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Phytochemical Compounds and Pharmacological Activities of *Vitis vinifera* L.: An Updated Review

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Abstract: Grapes (*Vitis vinifera* L.) are commonly known grape species that belong to the Vitis genus in the Vitaceae family and come from western Asia and southern Europe. This review consists of traditional uses, phytochemical compounds, nutritional constituents, pharmacological activities, genotoxicological studies, and toxicity studies of *V. vinifera*. The data were obtained from scientific databases and search engines such as PubMed, Elsevier, Springer, Frontiers, Google Scholar, Scopus, Science Direct, and MDPI. In some countries, grapes used for traditional uses, such as drug therapy for blood-forming, anemia, allergies, wound care, colds and flu, carminative, bronchitis, diarrhea, and anti-phlegm. The main phytochemical compounds in *V. vinifera* are phenolic compounds, aromatic acids, flavonoids, proanthocyanidins, and stilbenoids. Nutritional constituents can be found in grapevines, i.e., proteins, lipids, carbohydrates, minerals, and vitamins. Parts of the grapevines had a wide variety of biological activities, i.e., antioxidant, antiviral, antiplatelet, antifungal, anticataract, antiobesity, anticholinergic, anti-sunburn, anti-inflammatory, and wound-healing activities. The phytochemical compounds content in each part of the grapevines were different. Each pharmacological activity depends on the grapevine's phytochemical compounds, components used, and extraction type. However, more studies are needed regarding the genotoxicity and toxicity of *V. vinifera*.

Keywords: *Vitis vinifera;* phytochemical compounds; pharmacological activities; traditional uses.

1. Introduction

Vitis vinifera L. is a common grape species that belongs to the Vitis genus in the Vitaceae family. *V. vinifera* has seedless and non-seedless varieties, and they are red, black, and white. *V. vinifera* species are easier to find because they dominate any other species by 90% [1]. Grapes originate from western Asia and southern Europe [2]. Grapes are one of the largest commodities in agriculture. Therefore viticulture or grapes farming is one of the best forms of agriculture. There are about 10,000 varieties of grapes in the world. Different countries produce grapes in various forms. Countries that focus on growing fresh grapes are China, India, Iran, Egypt, Turkey, Brazil, and Mexico. In contrast, most wines are produced in Germany, France, Italy, Canada, the USA, and New Zealand. Raisin production is also quite popular with several countries such as Iran, Turkey, India, and the USA. China owns the most extensive agricultural land with over 750,000 hectares. Annual wine production can reach 77.44 million metric tons. The most considerable use of grapes is allocated for wine production, which requires 50-75%, followed by fresh fruits, dried fruits, and juice [1].

Various kinds of phytochemicals compounds can be found at the root, stem, cane, leaf, seed, fruit, pomace, and skin. The significant compounds found are phenolic compounds, aromatic acids, flavonoids, proanthocyanidins, and stilbenoids [3–5]. Apart from bioactive compounds, nutritional constituents are also found in grapes, such as minerals, proteins, carbohydrates, vitamin C, fibers, and sugar [6–8].

In Pakistan, Italy, and Turkey, grapes are showed as traditional uses, such as drug therapy for laxatives, carminatives, colds and flu, anemia, wound-care, allergies, and bronchitis [9–13]. Many researchers have proven that the bioactive compounds found in grapes had some pharmacological activities, such as antioxidant, antidiabetic, anticancer, antibacterial, antifungal, anti-inflammatory, anti-acne, anti-aging, antihypertensive, protective effect, anti-asthma, antiplatelet, antiviral, anticataract, antiobesity, anticholinergic, anti-sunburn, anti-hyperpigmentation, and wound-healing activities.

2. Materials and Methods

This article's data were obtained through search engines and scientific databases such as PubMed, Elsevier, Springer, Frontiers, Google Scholar, Scopus, Science Direct, and MDPI. The keywords used were as follows: *V. vinifera*, pharmacological effects of *V. vinifera*, antidiabetic, antioxidant, anti-aging, anti-cataract, ethnomedicinal of *V. vinifera*, the genotoxicity of *V. vinifera*, nutritional of *V. vinifera*, antispasmodic, the spasmolytic effect of grapes, phytochemicals of *V. vinifera*, anti-virus of *V. vinifera*, the toxicological study of *V. vinifera*, wound-healing of *V. vinifera*, antihypertension, and antiplatelet. The articles used in this review are articles published in the last ten years, at least 20 articles published in the previous two years. The report also has a digital object identifier (DOI).

3. Results and Discussion

3.1. Traditional uses of V. vinifera.

Various regions in Turkey, such as Malatya, Elazığ, and Manisa, use grapes as ethnomedicinal plants [9,10,12]. In the Malatya region, the grapes were beneficial in blood-forming [9], while in the Elazığ area, the grapes were beneficial for anemia [10]. For the people in Manisa, grape parts starting from seeds, branches, fruit, dried fruit, leaves, and latex can help treat allergies, wound care, anemia, cold and flu, carminatives, and bronchitis [12].

In Pakistan, grapes (*V. vinifera* L.) are widely used as traditional medicine. In the Northwest region of Pakistan, the grapes are consumed as carminatives [14]. Sudhanoti district (Pakistan), the leaves and whole grapes can be used as a blood purifier, anti-phlegm, and quench thirst [11].

Tuscany and Bologna are areas in Italy that use wine and alcoholic beverages from *V. vinifera* L. to treat diseases related to the digestive system [13]. Wine, vinegar, and spirit from *V. vinifera* L. are used as liniment, poultice, and mouthwash in the Republic of Cyprus [15].

V. vinifera L. are commonly used to treat diarrhea, varicose veins, bleeding, antiseptic, inflammatory, demulcent, diuretic, stomachic, and laxative [16]. According to research by Beni *et al.* (2013), raw grapes can be processed into edible products such as grape syrup [17].

