systematically, using the Scopus and Science Direct databases, between the years 2017 and 2025, using the following terms: “*Vitis vinifera*” AND “phytochemical,” “*Vitis vinifera*” AND “activity” and “*Vitis vinifera*” AND “traditional use.” In total, 415 articles were found, among which a representative number of articles were not included due to low affinity with the review topic, so 93 articles were selected for this document. Data were collected from February 2023 to March 2025. Some articles in the introduction section to provide additional information were included without considering the search parameters. The main data found in this review are displayed in Tables 1-9.

3. RESULTS

3.1. Traditional Uses

Given that traditional medical practices often rely on local flora, fauna, and mineral resources, *V. vinifera* has been utilized by various cultures since antiquity for its therapeutic properties [Table 1] [25,26].

Table 1: Traditional use of *Vitis vinifera* in different countries.

Country/Culture	Traditional use	Part used	Way of use	References
Turkey	Stimulate the immune system, cough	Fruit	Molasses	[29]
South Africa	High blood pressure	Root	No data	[25]
	Diphtheria	Fruit	Syrup	[27]
Kosovo	Rheumatism	Fruit	Macerated in alcohol	[102]
Albania	Cold	Fruit	Vinegar	[103]
Algeria	Sunburn, eye inflammation	Leaf	Decoction	[33]
Argentina	Urination problems	Leaf	Macerated in water	[34]
Bosnia and Herzegovina	Mash: strengthening the organism and the thyroid gland	Fruit	Mash, syrup	[32]
	Syrup: improving blood picture and strengthening the organism			
Polish-Lithuanian Commonwealth in the year 1613	Maintain normal liver function	Fruit	No data	[30]
Ancient India (Ayurveda)	Epilepsy	Fruit as part of a mix of plants	No data	[35]
Ancient/Modern India (Ayurveda)	Liver and spleen disorders; chronic cough, cold, breathlessness; digestive system disorders due to chemotherapy	Fruit as part of a mix of plants	No data	[36]
Unani medicine	Unripe fruit juice: cough	fruit	Unripe fruit juice, dried fruit, fruit juice	[31]
	Ripe dried fruit: cough, and for trachea: nutritive and expectorant			
	Fruit juice: prevents syncope			
Serbia	Abdominal pain	Fruit	Juice	[28]
Spain	Acute rhinopharyngitis	Fruit	Eat fresh fruit	[26]
	Toothache	Fruit	Decoction	

Table 2: Chemical composition of the fruit, root, and tendrils of *Vitis vinifera*.

<i>Vitis vinifera</i> varieties	Chemical composition	Part used	Extraction method	References
N.S.	Anthocyanins, trans-resveratrol, piceido, α -tocopherol, β -carotene, and monoterpenes	Fruit	Ultra-performance liquid chromatography	[37]
	Flavonoids (pelargonidin 3-O-glucoside, quercetin – 3-O-glucoside and cyanidin 3-O-glucoside), L-aspartic acid, phenolic acids (trans-4-hydroxycinnamic acid methyl ester), and panthothenol	Fruit	Ultra-performance liquid chromatography and tandem mass spectrometry	[42]
	Total phenolic and flavonoid content: 2.85 ± 1.10 mg gallic acid and 2.51 ± 1.27 mg quercetin/g dry weight	Fruit	Singleton and Rossi colorimetry	[40]
	Flavonoids	Fruit (pulp and whole)	Chromatography with mass spectrometry	[41]
	Total polyphenol content (236.31 ± 4.60 mg equivalent of gallic acid/g of ethanolic extract)	Root	Ultra-high-performance liquid chromatography	[104]
	Total flavonoid content (196.36 ± 4.19 mg quercetin/g of ethanolic extract)	Root	Aluminum chloride colorimetric method	
	Total polyphenols (rutin)	Tendril	Liquid chromatography with mass spectrometry	[105]
Airén	Flavonoids (quercetin and catechin)	Fruit (Must)		[4]
Cabernet Gernischt	Petunidin-3-glucoside, malvidin-3-glucoside, procyanidin B1, quercetin-3-glucoside, <i>cis</i> -resveratrol, and piceatannol	Fruit	Tandem mass spectrometry	[66]
SuoSuo	Cyanidin-3-O-glucoside, fructose, tartaric acid, and oleanolic acid	Fruit	Chromatography with mass spectrometry	[68]
Apyrena	Caftaric acid, p-hydroxybenzoic acid, astragalin, miquelianin, and procyanidins B1 and B2	Fruit	Ultra-high-performance liquid chromatography with mass spectrometry	[69]
Aglianico	Oleanolic acid	Fruit	Nuclear magnetic resonance and liquid chromatography with tandem mass spectrometry	[57]
Tempranillo	Malic acid, delphinidin, cyanidin, peonidin, petunidin and malvidin glucosides, coumaroyl-glucosides, acylated glucosides	Fruit (Must)	High-performance liquid chromatography with diode array detector	[67]
Moscato giallo	(3S)-(+)-linalool, geraniol, (E)-(3R,6S)-(-)-linalool oxide, (E)-(3S)-8-hydroxyl linalool		Gas chromatography with tandem mass spectrometry	[58]

N.S. = Not specified.

Ethnomedicinal data indicate that fruits have been employed for a range of health conditions, including immune system stimulation and cough suppression, often administered in the form of molasses or syrup to treat diphtheria. Alcoholic macerates of the fruit have been traditionally used for the management of rheumatism, while grape vinegar has been applied in the treatment of common colds. The juice is frequently consumed to relieve abdominal pain and toothaches, which may also be addressed using fruit decoctions. In addition, the consumption of fresh grapes has been associated with the alleviation of nasopharyngitis symptoms [25-29].

Historical sources also document the use of grapes for hepatic function maintenance [30] and describe both unripe grape juice and dried fruits as effective antitussive agents. Dried grapes are traditionally recognized for their expectorant properties, benefits to the trachea, and nutritional value. Moreover, grape juice has been used in folk medicine as a preventive measure against syncope [31], while fruit mash and syrup are reputed to strengthen general vitality, including the support of hematologic and thyroid functions [32].

Other plant parts have also been employed therapeutically: the root has been used to manage hypertension [25], and the leaves – either in decoctions or aqueous macerates – have been applied for treating sunburn, ocular inflammation, and urinary disorders [33,34]. Furthermore, Ayurvedic medicine includes *V. vinifera* in polyherbal formulations for the treatment of epilepsy and for managing conditions affecting the liver, spleen, respiratory system, and gastrointestinal tract, including complications arising from chemotherapy [35,36].

3.2. Chemical Composition

The fruit of *V. vinifera* is notably rich in flavonoids [37], with anthocyanins playing a pivotal role in pigmentation and exhibiting therapeutic potential, particularly in the management of type 2 diabetes mellitus (T2DM), due to their potent antioxidant properties [38]. In addition, anthocyanins have demonstrated neuroprotective effects by ameliorating memory impairment and protecting neural tissue against oxidative stress [39]. Quantitative analysis of the roots of *V. vinifera* revealed total phenolic and flavonoid contents of 2.85 ± 1.10 mg gallic acid equivalents per gram and 2.51 ± 1.27 mg quercetin

Table 3: Chemical composition of *Vitis vinifera* seeds.

<i>Vitis vinifera</i> varieties	Chemical composition	Extraction method	References
N.S.	Unsaturated fatty acid (linoleic acid and linolenic acid), glycerophospholipid	Liquid chromatography with mass spectrometry	[49]
	Linoleic acid (64.80–68.64%), oleic acid (18.41–21.58%), palmitic acid (18.41–21.58%)	Gas chromatography system	[50]
	Total phenolic content (TPC) (115.68–317.71 mg gallic acid/g dry weight)	Folin-Ciocalteu colorimetric method	
	Stearic acid (3.42–9.93%), palmitic acid (7.81–10.66%), oleic acid (14.29–19.92%), linoleic acid (66.85–72.47%)	Gas chromatography with mass spectrometry	[5]
	Total polyphenol content ranged from 0.24 to 1.13 mg gallic acid equivalent/g dry weight	Folin-Ciocalteu colorimetric method	
<i>Albariño</i>	Organic acids (79±4 mg/100 g fw)	Mud test	[51]
	Catachine oligomers (36.0±0.3 mg/g)	Chromatography	
N.S.	Polyunsaturated linoleic acid (64.77–75.37%) and oleic acid	Gas chromatography	[48]
<i>Marselan</i>	TPC of 301 mg gallic acid equivalents/g of dry matter. High content of catechins, gallic acid, epicatechins, caffeic acid, syringic acid, and protocatechuic acid	Folin-Ciocalteu colorimetric method, high-performance liquid chromatography with diode array detector	[85]
<i>Obeidi</i>	TPC of 206 mg gallic acid equivalents/g of dry matter. High content of catechins, gallic acid, epicatechins, caffeic acid, syringic acid, and protocatechuic acid		
N.S.	Phenolic acids (mainly pyrogallol, catechin, p-hydroxybenzoic acid, protocatechuic acid, chlorogenic acid, catechol, and benzoic acid) and flavonoids (mainly hesperidin)	High-performance liquid chromatography with diode array detector	[63]

N.S. = Not specified.

Table 4: Chemical composition of *Vitis vinifera* peel.

Chemical composition	Extraction method	References
14 flavan-3-ols: 4 monomers ((+)-catechin, (-)-epicatechin, epigallocatechin gallate and epicatechin gallate) and 10 oligomers (three dimers, four trimers, two tetramers and one pentamer)	Electrospray ionization with tandem mass spectrometry	[53]
Flavonols (catechin, epicatechin, quercetin-3-O-glucoside, dihydroquercetin-3-O-rhamnoside, isorhamnetin-3-O-hexose, rutin, isorhamnetin, myricetin, phenolic acids (methyl hydroxybenzoic acids, dihydroxybenzoic acid, 1-O-vanilloyl-β-D-glucose, P-cumarac-4-glucoside acid, caffeic acid), stilbenes (resveratrol, resveratrol-3-O-glucoside, viniferine, scripusin, piceatannol)	Ultra-high-performance liquid chromatography, tandem mass spectrometry with electrospray ionization	[8]
Flavonols (acetylated and p-coumaroylated derivatives, 3-O-glucosides, isorhamnetin, laricitrin, syringatin)	Ultra-high-performance liquid chromatography	[13]
Anthocyanins (delphinidin, cyanidin, petunidin, and malvidin), hydroxybenzoic acids (gallic acid and protocatechuic acid), hydroxycinnamic acids (caffeic, chlorogenic, and coumaric acids), one flavonol (rutin), three flavan-3-ols ((+)-catechin, (-)-epicatechin and (-)-epigallocatechin)), oligomer (procyanidin B2), stilbene (resveratrol) and organic acids (tartaric, malic, and citric acids) sugars (glucose and fructose)	Ultra-high-performance liquid chromatography	[56]
Saturated fatty acids (stearic acid, palmitic acid, lignoceric acid), oleanolic acid, and uvaol	Liquid chromatography with mass spectrometry	[49]
Phenolic acids (mainly pyrogallol, catechin, protocatechuic acid, benzoic acid, p-hydroxybenzoic acid, chlorogenic acid, salicylic acid, catechol, and caffeine), flavonoids (mainly hesperidin, rutin, and quercitrin)	High-performance liquid chromatography with diode array detector	[63]
Malvidin-3-O-glucoside, malvidin-3-O-(6-O-acetyl)-glucoside, malvidin-3-O-(trans-6-O-coumaryl)-glucoside, delphinidin-3-O-glucoside, cyanidin-3-O-glucoside, peonidin-3-O-glucoside, peonidin-3-O-(6-O-acetyl)-glucoside, petunidin-3-O-glucoside	High-performance liquid chromatography, tandem mass spectrometry	[70]

equivalents per gram of dry weight, respectively [40,41]. Furthermore, ultra-performance liquid chromatography coupled with tandem mass spectrometry enabled the identification of several key phenolic and flavonoid constituents in the fruits, including trans-4-hydroxycinnamic acid methyl ester, pelargonidin 3-O-glucoside, quercetin-3-O-glucoside,

and cyanidin 3-O-glucoside, all of which contribute to the plant's antioxidant capacity [40,42]. Among these, quercetin-3-O-glucoside has demonstrated inhibitory activity against glutamine synthetase and possesses antimycobacterial properties, indicating its potential as a lead compound for anti-tuberculosis drug development [43]. Cyanidin

Table 5: Chemical composition of *Vitis vinifera* stem.