3.2. Phytochemical compounds of V. vinifera.

Phytochemical compounds are various bioactive compounds found in these plants' parts and are beneficial to humans. *V. vinifera* L. contains many phenolic compounds and aromatic acid on multiple parts of the plant. The main blends of grapes are stilbenoid, flavonoids, proanthocyanidins [3], hydroxybenzoic acid [4], dan hydroxycinnamic acid [5]. Fruit grapes are rich in polyphenols, anthocyanins, flavonols, stilbenes, phenolic acids, protein, fats, and vitamins C [6].

Grape root extract contained stilbenoid compounds, which were stated by Esatbeyoglu *et al.* (2016): resveratrol, vitisins A and B, and picaetannol, and miyabenol C [7]. Other stilbenoid compounds in the grape root are trans-piecid, cis-piecid, vitisinol B, viniferether A, and viniferether B ampelopsin C, ampelopsin E, hopeaphenol, dan isohopeaphenol [5].

Grape leaves contain hydroxybenzoic acid (quinic acid, gallic acid, vanilic acid, and syringic acid), hydroxycinnamic acid (caftaric acid, caffeic acid, and fertaric acid), coumarin, dihydrochalcone, monomeric stilbenes, dimeric stilbenes, trimeric stilbenes, tetrameric stilbenes, flavan-3-ol compounds including gallocatechin, catechins, procyanidins, procyanidin B1, procyanidin A1, and epicatechins. The flavonol compounds were quercetin, quercetin-3-O-glucoside, kaempferol, and myricetin. Flavone (apigenin-7-O-glucoside and luteolin-7-O-glucoside), flavanone (taxifolin, naringenin, and hesperetin), anthocyanins, and coumarin (aesculin, fraxin, aesculutin, and umbelliferone) [5], condensed tannin [18], also be found in leaves.

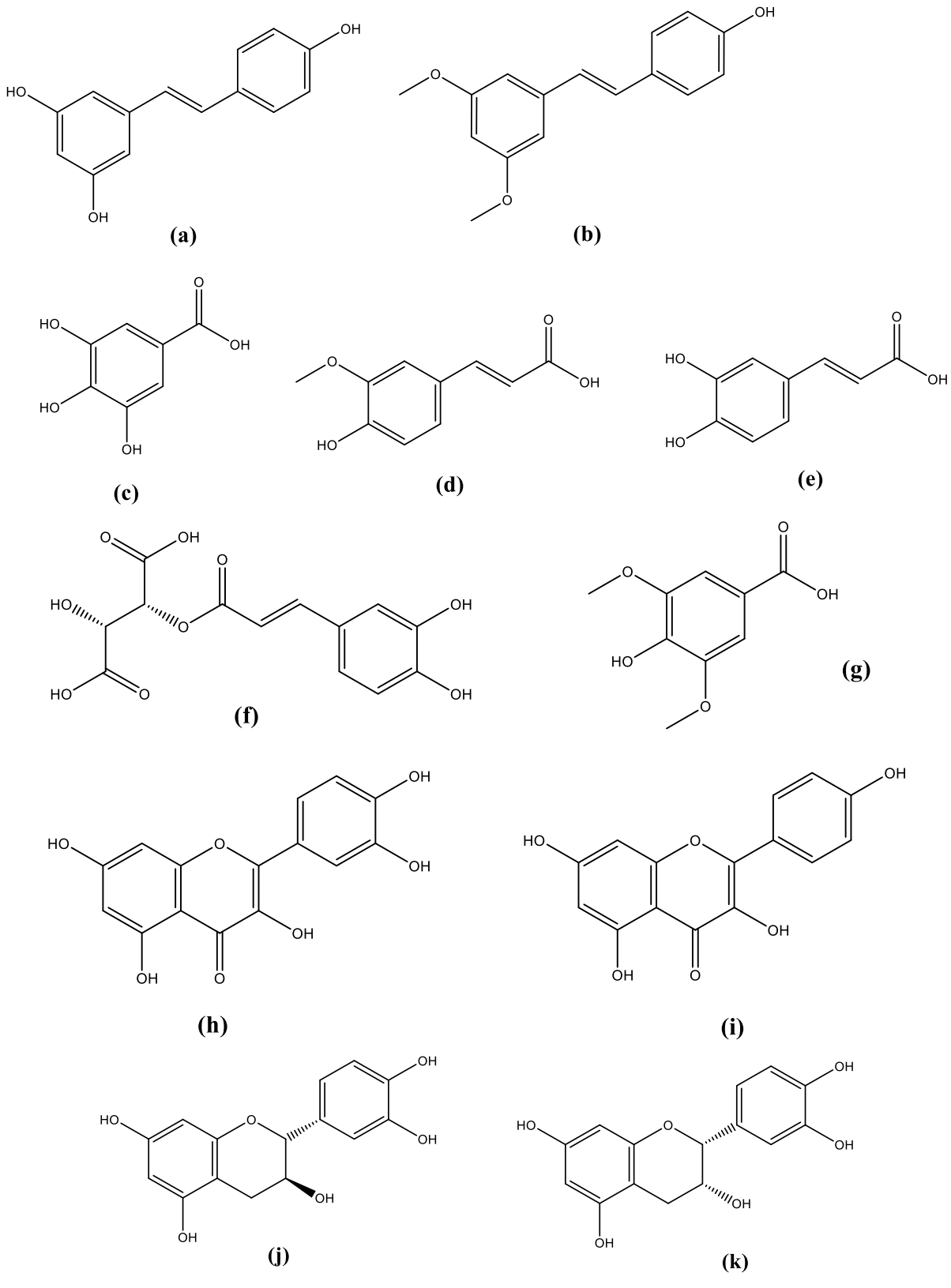
Grape seed extract contained the following: procyanidin, gallic acid, epicatechin, catechin, and quercetin [19]. The grape seed extract from white grape was analyzed by ultra-high-performance liquid chromatography-tandem mass spectrometry (UHPLC-ESI-QQQ-MS/MS) contained flavonol glycosides [20]. In black, the grape seed was exposed to flavonol glycosides, resveratrol, and anthocyanidins [20,21]. Sochorova *et al*. (2020) also stated that grape seed extract contained many phenolic compounds, including caffeic acid, coumaric acid, coutaric acid, ferulic acid, and fertaric acid, routine, quercetin-3-β-D-glucoside, quercitrin, myricetin, catechin, and epicatechin [22]. Using gas chromatography-mass spectrometry (GC-MS), linoleic acid, primaric acid, caffeic acid, p-hydroxy-phenylacetic acid, and gallic acid were found in grape seed extract [23].