Chemical composition	Extraction method	References
Potassium, calcium, magnesium, sodium, and phenolic compounds.	Flame atomic absorption spectrometry	[6]
Hydroxybenzoic acid (gallic acid, syringic acid, and caftaric acid), stilbenes (ϵ -viniferine), flavonols (procyanidin (+)-catechin, procyanidin B2, (-)-epicatechin, (-)-epigallocatechin gallate, (-)-epicatechin gallate, naringin, quercetin-3-galactoside, quercetin-3-glucoside, myricetin, and astilbine), OH-tyrosol	Ultra-high-performance liquid chromatography	[106]
Content of total phenols (94.71–123.09 mg gallic acid/g dry weight) and individual phenols (02–73.79 mg quercetin/g dry weight)	Folin-Ciocalteu colorimetric method	[59]
Polyphenols (caftaric acid, malvidin-3-O-glucoside, quercetin-3-O-glucuronide, mailvidin3-O-(6-O-caffeoyl)-glucoside and Σ -viniferine)	Ultra-high-performance liquid chromatography with electrospray ionization tandem mass spectrometry	[62]
Phenolic compounds (gallic acid 0.44 ± 0.02 – 2.03 ± 0.08 mg/g dry weight)	Folin-Ciocalteu colorimetric method	[59]
Total phenolic content (181 ± 12 mg gallic acid/g dry weight)	According to Singleton and Rossi	[9]
Phenolic acids (gallic acid)	High-performance liquid chromatography	
Phenolic acids (mainly pyrogallol) and flavonoids (mainly hesperidin)	High-performance liquid chromatography with diode array detector	[63]

Table 6: Chemical composition of *Vitis vinifera* leaves.

Chemical composition	Method of extraction	References
General tannins	Vanillin hydrochloride method	[14]
General flavonoids	Folin-Ciocalteu colorimetric method	
General phenols	Aluminum chloride colorimetric method	
Polyphenols, phenolic compounds (caffeic acid, catechin, kaempferol, and quercetin), phytosterols.	Fourier transform ion cyclotron resonance mass spectrometry	[64]
Alpha-linolenic acids, linoleic acid, and palmitic acid are 42%, 25%, and 22% of the total AG, respectively.	Gas chromatography	
Ellagic acid (770 mg/kg dry weight), rutin (450 mg/kg dry weight), and phenolic content (27.5–76.0 g quercetin/kg dry weight)	Ultra-high-performance liquid chromatography with electrospray ionization tandem mass spectrometry	[65]
Potassium (2.30–6.77 g/kg dry weight), calcium, sodium and boron	Inductively coupled plasma optical emission spectroscopy using a spectrometer	

3-O-glucoside has shown promise in the prevention and treatment of neurological disorders such as cerebral ischemia, Alzheimer's disease, and Parkinson's disease [44,45], in addition to exerting protective effects on intestinal health [46] and displaying therapeutic potential in non-alcoholic fatty liver disease [47]. A comprehensive summary of these bioactive compounds and their pharmacological attributes is presented in Table 2.

V. vinifera seeds [Table 3] are characterized by a high lipid content, with linoleic acid comprising over 50% of the total fatty acids [5,48-50]. Linoleic acid, an essential omega-6 polyunsaturated fatty acid, plays a crucial role in human metabolism due to the inability of endogenous synthesis [50]. Other significant fatty acids identified in the seeds include oleic, palmitic, and stearic acids [5,50]. In addition to lipids, *V. vinifera* seeds contain substantial quantities of polyphenols, flavonoids, phenolic acids, organic acids, and catechin oligomers, all of which contribute to their antioxidant potential [5,50,51]. Owing to this composition, grape seeds are considered promising candidates for health-beneficial oil production [5].

The skins of *V. vinifera* also represent a rich source of polyphenolic compounds, particularly flavan-3-ols [Table 4]. Four monomeric flavan-3-ols – (+)-catechin, (-)-epicatechin, epigallocatechin gallate, and epicatechin gallate – along with 10 oligomeric forms (comprising three dimers, four trimers, two tetramers, and one pentamer) have been identified [52,53]. Epidemiological evidence strongly correlates increased intake of flavan-3-ols with a decreased risk of cardiometabolic diseases [54]. In addition, (+)-catechin and (-)-epicatechin exhibit significant α -glucosidase inhibitory activity, highlighting their utility in glycemic control [55]. Flavonols such as catechin, epicatechin, quercetin-3-O-glucoside, myricetin, and isorhamnetin-3-O-hexose, alongside stilbenoids such as resveratrol-3-O-glucoside, serve as key biochemical markers of grape ripening [8,13]. These compounds not only inform optimal harvest periods but also play essential roles in the antioxidant properties of grape skins. Furthermore, anthocyanins, hydroxybenzoic acids, hydroxycinnamic acids, and various organic acids contribute to the strong antioxidant activity of grape skins, primarily due to the extensive diversity of polyphenols [8,13,56]. This chemical profile holds relevance to the enological sector, where such

Table 7: *In vitro* effects of the phytochemical components of *Vitis vinifera*.

Pharmacological effect	Plant part	Form of preparation	Metabolite	Description of the activity	References
Antiadhesive	Fruit	Vacuum expansion technology	Polyphenols	Reduction in the adhesion of the pathogens <i>S. enterica</i> , <i>K. pneumoniae</i> , <i>S. aureus</i> , and <i>E. coli</i> to human colorectal adenocarcinoma cell (Caco-2) and human keratinocyte (HaCaT) monolayers through Nrf2 activation, while preserving cellular integrity	[73]
Antibacterial	Seed	Hydroalcoholic extract	Gallic acid	Antimicrobial activity with affinity to Gram-positive bacteria	[71]
	Tendrils and leaves	Ethanol extract	Flavonoids and stilbenes	Inhibited the growth of <i>Porphyromonas gingivalis</i> , fecal <i>Enterococcus</i> , <i>Streptococcus mutans</i> , and <i>Staphylococcus aureus</i> .	[105]
	Pomace	Hydromethanolic extract	Benzoic acid derivatives, dipeptides, phenols	Antibiofilm and antimicrobial activities against <i>Staphylococcus epidermidis</i> ATCC 35984 and <i>Pseudomonas aeruginosa</i> PA14	[74]
	Seed	Hydroalcoholic extract	Ellagic acid and gallotannins or quercetin	5 mg/mL MIC against multi-resistant <i>Staphylococcus aureus</i>	[51]
	Scrape or stalk	Hydroalcoholic extract	Phenolic compounds (catachine)	Antimicrobial activity against Gram-positive bacteria, especially <i>S. aureus</i> , and <i>Enterococcus faecalis</i>	[59]
Antivirus	Stem bark	Ethanol extract	Vitisin B	Inhibited influenza A virus replication by dual targeting through inhibition of neuraminidase-induced oxidative stress and suppression of virus-induced ROS production. Suppresses H1N1 viral replication in MDCK and A549 cells. Ameliorated the inflammatory response through NF- κ B downregulation, decreased ROS generation, and increased expression of Nrf2-mediated antioxidant gene as glucose-6-phosphate dehydrogenase during Influenza A virus infection.	[79]
Anticancer	Leaf	Ethanol extract	Flavan-3-ol	Decreased the proliferation of MCF-7 breast cancer cells and HepG2 hepatocarcinoma cells. In addition, the expression of the pro-apoptotic gene Bax increased, and that of the anti-apoptotic gene Bcl-2 decreased in a dose-dependent manner.	[80]
	Fruit	Methanolic extract	Oleanolic acid	IC ₅₀ =40 μ g/mL after 48 h of incubation for HCT-116 human colon adenocarcinoma cells.	[75]
	Seed	Hydroalcoholic extract	Phenols in nanocarrier formulation	Both nanoparticles and crude extracts suppressed the proliferation of B16-F10 melanoma cells.	[85]
	Seed oil	Hexane extract	Fatty acids	Cytotoxic effects on MCF-7 induced apoptosis and suppressed the growth of Ehrlich ascites carcinoma in rats. Prevented cancer cell migration by down-regulating the level of CD44+cells in EAC and competitive inhibitory effects on MMP9 and cathepsin B activities.	[83]
	Seed oil	Hexane extract	Phenols, vitamins	Cytotoxic effects on Caco-2, PC-3, NFS-60, and HepG-2 cells, with superior efficacy in HepG-2 cells.	[82]
	Seedless fruit	Hydroethanolic extract	Polyphenols	Apoptosis-mediated cytotoxicity with IC ₅₀ values between 1.0-4.2 mg/mL for HepG2 and 0.5-3.4 mg/mL for Huh7 hepatocarcinoma cell lines.	[84]
	Fruit skin	Wet pomace extract	Phenol, flavonoids and tannins	Average antioxidant capacities 2.7 g AA eq/L	[11]
Anti-inflammatory and antioxidant		Dry pomace extract	Polyphenols, flavonoids, flavanols, and tannins	Average antioxidant capacities 1.5 g AA eq/L	