Grape skin contained flavonols, anthocyanins [24], flavan-3-ols, stilbenes, and phenolic acid [25]. While in the grape pomace extract of *V. vinifera* L. var. Chilean was found quercetin, vanillic acid, kaempferol, syringic acid, and gallic acid [26].

Grape juice from *V. vinifera* L. var. Sangiovese detected by liquid chromatography–high-resolution mass spectrometry (LC-HRMS) contained caffeic acid, coumaric acid, ferulic acid, caftaric acid, coutaric acid, fertaric acid, (-) epicatechin, (+) catechin, resveratrol, procyanidin, and flavonols such as quercetin, rutin, kaempferol, quercetin-3-O-glucoside, and quercetin-3-O-glucuronide [27].

Grape stem contained gallic acid, syringic acid, caftaric acid, chioric acid, gallocatechin, caffeic acid, syringic acid, ferulic acid, procyanidin B1, procyanidin A1, procyanidin C1, epicatechin, catechin, catechin gallate, anthocyanin, flavanone, flavone, and flavonol (quercetin, quercetin-3-O-glucoside, and kaempferol). Stilbenic compounds are also found in stem parts such as trans-astringin, trans-resveratrol side, ampelopsin A, D, and F, vitisin A, B, and C, and miyabenol C [5].

Grapevine canes contained gallic acid, protocatechuic acid, vanillic acid, ellagic acid, caftaric acid, coutaric acid, caffeic acid, syringic acid, ferulic acid, flavan-3-ol (procyanidin B1, procyanidin A1, procyanidin C1, procyanidin B2, catechin, and epicatechin), and flavonols including quercetin-3-O-galactoside and quercetin-3-O-arabinose. The stilbenic compound in canes includes trans-resveratrol-2-C-glucoside, trans-resveratrol, and ampelopsin A and D [5].



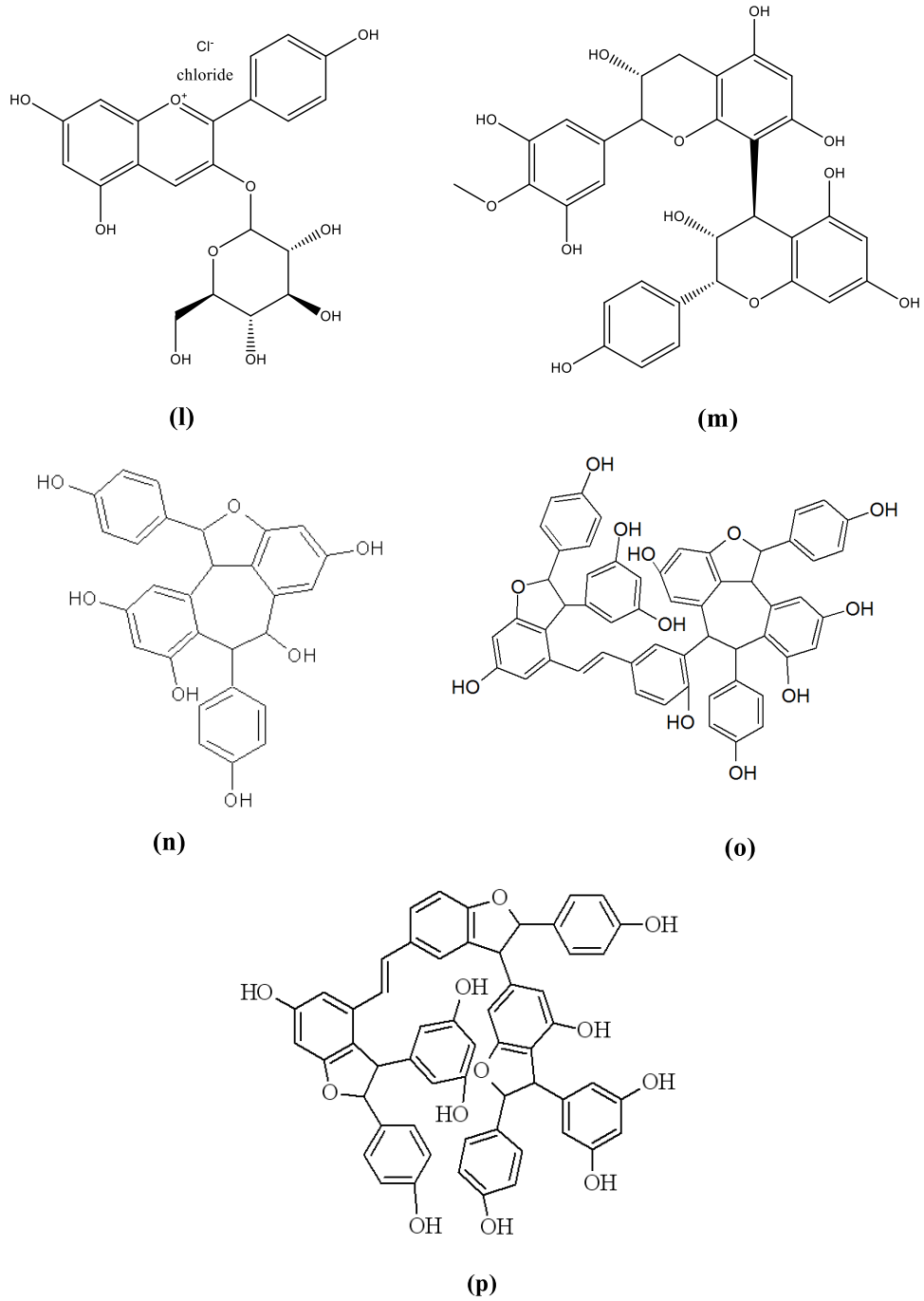


Figure 1. Several structure of phytochemicals compounds in *V. vinifera* L.they should be listed as (**a**) Resveratrol; (**b**) Pterostilbene; (**c**) Gallic acid; (**d**) Ferulic acid; (**e**) Caffeic acid; (**f**) Caftaric acid; (**g**) Syringic acid; (**h**) Quercetin; (**i**) Kaempferol; (**j**) (+) Catechin; (**k**) Epicatechin; (**l**) Anthocyanin; (**m**) Proanthocyanidin; (**n**) Ampelopsin A; (**o**) Vitisin A; (**p**) Vitisin B.

3.3. Nutritional constituent.

Various nutritional constituents were also found in grapes (*V. vinifera* L.). The nutritional content of grapes includes proteins, lipids, carbohydrates, minerals, and vitamins. Each part of the grapevines or any other grape-based product contains different nutrients.

Table 1. Parts of grapevines or product with nutritional constituents

Plant part or product used	Nutritional constituents	References
Seed	Minerals, proteins, lipids, carbohydrates, and fibers.	[7,28]

Plant part or product used	Nutritional constituents	References
Fruit	Proteins, fats, vitamin C, calcium, and boron phosphorus.	[6]
Raisins	Sugars, insoluble fibers, and minerals.	[8]
Leaves	Reducing and non-reducing sugars, lipids, vitamins, and minerals (K, Mg, Zn)	[28,29]
Stem	Dietetic fibers	[28]
Pomace	Crude proteins, neutral detergent fibers, acid detergent fibers, and minerals (P, Mg, S, Na, Fe, Al)	[30]
Pomace Flour	Proteins, fibers, carbohydrates, pection, iron, potassium, zinc, fructose, and glucose	[31]

K, Potasium; Mg, Magnesium; Zn, Zinc; P, Phosporus; S, Sulfur; Na, Sodium; Fe, Iron; Al, Aluminum.

3.4. Pharmacological activities of V. vinifera.

3.4.1. Antioxidant activity.

Grape seeds extracts were tested for their antioxidant activity using Trolox equivalent antioxidant capacity (TEAC), ferric reducing antioxidant power (FRAP), and oxygen radical absorbance capacity (ORAC) with values of 6.1 ± 0.8 mmol TE/g, 6.5 ± 0.5 mmol FE/g, and 8.6 ± 0.7 mmol TE/g [19]. Grape seeds of ten vine varieties (Laurot, Kofranka, Hibernal, Blaufrankisch, Zweigeltrebe, Erilon, Palava, Welschriesling, Cerason, and Gewürztraminer) of *V. vinifera* antioxidant activity were tested by the 2,2-diphenyl-1-picryl-hydrazyl (DPPH), FRAP, 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS), and chlorophyllin free radical (CHFR) methods. The average value of antioxidant activity in ten vine varieties in 2017 showed 11.624 µg/g GAE on the DPPH method, 14.807 µg/g GAE on the FRAP method, 6518 µg/g GAE on the ABTS method, and 3084 µg/g GAE on the CHFR form. The variety that showed antioxidant activity in each technique is Cerason [22]. Grape seeds ethanol extract had the highest antioxidant activity by testing for DPPH, FRAP, and α-tocopherol [23].

Vitis vinifera's hydroalcoholic fruit extract observed its antioxidant activity throµgh DPPH, ABTS, FRAP, and ORAC tests. The IC_{50} value of *Vitis vinifera* fruit showed 0.270 ± 0.001 mg/ml on the DPPH method, 0.040 ± 0.003 mg/ml on the ABTS method, 0.98 ± 0.01 mg/ml on the FRAP method, and 2036 ± 46 mg/ml on the ORAC method [32].

Grape skin extract of red color var. Hamburg Misketi had an antioxidant activity of 6,681.75 ± 307.34 µmol TE/100 g FW, during grape skin extract of white color var. BX1-166 is 5,602.63 ± 257.35 µmol TE/100 g FW were measured using the FRAP method [33]. The antioxidant activity of grape skin extract from *V. vinifera* L. var. Blaufränkisch and Merlot were estimated using the DPPH method. Blaufränkisch has the most extensive DPPH radical scavenging activity, which was 57.06 ± 0.08% obtained after defoliation treatment before the veraison phase Merlot was 57.50 ± 0.63, which brought after defoliation treatment before blooming [34].

The antioxidant activity of grape pulp extract white and red color (*V. vinifera*) was measured using the FRAP method. Antioxidant activity with the FRAP method for white color var. 130/1 seedless of 153.80 ± 19.28 µmol TE/100 g FW, white color non-seedless var. BX1-166 is 285.63 ± 44.35 µmol TE/100 g FW, while for red color seedless 2/B-56 it is 290.83 ±

8.55 µmol TE/100 G FW, and red color var. Hamburg Misketi (non-seedless) of 297.46 ± 45.05 µmol TE/100 g FW [33]. The antioxidant activity of pulp from seedless grape, among others, seedless red grape (California), seedless red grape (Victoria), and seedless green grape (Xinjiang) which was determined through the FRAP method in research from Liu *et al.* (2018), stated that seedless red grape (California) had FRAP values with 7.880 µmol Fe (II) / g FW > seedless red grape (Victoria) and seedless green grape [35].

3.4.2. Anti-inflammatory activity.

Leaf extract of *V. vinifera* at high doses showed vigorous anti-inflammatory activity, demonstrated by edema reduction at a dose of 400 mg/kg (50.02%) at 4 hours via carrageenan-induced hind paw edema test. Components that played an anti-inflammatory role were quercetin, kaempferol, resveratrol, and quinic acid [18]. Leaf extract of *V. vinifera* var. Fetească Neagră with high concentrations had anti-inflammatory activity by reducing inflammatory cytokines (IL-8, IL-6, IL-1β) in lipopolysaccharide-induced cells [36]. According to Balea *et al*. (2020), Grape pomace from *V. vinifera* L. var. Fetească Neagră and Pinot noir also presented anti-inflammatory activity. Compounds that played an important role as an anti-inflammatory agent were miricetol and quercitrin [37].