(Contd...)

Table 7: (Continued).

Pharmacological effect	Plant part	Form of preparation	Metabolite	Description of the activity	References
	Fruit	Methanolic extract	Oleanolic acid	Antioxidant property with the DPPH method (IC_{50} =61.5 μ g/mL)	[75]
	Seed	Oil	Unsaponifiable fraction	Anti-inflammatory and antioxidant activity	[76]
	Seed	Aqueous extract	Phenols, fatty acids	Antioxidant activity (IC_{50} =38.60 and 42.83 μ g/mL)	[78]
	Marc	Pomace extract	Polyphenolic compound	Fresh pomace extract exhibited better antioxidant activity (IC_{50} =29.58 μ g TE/mL) than fermented pomace extracts (IC_{50} =29.06 μ g TE/mL).	[18]
	Root	Hydroethanolic extract	Polyphenols and flavonoids	Protective effects on Chang's liver cells by increasing cell viability and decreasing the production of intracellular reactive oxygen species.	[104]
	Scrape or stalk	Polyphenolic extract	Total and individual phenols	Antioxidant power 0.37–1.17 mmol Trolox g – 1	[62]
Anti-aging	Scrape or stalk	Hydroethanolic extract	Undetermined	Antiaging effect by inhibiting antityrosinase up to 54% and anti-elastase activities up to 98%	[72]
Neuroprotective	Stem bark	Ethanolic extract	Vitisin A	Viability improvement of human neuroblastoma cell line and protection of scopolamine-induced impairment of long-term potentiation in mice hippocampus.	[91]

ROS: Reactive oxygen species, MMP-9: Matrix metalloproteinase-9.

Table 8: *In vivo* effects of the phytochemical components of *Vitis vinifera*.

Pharmacological effect	Plant part	Route of administration	Form of preparation	Metabolite	Description of the activity	References
Antioxidant effect	Seed	Oral	Hydroethanolic extract	Polyphenols	Decreased lipid peroxidation in rat's muscles	[15]
	Marc	Oral	Hydroethanolic extract	Polyphenols	Improved ECG changes, cardiac markers, and oxidative stress, thus reducing oxidative stress in rats.	[77]
Cataract	Fruit powder	Oral	Freeze-dried	Polyphenols, flavonols, phenolics	Dose-dependently inhibited ultraviolet-induced cataracts and preserved glutathione pools in mice.	[93]
Cognitive disorders	Seed	Intraperitoneal	Proanthocyanidin extract	Proanthocyanidin	Changes in the behavior of the treated mice derived from anxiolytics, anticonvulsants, sedatives, and decreased core temperature.	[90]
	Seed	Intraperitoneal	Proanthocyanidin extract	Proanthocyanidin	Slowed memory impairment after convulsive status epilepticus in rats	[89]
	Stem bark	Pre-implanted cannula	Ethanolic extract	Vitisin A	Elevated spatial learning and memory function might act to slow down Alzheimer's disease progression through possible upregulation of brain-derived neurotrophic factor-cAMP response element-binding protein-calcium/calmodulin-dependent protein kinase II signaling in mice hippocampus.	[91]
Diabetes mellitus	Seed	Intragastrical	No data	Proanthocyanidins	Protective role in Type 2 diabetes mellitus in diabetic rats by inhibiting ferroptosis. Increased the expression of glutathione peroxidase 4 and cystine/glutamate antiporter, effective ferroptosis inhibitors. Improved β -cell viability through the Nrf2 pathway.	[87]

(Contd...)

Table 8: *In vivo* effects of the phytochemical components of *Vitis vinifera*.

Pharmacological effect	Plant part	Route of administration	Form of preparation	Metabolite	Description of the activity	References
Hypoglycemic	Seed	Oral	Aqueous extract	Phenols, fatty acids	Hypoglycemic effect in rats	[78]
Anticancer	Shell and Seed	Topical	Nanoparticles of gold	Polyphenols	Stimulated antioxidant enzymes within cells and suppressed abnormal cell proliferation that occurred during skin papillomagenesis in mice.	[81]
Anticancer	Seed oil		Hexane extract	Fatty acids	Suppressed cancer growth in Ehrlich ascites carcinoma-bearing mice, confirmed by reducing cancer cell count and viability. Induced apoptosis by accumulating ROS and induced oxidative stress. Prevented cancer cell migration by down-regulating the level of CD44+cells and competitive inhibitory effects on MMP9 and cathepsin B activities.	[83]
Anticancer	Seed oil	Intraperitoneal	Hexane extract	Phenols, vitamins	Reduced hepatic lipid peroxidation boosts glutathione levels due to its antiradical activities, elevating caspase-3/7 activities in the liver. Apoptotic effect by upregulating p53 and BAX and downregulating Bcl-2 fold expression in mice hepatocellular carcinoma.	[82]
Anticancer	Seedless fruit	Intraperitoneal	Hydroethanolic extract	Polyphenols	Inhibition of sustained proliferation, resistance, angiogenesis, invasion, and metastasis in p-DAB-induced hepatocellular carcinoma in mice. Modulation of the expression of several key molecules associated with hepatocellular carcinoma.	[84]
Nephroprotective	Seed and skin	Oral	Ethanolic extract	Polyphenols, selenium	Reduced renal dysfunction in OTA-induced rats by lowering lipid peroxidation indicators, lipid and kidney profiles, and enhanced enzymatic and non-enzymatic antioxidant biomarkers.	
Parkinson's disease				α -Viniferin	Parkinson's disease-related akinesia and cataleptic behavior were attenuated due to an increase in striatal dopamine. Strongly inhibited monoamine oxidase activity in mice.	
Antinociception in temporomandibular joint disorder	Seed	Oral	No data	Polyphenols	Dietary inclusion of grape seed extract maintained normal levels of GABA-producing enzymes and inhibitory Gi-coupled GABA B receptors to prevent the sustained level of nociception observed in the temporomandibular joint disorder model in rats.	[88]

MMP9: Matrix metalloproteinase-9, ROS: Reactive oxygen species, GABA: γ -aminobutyric acid, OTA: Ochratoxin A.