Cádiz-Gurrea *et al.* (2017) showed that grape seed extracts with concentrations of over 50 and 60 mg/ml showed anti-inflammatory activity by reducing mRNA expression of monosit chemoattractant protein-1 (MCP-1) in human umbilical vein endothelial cell (HUVEC) [19]. Grape root extract (20 µg/mL) was reported by Esatbeyoglu *et al*. (2016) research to have anti-inflammatory activity by lowering the Nf-kb target genes IL-1β and inducible nitric oxide synthase (iNOS) in lipopolysaccharide-induced macrophages [7].

V. vinifera var. Exalta and Albarossa showed anti-inflammatory activity by inhibiting IL-8 on TNF-α-induced released with low IC_{50}, Albarossa skin extract (IC_{50} 51.47 µg/ml and Exalta skin extract (IC_{50} 9.77 µg/ml). The anti-inflammatory activity is related to high levels of anthocyanins in Albarossa skin, flavonols in Exalta seeds, and procyanidins in both varieties [24].

In inflammatory skin disease, IL-8 is a chemokine produced by keratinocytes during the inflammation process. Aqueous leaf extract of *V. vinifera* (50 µg/ml) showed a decrease in the release of IL-8 in TNF-α (IC_{50} 2.60 µg/ml) and lipopolysaccharide (LPS) (IC_{50} 14.04 µg/ml) induced by inflammation [38].

The phenol and proanthocyanidin compounds were found in Turkish and Portuguese raisin had anti-inflammatory activity. Turkish and Portuguese raisins' hydroalcoholic extract showed an anti-inflammatory mechanism by inhibiting the release of TNFα-induced IL-8 release in human gastric epithelial cells. Turkish raisin extracts were able to inhibit the Nf-kB pathway [8].

3.4.3. Antifungal activity.

Pterostilbene contained in grape pomace and leaves have antifungal capabilities [39,40]. This was proven by testing 16 µg/ml of pterostilbene placed on poly (lactic-co-glycolic) acid nanoparticles (PLGA NP's) to reduce *C. albicans* biofilm formation by 63% and 50% reduction in mature biofilms [39].

Fraternale *et al.* (2015) stated that ethanol extract of grape (*V. vinifera* L. var. Sangiovese) tendrils has antifungal activity. The types of fungi that can against by grape

tendrils were *Botrytis cinerea*, *Alternaria solani*, *Rhizoctonia solani*, *Fusarium solani*, *F. coeruleum*, *F. sporotrichioides*, *F. culmorum*, *F. oxysporum*, *F. tabanicum*, and *F. verticillioides* [41].

Grape (*V. vinifera* L.) seeds extract had antifungal activity against *Candida albicans*, *Malassezia furfur*, and *Trichophyton mentagrophytes* [42–44]. Compound that act as anti-fungal was flavan-3-ols [43,44]. The higher extract concentration gave greater inhibition zone diameter formed against *C. albicans* [42].

The contents of grape (*V. vinifera* L.) canes were 3,4'-dimethoxy-resveratrol and 3,5-dimethoxy-resveratrol. Both compounds showed antifungal activity with a minimum inhibitory concentration of 29-37 µg/ml against *Candida* sp. [45].

3.4.4. Antibacterial activity.

Grape (*V. vinifera* L.) seed extract exhibited antibacterial activity [4,42]. The higher extract concentration showed higher inhibition zone diameter against *Streptococcus mutants* [42]. Grape seeds extracts of *V. vinifera* var. Muscat Hamburg and Merlot have a strong ability to fight the bacteria *Leuconostor* sp. and *Micrococcus* sp. with MIC of 380 and 450 µg/ml [4].

The antibacterial activity of *V. vinifera* var. Feteasc Neagr leaf extract was indicated by inhibition zone diameter on *Porphyromonas gingivalis* ATCC 33277, which was 13 ± 1.41 mm, *Enterococcus faecalis* ATCC 29212 and *Staphylococcus aureus* ATCC 25923 was 12 ± 1.41 mm, *Streptococcus mutans* ATCC 25175 and *Escherichia coli* ATCC 25922 was 11.5 ± 0.71 mm. Meanwhile, the tendril extract of *V. vinifera* var. Feteasc Neagr, antibacterial activity was seen by inhibition zone diameter in bacterial or fungal strains *Porphyromonas gingivalis* ATCC 33277, *Enterococcus faecalis* ATCC 29212 and *Streptococcus mutans* ATCC 25923 were 10.00 ± 0.00 mm, *S. aureus* ATCC 25923 was 14.5 ± 0.71 mm, and *E. coli* ATCC 25922 was ten ± 1.41 mm. The antibacterial activity on the leaves and tendrils of *V. vinifera* is possible due to the high concentration of flavonoids and stilbenes in these sites [36].

Grape (*V. vinifera* L.) skin extract had intense antibacterial activity [4,23,34]. *V. vinifera* var. Muscat Hamburg had strong antibacterial activity against *Lactococcus* sp. and *Streptococcus* sp. with minimum inhibitory concentration (MIC) of 4500 and 4250 µg/ml. *V. vinifera* var. Pinot Noir and Feteasc Neagr against *Bacillus* sp. with MIC 3750 µg/ml and 4800 µg/ml [4]. Antibacterial activity was also found in the Blaufrankisch and Merlot variants; both variants had antibacterial activity against *E. coli*, *P. aeruginosa*, *B. subtilis*, and *S. aureus* [34].

White grape (*V. vinifera* L.) juice could inhibit the growth *S. aureus*, *E. coli*, and *P. aeruginosa* [3]. Also, Leal *et al.* (2020) stated that grape stem extract from white grape also has strong antibacterial activity against *S. aureus* and *E. faecalis* [46].

3.4.5. Antidiabetic activity.

Grape seeds, skins, and flesh from *V. vinifera* L. var Seyval Blanc, Hibernal, Pinot Gris, Freiminer, Roter Taminer, Regent, and Rondo presented antidiabetic activity by IC_{50} ranging from 0.27 to 1.13 mg dry sample/ml in inhibiting α-amylase and α-glycosidase [25]. Ostberg-Potthoff *et al*. (2019) also reported red grape juice activity concentration in α-amylase and α-glycosidase; the best action was anthocyanin fraction, followed by co-pigment fraction red grape juice concentrate [47]. Grape seeds, skins, and stems from var. Pusa Navrang and Merlot were able to increase insulin secretion in isolated mice pancreatic islets 2-8 fold from regular

[48]. Gharib *et al.* (2013) exposed that cyanidin and delphinidin compounds were found in *V. vinifera* L. to reduce the rate of albumin and HbA1c measured *in vivo* (mice diabetic) and *in vitro* (ELISA assay) [49]. Increased insulin secretion also occurred in alloxan-induced diabetic mice treated with grape skin extract [50].

3.4.6. Antihypertension activity.

Skin grape aqueous extract (*Vitis vinifera* L.) could prevent increasing systolic blood pressure in spontaneously hypertensive rats measured using the tail-cuff method. The results demonstrated that hypertensive rats had blood pressure > 200 mmHg, and hypertensive rats treated with grape skin extract had blood pressure < 150 mmHg [51]. Godse *et al.* (2010) stated that the myricetin content found in grape raisin could reduce systolic blood pressure in fructose-induced rats [52] and also in deoxycortisone acetate (DOCA)-salt-hypertensive rats [53].

3.4.7. Antiobesity and fatty liver activity.

Grape skin extract could prevent weight gain when weight gain causes obesity and fatty liver risk[54,55]. Fan *et al.* (2019) reported that grape skin extract of *Vitis vinifera* L., which contains proanthocyanidins, could act as an anti-fatty liver high-fat-diet-induced NAFLD mice. Prevention of fatty liver, apart from weight loss, was also followed by reducing alanine transaminase (ALT), alkaline phosphatase (ALP), aspartate transaminase (AST), total protein (TP), total cholesterol (TC), low-density lipoproteins (LDL), and triglyceride (TG) values, and decreasing the number of abnormal cells (lesion area) [56]. Ethanolic grape seed extract from the Muscat variety could also reduce blood serum levels in diabetic rats [57].

3.4.8. Antiviral activity.

3.4.8.1. Anti-influenza.

The procyanidin contained in grape seeds shows anti-influenza activity. Procyanidin concentration of 6.25 - 25 µg/ml could inhibit viral replication as measured by plaque inhibition assay. It can also work as an anti-influenza by inhibiting the accumulation of autophagosomes induced against influenza virus by reducing the ratio LC3II (light chain of the microtubule-associated protein) β-actin in the treatment group [58].

3.4.8.2. Anti-MERS-CoV.

Resveratrol (trans-3,5, 4 '- trihydroxystilbene) is one of the compounds in grapes (*V. vinifera* L.), reducing cell death MERS-CoV. Moreover, neutral red uptake (NRU) assays with resveratrol concentrations of 250 - 125 µM. Besides, resveratrol also suppressed replication of MERS-CoV RNA in high concentrations. Concomitant administration of resveratrol with MERS-CoV or after that had been shown to stop MERS-CoV infection [59].

3.4.9. Anticataract activity.

Grapes (*V. vinifera* L.) contained citronellol, which acts against glucose toxicity through an aldose reductase inhibitor mechanism, which prevents the onset of diabetic cataract [60]. Additionally, according to Higashi *et al.* (2018), the resveratrol content found in grapes

could also act as an anti-cataract, as tested on 7-week-old male Wistar type 1 diabetes-induced by preventing oxidative damage of lens protein [61].

3.4.10. Antipyretic activity.

The antipyretic activity was determined using the yeast-induced pyrexia model. It was found that the effect of *V. vinifera* leaf extract was able to reduce the rectal temperature at a dose of 100 mg/kg, 200 mg/kg, and 400 mg/kg after 22 h of injection of yeast. And a significant reduction occurred at doses of 200 and 400 mg/kg after 23 h of injection [18].

3.4.11. Antinociceptive activity.

Aqueous ethanol extract of *V. vinifera* L. through acetic-acid induced writhing and formalin test showed antinociceptive activity. In acetic-acid-induced writhing in mice, the extract produced an inhibitory effect of 65.5%. In contrast, the formalin test (chronic pain model) could reduce licking time and inhibit licking response [18].

3.4.12. Prevent bone loss activity.

Seeds extract of red grape, which contained proanthocyanidin was able to prevent bone loss. The proanthocyanidin reduced inflammatory osteolysis, inhibiting osteoclast differentiation, apoptosis and promoting proliferation in mice induced by lipopolysaccharide (LPS) [62].

3.4.13. Anticholinergic activity.

Based on the research of Tkacz *et al*. (2019), grape seeds, skins, and flesh from *V. vinifera* L. var Seyval Blanc, Hibernal, Pinot Gris, Freiminer, Roter Taminer, Regent, and Rondo can inhibit acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE). Grape skin var Rondo has the highest AChE-inhibition activity of 55.33%. The highest BuChE-inhibition activity of 36.84% was grape seeds var. Freiminer. In general, Rondo skin had the most potent anticholinergic activity [25].

3.4.14. Anticancer activity.

3.4.14.1. Prostate cancer.

Proanthocyanidin (structure of epicatechin octamer) contained in grape stems is related to the anticancer activity. Anti prostate cancer activity was proven by the presence of cell growth inhibition from prostate cancer cells. Another proanthocyanidin anticancer mechanism is to increase apoptotic activity in prostate cancer cells and suppress the expression of prostate cancer-promoting gene fatty acid-binding protein five at mRNA and protein levels [63].