Table 9: Techniques used to modify the chemical composition of the fruit of *Vitis vinifera*.

Technique	Description of effects	References
Foliar application of monosilicic acid	Reduction of the levels of gluconic acid and glycerol and increase in the content of total phenols, anthocyanins, and tannins	[98]
Exogenous application of kaolin before veraison (5% w/v)	Increased berry size (up to 62.2%) reduced the skin-to-pulp weight ratio and, consequently, the anthocyanin content (up to -41.7%). Improved metabolite production secondary (up to 49.40%) and the antioxidant capacity in the seed (up to 48.29%).	[99]
Effect of the winemaking process	The prolonged post-fermentative maceration in 21 days (TM21) increased the total flavon-3-ols content by 25%. 48h fermentative maceration heating at 45°C followed by the 8-day standard maceration (TPHT) increased the content of hydroxynamic acids. TM21 and TPHT increased the concentration of hydroxybenzoic acids, in addition to a positive influence on the taste attributes.	[100]
Winemaking technique	The maceration treatment increased the concentration of flavon-3-ols and phenolic compounds, and the pre-fermentative cold maceration increased the content of phenolic compounds without accentuating the sensation of astringency and bitterness. The prolonged post-fermentative maceration affected the intensity of color and phenolic composition.	[101]
Chitosan and gelatin incorporated with the seed	The content of total phenols increased, obtaining more elastic behavior and preventing the growth of microorganisms.	[10]
Chemical elicitation with sodium selenite, aluminum sulfate, and chitosan	Increased phenolic compounds, the associated antioxidant and anticancer properties in cultured grape cells.	[17]
Variation of soil components	Contributed significantly to the amount of expression of phytochemicals and antioxidants.	[2]
Improvement in grape maturity with reflective mulch treatment	Enhanced accumulation of total phenols, total tannins, and total anthocyanins in grape skin. This led to elevated levels of phenolic compounds in wines and heightened color intensity. Consistently increased total flavan-3-ols.	[66]

metabolites significantly influence fermentation dynamics and final product quality [49].

In addition to polyphenolic compounds, the fruit of *V. vinifera* contains triterpenic acids with significant pharmacological potential, particularly oleanolic acid. This compound exhibits a broad spectrum of bioactivities, including antidiabetic, antitumor, anti-inflammatory, antibiotic, and antiviral effects. Notably elevated levels of oleanolic acid have been identified in specific grape cultivars, such as Aglianico [57]. Regarding the terpenoid profile, substantial enantiomeric excesses in volatile compounds have been observed in Moscato Giallo grapes and wines, suggesting biosynthetic pathway specificity within *V. vinifera*. These findings represent the first reported investigation into the chiral characteristics of grape-derived terpenoids [58].

The stems (or stalks) of *V. vinifera* [Table 5] are particularly rich in phenolic compounds, with gallic acid emerging as the most abundant [9,59]. Gallic acid has demonstrated therapeutic potential for a variety of oxidative stress-related diseases, including cancer, cardiovascular and neurodegenerative disorders, and metabolic syndromes. Its anti-inflammatory properties are mediated primarily through modulation of the mitogen-activated protein kinases and nuclear factor- κ B (NF- κ B) signaling pathways, resulting in reduced expression of pro-inflammatory cytokines, chemokines, adhesion molecules, and immune cell infiltration [60,61]. Additional phenolic compounds identified in grape stems include caftaric acid, malvidin-3-O-glucoside, quercetin-3-O-glucuronide, malvidin-3-O-(6-O-caffeoyl)-glucoside, and Σ -viniferin [62]. The flavonoid profile includes (+)-catechin, procyanidin, procyanidin B2, (-)-epicatechin, (-)-epigallocatechin gallate, (-)-epicatechin gallate, naringin, quercetin-3-galactoside, quercetin-3-glucoside, myricetin, astilbin, and apigenin. Hydroxycinnamic acid derivatives such as syringic and caftaric acids, along with hydroxytyrosol, further contribute to the antioxidant capacity of grape stems [3,63]. In addition, stems

are a source of essential minerals, including potassium, calcium, magnesium, and sodium [6]. These attributes support the potential repurposing of grape stems as sustainable and economically viable sources of bioactive compounds for pharmaceutical, nutraceutical, and functional food applications [3,9].

The leaves of *V. vinifera* [Table 6] also present a rich phytochemical profile, containing substantial quantities of tannins, flavonoids, and total phenolic compounds [14]. Identified constituents include caffeic acid, catechin, kaempferol, quercetin, rutin, ellagic acid, and phytosterols [64,65]. The high antioxidant activity of grape leaves is attributed to these compounds [64]. Fatty acid profiling revealed alpha-linolenic acid as the predominant species (42%), followed by linoleic (25%) and palmitic (22%) acids. Leaves also contain relevant mineral elements such as calcium, sodium, boron, and potassium [65]. These findings underscore the utility of grape leaves as an affordable source of functional ingredients with applications in the food and pharmaceutical industries [14,64,65].

Despite the broad chemical characterization of grape tissues, it is well-established that both environmental and anthropogenic factors significantly influence the qualitative and quantitative expression of phytochemicals. For instance, reduced sun exposure leads to diminished phenolic content, whereas the use of silver reflective mulch enhances their accumulation [66]. Similarly, the application of plant hormones such as methyl jasmonate has been shown to elevate secondary metabolite production [67]. The developmental stage also plays a crucial role, as demonstrated in Suo Suo grapevines, where the maximal concentrations of cyanidin-3-O-glucoside, fructose, tartaric acid, and oleanolic acid were recorded between the 105th and 135th day of growth [68].

Moreover, the phenolic content varies between free and bound forms. In the Corinthian grape variety, bound phenolics were predominant, with p-hydroxybenzoic acid as the principal aglycone, while

caftaric acid and miquelanol represented the main free phenolic compounds [69]. Moreover, genetic background and mutations further contribute to the phenolic diversity in grapes. An investigation encompassing 27 clones from eight cultivars across two growing seasons examined 24 polyphenolic compounds along with the physicochemical properties of the grapes and resultant wines. The study revealed significant inter- and intra-varietal variation. Orthogonal partial least squares discriminant analysis identified malvidin-3-O-glucoside, peonidin-3-O-glucoside, and epicatechin as key biomarkers for distinguishing grape and wine samples [70].

3.3. Pharmacological Activities

Table 7 presents a summary of the *in vitro* bioactivities of phytochemical constituents derived from *V. vinifera*. Among these, ellagic acid, gallotannins, and quercetin have demonstrated notable antibacterial activity, primarily through the inhibition of bacterial DNA gyrase, thereby disrupting DNA replication processes [51,71]. Gallic acid exerts its antimicrobial effects through the chelation of divalent metal cations and by promoting the permeabilization and structural disintegration of the outer membrane in *Salmonella* species [71].

Overall, *V. vinifera* phytochemicals display greater antibacterial efficacy against Gram-positive bacteria compared to Gram-negative species. This differential activity is attributed to the complex outer membrane of Gram-negative bacteria, which contains lipopolysaccharides (LPSs) that form a robust, hydrophilic barrier limiting the diffusion of antimicrobial agents. In contrast, the simpler peptidoglycan-rich membrane of Gram-positive bacteria permits easier penetration of lipophilic compounds. Furthermore, Gram-negative bacteria possess multiple efflux pump systems that actively expel antimicrobial molecules, thereby reducing their intracellular accumulation and effectiveness [71,72].

In addition to their bactericidal properties, polyphenol-rich grape extracts have been shown to significantly inhibit the adhesion of key pathogenic bacteria – including *Salmonella enterica*, *Klebsiella pneumoniae*, *Staphylococcus aureus*, and *Escherichia coli* – to human epithelial cell lines (Caco-2 and HaCaT), while preserving host cell integrity. These extracts selectively impede the adhesion of pathogenic species while promoting colonization by commensal microorganisms, thereby contributing to microbial homeostasis at mucosal surfaces. Furthermore, the extracts mitigate oxidative stress, reinforce epithelial barrier function, and downregulate pro-inflammatory cytokines such as IL-6 and IL-8 in LPS-stimulated cells. These cytoprotective effects are mediated predominantly through the activation of the Nrf2 signaling pathway [73].

Further evidence of the antimicrobial potential of grape by-products was provided by a study examining the effects of grape residue extracts on *Staphylococcus epidermidis* ATCC 35984 and *Pseudomonas aeruginosa* PA14. Hydromethanolic grape pomace extract – obtained through ultrasound-assisted extraction with 80% methanol – exhibited the highest antibiofilm efficacy, inhibiting biofilm formation by 99% in *S. epidermidis* and 80% in *P. aeruginosa*. This extract also disrupted existing Gram-negative bacterial biofilms, enhanced swarming motility, and induced marked morphological alterations in bacterial cells. Toxicological evaluation using the *Caenorhabditis elegans* model demonstrated the extract's safety profile, with no observed acute or chronic toxicity, underscoring its potential as a safe and effective antimicrobial agent [74].

The antioxidant capacity of *V. vinifera* has been extensively evaluated using established *in vitro* assays. These include the ABTS^{•+} radical

cation decolorization assay and the DPPH free radical scavenging method, both of which demonstrated a strong positive correlation between antioxidant activity and the total phenolic, flavonoid, and tannin content of the fruit [11,18,62]. Oleic acid, a key fatty acid present in *V. vinifera*, has also been reported to exhibit significant free radical scavenging activity, contributing to its antioxidant potential [75]. In addition, the unsaponifiable fraction of *V. vinifera* seed oil has demonstrated both antioxidant and anti-inflammatory properties. This bioactivity is mediated through the modulation of monocyte plasticity, favoring the anti-inflammatory CD14⁺CD16⁺ phenotype and suppressing pro-inflammatory responses by downregulating the expression and secretion of tumor necrosis factor- α , interleukin (IL)-1 β , and IL-6 in human primary monocytes [76].

In vivo investigations [Table 8] corroborate the antioxidant potential of *V. vinifera*, demonstrating reductions in lipid peroxidation within muscle tissue [15] and improvements in oxidative stress markers, including cardiac parameters [77]. Although the specific bioactive molecules responsible for these effects remain unidentified, the antioxidant activity of the extracts is directly proportional to their polyphenolic concentration [15,77]. Further *in vitro* assays performed on seed extracts from Muscat and Quebranta grape varieties demonstrated significant antioxidant capacity, as evidenced by DPPH radical scavenging (IC₅₀ values of 38.60 $\pm$ 0.624 μ g/mL and 42.83 $\pm$ 0.306 μ g/mL, respectively) and ferric reducing antioxidant power assays (0.79 $\pm$ 0.030 μ g Trolox equivalent [TE]/g and 0.61 $\pm$ 0.038 μ g TE/g, respectively). Notably, these extracts also exhibited hypoglycemic activity in an alloxan-induced hyperglycemia model in *Rattus norvegicus*, with oral administration of 500 mg/kg of biophenol and polyunsaturated fatty acid-rich extracts, significantly reducing blood glucose levels [78].

The antiviral activity of *V. vinifera* phytochemicals has also been documented. Vitisin B, a pyranoanthocyanin compound, was shown to inhibit neuraminidase activity and suppress H1N1 influenza virus replication in MDCK and A549 cell lines. Mechanistically, vitisin B mitigates virus-induced ROS generation by upregulating glucose-6-phosphate dehydrogenase expression and Nrf2 pathway activation while concurrently inhibiting NF- κ B nuclear translocation through I κ B kinase dephosphorylation. In *in vivo* models, vitisin B attenuated body weight loss, reduced viral titers, and diminished lung inflammation, thereby enhancing survival in influenza A-infected mice [79].

The anticancer potential of *V. vinifera* has been validated through both *in vitro* and *in vivo* models. *In vitro* analyses [Table 7] indicate that extracts from various plant parts can induce apoptosis through intrinsic (mitochondria-dependent) and extrinsic (death receptor-mediated) pathways. Central to the intrinsic pathway is the Bax/Bcl-2 ratio, with increased Bax expression and decreased Bcl-2 levels promoting apoptotic progression. Ethanolic leaf extracts reduced Bcl-2 expression and increased Bax levels in breast and hepatocarcinoma cell lines, likely due to polyphenolic constituents, particularly flavan-3-ols, with high antioxidant activity [80]. Similarly, methanolic grape extracts exhibited pro-apoptotic effects against human colon adenocarcinoma cells, with oleonic acid identified as the principal active compound [75].