3.4.14.2. Skin cancer.

The high concentration of skin and seed extract from *V. vinifera* L. increases A431 skin cancer cells' growth inhibition. The mechanism of its inhibition can be seen through induction of cytotoxicity, measured the cytotoxic effect of the two extracts via MTT assay using A431 cells and human keratinocytes cell line (HaCaT). The IC_{50} values of grape seeds and skin extract on A431 cells were 111.11 µg/ml and 319.14 µg/ml, followed by increases in reactive

oxygen species (ROS) production induced apoptotic cells, which showed by green fluorescence through a fluorescence microscope [64]. However, Decean *et al*. (2016) said that grape seeds extract could induce apoptotic cells but did not increase ROS production but decreased it [65].

3.4.14.3. Breast cancer.

Grape pomace from *V. vinifera* L. var. Negroamaro produced a phenolic fraction of grape seeds extract, which would induce apoptosis of cell death in MCF-7 breast cancer cells with an adequate concentration of 25-50 µg GAE/ml [66]. Grape seeds extract was also a chemopreventive agent that works by increasing transient gap-junction-intercellular communications (GJIC), increasing connexin-43 gene (*cx34*) expression in MCF-7 cells, relocating connexin-43 protein (Cx43), and suppress estrogen [66,67]. The stilbenoid compounds in grape extract had antiproliferative activity on breast cancer cells [68].

3.4.14.4. Hepatocelluler carcinoma.

The grape cane extract contained natural stilbene oligomers (resveratrol, ampelopsin, trans-e-viniferin), which had anticancer activity on hepatocellular carcinoma cells reducing the viability of HepG2 and Hep3B, and chemoprevention. Treatment of liver cancer by increasing ROS intracellular, caspase-3 activity, and inducing death of HepG2 by a caspase-dependent mechanism [69].

3.4.14.5. Oral squamous carcinoma.

Grape seeds extract with IC_{50} of 245.984 µg/ml could induce apoptosis in oral squamous cell carcinoma (KB cell) as measured by cell death detection ELISA plus kit. The apoptotic effect was given by grape seeds extract was the highest at 69.56%. Also, grape seed extract enhanced DNA fragmentation [2].

3.4.15. Anti-Alzheimer activity.

Grape skin, seeds, and fruit had anti-Alzheimer's activity by various mechanisms [70–72]. Grape powder and ethanolic extract as anti-Alzheimer's agents worked by recovering memory deficit and improved recall in Alzheimer's rats, followed by decreasing mRNA expression of amyloid precursor protein and clearing the tau tangles [70,72].

3.4.16. Anti-acne activity.

Acne vulgaris is a skin problem caused by *Propionibacterium acnes*. Based on Nelson's research, extracts from grape leaves had an anti-acne activity shown by MIC_{50} and MIC_{90} values of 64 µg/ml when against *P. acnes* [73].

3.4.17. Anti-aging activity.

Aging on the skin may be caused by radiation and pollutants. Based on Cronin's research, those grape seeds extract from *V. vinifera* L. containing t-resveratrol could slow the onset of aging and had the potential to be an ingredient for anti-aging products [74]. However, Based on Sharif's research, seed extract of *Vitis vinifera* L. var. Muscat Hamburg could be an ingredient for an anti-aging product because it is rich in antioxidants and works by increasing skin elasticity [75].

3.4.18. Anti-Sunburn activity.

The anti-sunburn activity of resveratrol from *V. vinifera* L. was proven by skin color parameters measured using a CM-2500d spectrophotometer. In the skin color parameters, there was a decrease in degrees of lightness (L *) from 64.20 to 59.3 and an increase in degrees of green to red (a *) from 7.51 to 13.43 in the test group with resveratrol treatment on skin exposed to UV irradiation for 4 d, which indicated reducing sunburn in the test group [76].

3.4.19. Anti-hyperpigmentation and skin lightening activity.

The anti-hyperpigmentation activity of red vine leaf extract of *V. vinifera* L., which contained flavonoids, resveratrol, gallic acid, chlorogenic acid, and epicatechin, could inhibit tyrosinase with IC_{50} 3.84 mg/ml, where tyrosinase was responsible for skin pigmentation [77]. Skin lightening activity showed on the Yucatan swine test on dark skin, treatment for eight weeks, five days per week, and twice a day using a topical preparation containing 1% resveratrol showed skin lightening without any irritation [76].

3.4.20. Anti-asthma activity.

Gallic acid contained in the alcoholic extract of dried fruits *V. vinifera* acts as an anti-asthma drug. The mechanism of the extract's action as an anti-asthma such as inhibition of histamine release, reduction of cytokine production (IL-4, IL-5, TNF, IL-1β) by alcoholic extract of dried fruits *V. vinifera* (concentration 31 mg/kg and 42.5 mg/kg). Followed by another mechanism, i.e., improves lung functioning with evidence of increasing lumen size and decreasing cellular infiltration and reduced numbers of leukocytes and white blood cells (eosinophils and neutrophils) [6].

3.4.21. Antiplatelet activity.

Grape skin extract, which contained poliflavan-3-ol, could act as an antiplatelet by inhibiting human platelet aggregation [78]. Based on research on antiplatelets by Bijak *et al*. (2019), where grape seeds extract was tested using the vasodilator-stimulated phosphoprotein (VASP) assay, it could reduce adenosine diphosphate (ADP)-induced aggregation in white blood [79].

3.4.22. Wound-healing activity.

Grape oil contained 20.10 ± 0.02 mg/g of hydroxyproline, which acts as a wound-healing as evidenced by reducing wound area on the 13^{th} day by 84.6% after grape oil administration [80]. In previous research, Nayak *et al*. (2010) exposed that grape skin also had wound-healing activity, where the wound area was closed on the 13^{th} day [81].

3.4.23. Antispasmodic activity

Leaves extract from *V. vinifera* L. had a spasmolytic effect [82,83]. According to the research of Glerisk *et al*., the isolated compound from grape seeds extract was 1- (3 ', 4'-dihydroxyphenyl) -3- (2 ", 4", 6 "-trihydroxyphenyl) -propan-2-ol, which had potential as an antispasmodic by decreasing the concentration of histamine-induced contraction [84].