In *in vivo* models [Table 8], anticancer activity was demonstrated using gold nanoparticles synthesized from grape peel and seed extracts, which inhibited tumor cell proliferation during papilloma genesis. Although the specific active constituents were not identified, the chemopreventive effect was attributed to the antioxidant capacity of grape polyphenols [81]. Furthermore, the saponifiable fraction

of black grape seed oil exhibited potent cytotoxic activity against Caco-2, PC-3, NFS-60, and especially HepG-2 cells, as well as in a p-dimethylaminoazobenzene-induced hepatocellular carcinoma (HCC) mouse model, outperforming the chemotherapeutic agent 5-fluorouracil (5-FU). The observed effects were associated with the phenolic, fatty acid, and vitamin content of the extract, which contributed to its antioxidant, apoptotic, anti-inflammatory, anti-metastatic, and anti-hypoxic properties. In addition, this fraction competitively inhibited several oncogenic targets, including NBD-NOX2, HDAC1-MTA1, and SepR [82].

Moreover, the saponifiable fractions from both black and green grapes demonstrated superior cytotoxic activity against MCF-7 breast cancer cells and Ehrlich ascites carcinoma cells compared to 5-FU. These effects were associated with the induction of oxidative stress in cancer cells and were independent of AMP-activated protein kinase signaling. In addition, these extracts inhibited cancer cell migration through the downregulation of CD44+ cells and proposed competitive inhibition of matrix metalloproteinase-9 and cathepsin B activities [83].

Further *in vitro* studies with polyphenolic fractions from *V. vinifera* (VVF1, VVF2, and VVF3) revealed significant anticancer activity against HepG2 and Huh7 HCC cell lines, with efficacy surpassing that of 5-FU. These fractions displayed cytotoxicity within safe therapeutic margins and effectively eliminated CD133+ cancer stem cell (CSC) populations, indicating a potential anti-CSC mechanism. In a p-DAB-induced HCC mouse model, VVF1 and VVF2 targeted key hallmarks of CSC-mediated tumor progression – including sustained proliferation, therapeutic resistance, angiogenesis, invasion, and metastasis – through the modulation of apoptosis, inflammation, drug resistance, hypoxia, epithelial-mesenchymal transition, and extracellular matrix degradation pathways. Among the three, VVF1 exhibited the most potent anticancer effects. These outcomes were attributed to synergistic interactions among phenolic constituents, which also exerted inhibitory activity against oncogenic enzymes such as NADPH-NOX2, HDAC1-MTA1, and SepR, validating their potential as therapeutic targets in HCC [84].

Recent studies have identified novel bioactivities associated with *V. vinifera* by-products. For the first time, anti-tyrosinase activity was reported in wet pomace extracts [Table 7] [11]. Similarly, the hydroethanolic extract of grape stems exhibited an anti-aging effect through the inhibition of both tyrosinase and elastase enzymes [Table 8] [59]. Although the specific compounds responsible for these effects have yet to be fully characterized, known tyrosinase inhibitors such as quercetin and gallic acid are likely contributors [11]. In addition, the antiproliferative efficacy of grape extracts was significantly enhanced through nanoencapsulation techniques. Notably, nanoencapsulated grape extracts (NEGEs) derived from Marselan and Obeidi varieties markedly suppressed the proliferation of B16–F10 melanoma cells, with the Obeidi-derived NEGEs exhibiting the strongest activity [85].

The nephroprotective properties of *V. vinifera* have also been substantiated in experimental models. Co-administration of 2% grape seed extract (GSE) and selenium (1:1 ratio) significantly mitigated ochratoxin A (OTA)-induced renal damage in rats. This combination reduced lipid peroxidation and improved enzymatic and non-enzymatic antioxidant defenses. The most robust protective effect was observed with the GSE 2% + selenium combination, followed by GSE 2% alone and selenium alone (0.4 mg/kg). Histopathological analyses supported these findings, revealing severe renal tubular degeneration in OTA-treated rats, while those treated with GSE and grape peel

extract displayed only mild renal alterations. The GSE 2% + selenium group exhibited nearly normal kidney histology, underscoring the combination's superior protective efficacy [86].

Grape-derived compounds have also shown promise in managing metabolic disorders. Grape seed proanthocyanidin extract (GSPE) demonstrated a protective role in T2DM by inhibiting ferroptosis in pancreatic β -cells. GSPE treatment enhanced the expression of glutathione peroxidase 4 and cystine/glutamate antiporter, key regulators of ferroptosis. Both *in vitro* and *in vivo* studies confirmed that GSPE attenuated ferroptosis and improved β -cell viability through activation of the Nrf2 signaling pathway [87].

In the context of nociception, dietary supplementation with GSE preserved normal levels of γ -aminobutyric acid (GABA)-synthesizing enzymes and Gi-coupled GABA B receptors in a rat model of temporomandibular disorder (TMD). This preservation effectively prevented the development of prolonged nociceptive responses following sustained jaw opening. These findings suggest that GSE supplementation may reduce the risk of chronic TMD in susceptible individuals [88].

The neuroprotective and cognitive benefits of *V. vinifera* have also been investigated. Proanthocyanidin extracts administered intraperitoneally in mice demonstrated anxiolytic, anticonvulsant, and sedative effects and ameliorated memory deficits following status epilepticus [Table 8] [89]. While the precise mechanisms remain unclear, these effects may be mediated through enhanced synaptic transmission in the hippocampus and inhibition of beta-amyloid oligomer aggregation [89,90]. In addition, vitisin A, a resveratrol tetramer, exhibited neuroprotective properties when centrally administered, promoting synaptic plasticity and neuronal viability while restoring memory and cognitive function in scopolamine-treated mice. These effects are partially attributed to the upregulation of brain-derived neurotrophic factor, cAMP response element-binding protein, and calcium/calmodulin-dependent protein kinase II signaling pathways [91]. Another resveratrol derivative, α -viniferin, a trimer, significantly inhibited monoamine oxidase, thereby elevating striatal dopamine levels and enhancing behavioral performance in mice, suggesting its potential for neurodegenerative disease therapy [92].

Ophthalmological benefits have also been observed. A diet enriched with grape powder (GP) effectively suppressed ultraviolet (UV)-induced cataractogenesis in a dose-dependent manner and maintained intraocular glutathione levels. Notably, GP-fed groups did not exhibit UV-induced Nrf2 activation, implying that GP promotes redox homeostasis independently of this pathway. Proteomic analysis identified 471 proteins modulated by GP intake, with the X-linked inhibitor of apoptosis protein (XIAP) emerging as a key molecular target. Bioactive compounds such as resveratrol, catechin, quercetin, and anthocyanins were found to interact with XIAP. Experimental validation confirmed that GP prevented UV-induced XIAP suppression, thereby implicating XIAP in the molecular mechanism underlying GP's protective effect against cataract formation [93].

Recent clinical studies have provided evidence supporting the therapeutic efficacy of *V. vinifera*-derived products in the management of various pathological conditions and symptomatic relief. Notably, Cognigrape®, a dietary supplement formulated from grape extract, demonstrated significant cognitive benefits in healthy older adults. Participants receiving Cognigrape® showed marked improvements in Mini-Mental State Examination scores relative to both baseline and placebo controls. Furthermore, reductions of 15.8% and 24.9% were

observed in the Beck Depression Inventory and Hamilton Anxiety Rating Scale scores, respectively. The Repeatable Battery for the Assessment of Neuropsychological Status total score also significantly increased following supplementation. Compared to the placebo group, Cognigrape® administration was associated with improved performance in attention, language, and both immediate and delayed memory domains, while visuospatial/constructional abilities remained unchanged. No adverse events were reported during the intervention, indicating a favorable safety profile [94].

In vascular health, a randomized non-inferiority clinical trial evaluated the effects of *V. vinifera* seed extract compared to micronized purified flavonoid fraction (MPFF) in patients with chronic venous disease. A total of 303 participants were randomly assigned to receive either *V. vinifera* seed extract (n = 154) or MPFF (n = 149) over 8 weeks. Both groups exhibited statistically significant improvements in Chronic Venous Insufficiency Questionnaire 20 scores from baseline, with no significant difference between the two treatments. The lower bound of the confidence interval for the difference in mean score reduction remained within the predefined non-inferiority margin of 6.9, confirming the non-inferiority of the GSE. Additional clinical outcomes, including scores on the Aberdeen Varicose Vein Questionnaire, Visual Analog Scale, and Venous Clinical Severity Score, improved significantly in both groups at weeks 4 and 8. Importantly, patients receiving *V. vinifera* seed extract exhibited a significant reduction in calf circumference by week 8, further supporting its efficacy [95].

In addition, the potential genoprotective effect of red grape juice was assessed in a controlled study involving 20 healthy adults (10 males and 10 females), randomized into a grape juice group and a control group receiving water. Participants in the treatment group consumed a single 250 mL dose of additive-free commercial red grape juice. Analysis revealed a statistically significant reduction in DNA damage among individuals who consumed grape juice compared to the control group. These findings suggest that even a single dose of red grape juice may confer short-term protection against oxidative stress-induced genotoxicity [96].

3.4. Techniques Used to Modify the Chemical Composition of *V. vinifera*

One of the principal consequences of global climate change is the acceleration of vegetative and reproductive phases in grapevines. Elevated temperatures pose a significant threat to grape berry development by inducing heat stress, which may compromise both the compositional integrity and the medicinal and commercial value of grapes. Climate-driven alterations extend beyond primary metabolites – such as organic acids (notably malic acid), sugars, and amino acids – to secondary metabolites, including flavonoids and aroma precursors. Multi-omics approaches (transcriptomic, proteomic, and metabolomic analyses) have elucidated these complex shifts in grape biochemical profiles under thermal stress conditions [97].

To mitigate the adverse impacts of climate change and enhance the accumulation of desirable compounds, various agronomic and enological strategies have been developed. These include hormonal treatments, soil amendment practices, the incorporation of bioactive compounds, and targeted interventions during both pre- and post-fermentation maceration stages. For instance, foliar application of monosilicic acid during grape ripening resulted in wines with reduced levels of acetic acid, acetaldehyde, ethyl acetate, and diacetyl while simultaneously increasing the concentrations of total phenolics, anthocyanins, and tannins – compounds typically diminished in wines derived from *Botrytis cinerea*-affected grapes [98].

Soil composition has also emerged as a critical determinant of phenolic compound accumulation. Soils with low water-holding capacity are associated with reduced foliar phenolic content, while environmental stressors such as cold exposure, water deficits, and temperature variability have been shown to decrease overall phenolic concentrations in grapevines [2]. Nonetheless, the exogenous application of kaolin before veraison significantly improved berry quality by enhancing berry size, secondary metabolite levels, and seed antioxidant activity, suggesting its potential as an adaptive strategy under climate stress conditions [99]. Furthermore, combining chitosan and gelatin with GSE augmented its antioxidant capacity by increasing total phenol content, improving elasticity, and inhibiting microbial proliferation [10].

Winemaking techniques also exert a substantial influence on the final phenolic profile and organoleptic properties of wine. Interventions such as maceration and exogenous tannin addition have been shown to modify phenolic composition, color characteristics, and the macro- and micro-elemental profile of wines [100,101]. Specifically, pre-fermentative heating in combination with maceration significantly enhanced antioxidant capacity, while extended post-fermentative maceration (21 days) elevated the levels of hydroxybenzoic acids, flavan-3-ols, and macro-elements [102]. Cold pre-fermentative maceration selectively increased phenolic content without exacerbating astringency or bitterness, whereas prolonged post-fermentative maceration was more influential in modulating color intensity and the broader phenolic spectrum, underscoring the importance of tailoring winemaking strategies to desired outcomes [103].

In addition, the implementation of silver reflective mulch has consistently improved grape maturity by enhancing the accumulation of total phenols, tannins, and anthocyanins in grape skins. This technique contributes to elevated phenolic content in the resulting wines and enhances color expression, thus representing another viable method for quality preservation in the face of climatic variability [66].

4. CONCLUSION

A recent systematic review highlights the extensive traditional use of *V. vinifera* for its analgesic and anti-inflammatory properties. Phenolic compounds constitute the primary class of phytochemicals in *V. vinifera* and are largely responsible for its diverse pharmacological activities demonstrated in both *in vitro* and *in vivo* studies, including antibacterial, anticancer, anti-inflammatory, antioxidant, and neuroprotective effects. To enhance the biosynthesis and accumulation of these bioactive compounds – particularly in the context of climate change-induced stressors – multiple agronomic and technological interventions have been developed. These include the application of hormonal elicitors, soil composition modifications, incorporation of specific exogenous substances, and strategic treatments during pre- and post-fermentation maceration phases. Collectively, these approaches aim to optimize phytochemical yields and preserve the medicinal and commercial value of *V. vinifera* under increasingly variable environmental conditions.

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6. AUTHORS' CONTRIBUTIONS

All authors made substantial contributions to the conception and design, acquisition of data, or analysis and interpretation of data;

took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agreed to be accountable for all aspects of the work. All the authors are eligible to be an authors as per the International Committee of Medical Journal Editors (ICMJE) requirements/guidelines.

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All the data are available with the authors and shall be provided upon request.

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