3.4.24. Protective effect.

3.4.24.1. Colonprotective effect.

Grape seeds have a protective effect against colitis [21,85]. Grape seeds were provided protective effect by suppressing inflammation and apoptosis [85]. According to Niknami *et al.* (2020), hydroalcoholic black grape seeds extract and black grape seeds oil also had a protective effect by decreasing colon weight, ulcer index, and total colitis index [21]. The grape root extract has a protective impact towards oxidative DNA damage by hydrogen peroxide on human colonic adenocarcinoma cells (HT-29 cells), where the extract could prevent H_2O_2 induced-DNA damaged as evidenced by a comet assay [7].

3.4.24.2. Neuroprotective effect.

Research from Jin *et al.* (2013) reported that grape seeds extract administered for 12 weeks at a concentration of 100 or 250 mg/kg in high-fat diet-induced mice could increase intraepidermal nerve fiber density, a potential nerve protective [86]. In colorectal cancer treatment, oxaliplatin is used as an anticancer agent. However, oxaliplatin could induce neurotoxicity. Hydroalcoholic extract of *V. vinifera* red leaf can protect nerve cells from oxidative damage by decreasing O_2^- production and preventing lipid peroxidation of protein. Administration of *V. vinifera* L. extract at a daily dose of 300 mg/kg can reduce the pain caused by oxaliplatin [87]. Based on Ismail *et al.* (2015), grape seed oil was indicated to have a neuroprotective effect, which could suppress inflammation and inhibit iNOS and XO expression in gamma-irradiated rats induced by carbon tetrachloride and could cause neurotoxicity [88]. Besides, Lakshmi *et al*. (2014) stated that hydroalcoholic extract from black grapefruit could regulate antioxidant levels in rat brains induced by aluminum [89].

3.4.24.3. Cardioprotective effect.

The pomace of pinotted and unfermented *V. vinifera* L. var. Fetească Neagră was able to against isoprenaline (ISO)-induced myocardial ischemia on rats by reducing oxidative stress markers [90]. Polyphenol extract of *V. vinifera* L. var. Fetească Neagră and *V. vinifera* L. var. Aglianico N. could increase antioxidant capacity in rats treated with doxorubicin [91,92]. The cardioprotective effect of the grape comes from phenolic compounds [90,92].

Abdelsalam *et al*. (2019) stated ethanolic grape seed extract could be used for cardiorenal injury. Phenolic compounds of this extract could reduce total cholesterol, triglycerides (TGL), high-density lipoprotein (HDL), LDL, high-sensitivity C-reactive protein (hs-CRP), serum urea, creatinine, and blood urea nitrogen (BUN). Increases followed them in gene expression of Nrf2 [93].

3.4.24.4. Hepatoprotective effect.

The polyphenol compounds found in grape skin extract could improve hepatic steatosis and adiposity in high-fat-diet mice by regulating mRNA expression (changing lipogenesis and β-oxidation genes) [94]. Grape seeds extract was able to guard liver injury caused by alcohol induction. Grape seeds extract administered to rats induced by 20% ethanol in rats could decrease AST and LDH [95]. In rats induced by paracetamol treated by grape dried seed, the ALP level could be reduced [96].

3.4.25. Cytotoxic effect.

Grape seeds and skin extracts from the muscat family (*V. vinifera* L.) had a cytotoxicity effect measured by MTT assay with IC_{50} of 111.1 µg/ml 319.4 µg/ml on A431 cells but not toxic to HaCaT cells [64]. The phenolic fraction of grape seeds extract obtained from grape pomace var. Negroamora with high concentrations (75-100 µg GAE/ml) showed cytotoxic activity in breast cancer cells, as evidenced by late apoptosis [66]. Aqueous extract from *V. vinifera* L. var. Carbanet Sauvignon marc with a volume fraction of 3.2% had a cytotoxic effect by reducing cell viability by 20%, as evidenced by MTT assay [97].

Sales *et al.* (2018) reported that grape pomace extract from *Vitis vinifera* L. var Pinot Noir had a cytotoxic effect as indicated by an IC_{50} of 200 µg/mL, followed by 80% HepG2 cell lysis after incubating for 24 hours with grape pomace extract [98]. In contrast, according to Liang *et al.* (2014), *Vitis vinifera* fruit at 150 mg/mL had no cytotoxicity effect on HepG2 cells tested by methylene blue assay [99].

3.5. Genotoxocicity test.

Lluis *et al*. (2011) showed that skin and seed extract of *V. vinifera* L. var. Syrah was slightly mutagenic, proven by a bacterial reverse mutation test using bacterial strains of *Salmonella typhimurium* (TA 1535, TA 1537, TA 98, TA 100), where there was increasing in the number of revertant colonies in the TA 1537 strain (5 mg/plate). Apart from this test, the degree of genotoxicity of grape skin and seed extract was also tested through an *in vivo* test, namely the micronucleus test. However, the degree of genotoxicity could not be determined because several micronucleated cells did not appear after 72 h of incubation with the extract [100].

3.6. Toxicity study.

Grape seeds and skin extract were measured for their acute oral toxicity through a limit test. The tests were carried out on six female Wistar rats, of which three of them as a control group (p.o saline solution), and the other three were treated using extracts dissolved in saline solution (p.o 5000 mg/kg). All three rats showed no toxic effect after 14 days of treatment [100].

4. Conclusions

Vitis vinifera L., with its various varieties, Vitis vinifera L still has phytochemical compounds similar to each other. The major phytochemical compounds are stilbenoid, phenolic compounds, aromatic acids (hydroxycinnamic and hydroxybenzoic acid), flavonoids, proanthocyanidin. Every part of *V. vinifera* L. was rich in phytochemical compounds, which differ from one component to another. Every part and compound contained therein had benefits for humans, as evidenced by the many pharmacological activities found. The pharmacological activity depends on the part of the grapevines and the type of extract used. Therefore, *V. vinifera* can be beneficial for humans in traditional use and research development. There is a lack of recent studies on genotoxicity and toxicity. Much recent research is needed regarding the genotoxicity and toxicology study of *V. vinifera*.

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Conflicts of Interest

The authors declare no conflict of interest.

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