Chemical constituents and pharmacological effects from different parts of grape *Vitis vinifera* L. (Vitaceae): A review

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ABSTRACT
Vitis vinifera fruit (grape) possesses phenolic compounds, flavonoids, and stilbenes. Active substances have recently been found in the whole fruit, flesh, seed, skin, pomace, leaf and tendril, and root of grapes. This article reviews the active constituents of different parts of V. vinifera and their pharmacological effects, including antioxidant, anticancer, anti-inflammatory, antidiabetic, hepatoprotective, cardioprotective, and neuroprotective properties. Intriguingly, the cultivars and extraction technology play a pivotal role in determining individual extracts' biological activity.

Keywords: *Vitis vinifera, grape pomace, grape seed, resveratrol*

1. INTRODUCTION

Grape (*Vitis vinifera* L. Vitaceae) is globally grown, and it is the world's largest fruit crop with an annual production of more than 67 million tons [1]. Effects of polyphenols (including anthocyanin, flavanol, and resveratrol) in V. vinifera have been investigated intensively regards health benefits such as anticancer, anti-inflammation, and anti-aging [2]. Recently, grape-based wine and other products (like fresh fruit, dried fruit, and juice) are popularly consumed worldwide. In Vietnam, some varieties such as NH.01.48 and Red Cardinal are cultivated at Phu Yen, Khanh Hoa, Ninh Thuan, Binh Thuan, Lam Dong, and Ho Chi Minh city to obtain fruits and manufacture fruit-derived productions [3]. Our research previously figured out various phytochemical compounds and antioxidant activity of some varieties of grape harvested in Ninh Thuan province, Vietnam [4]. In current years, although numerous reviews [2, 5 - 6] have published the phytochemical and physiological effects of grape and the bioactive constituents originated from fruits, this review describes the phytochemicals and pharmacological activities of the particular parts of grape in order to facilitate by-product as a sustainable the material in the nutraceutical and pharmaceutical industry in Vietnam.

Plant metabolite is majorly classified into a primary and secondary metabolite, which performs different plants' tasks. While the primary metabolite is connected to growing, developing, and reproducing, the secondary metabolite contributes to ecological function like defenses against predators, parasites and diseases, interspecies competition, and the reproductive processes (coloring agents, attractive smells).

Phenolic compounds are considered as the most abundant bioactive components of grapes. However, other different chemical groups in different parts of V. vinifera are studied sparsely. Thus, this review will focus on the effects of extracts from individual parts of *V. vinifera.*

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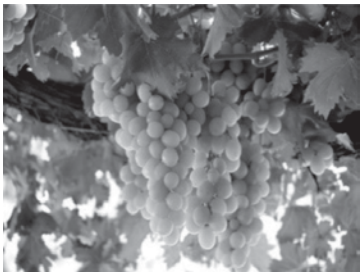
NH01-48 (White Malaga)

Red Cardinal

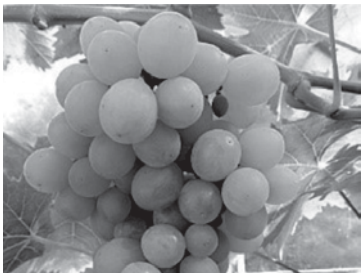
Red Star

NH01-93 (Black Queen)

NH01-152 (Mariaue finger)



NH01-96 (Italia)



Muscat Alexandria

Chardonnay

Cabernet Sauvignon

NH02-90

NH02-90 (Syrah1)

Sauvignon Blanc

Chenin Blanc

NH02-10 (Chambourcin)

Figure 1. Current varieties of Vitis vinifera L. in Vietnam

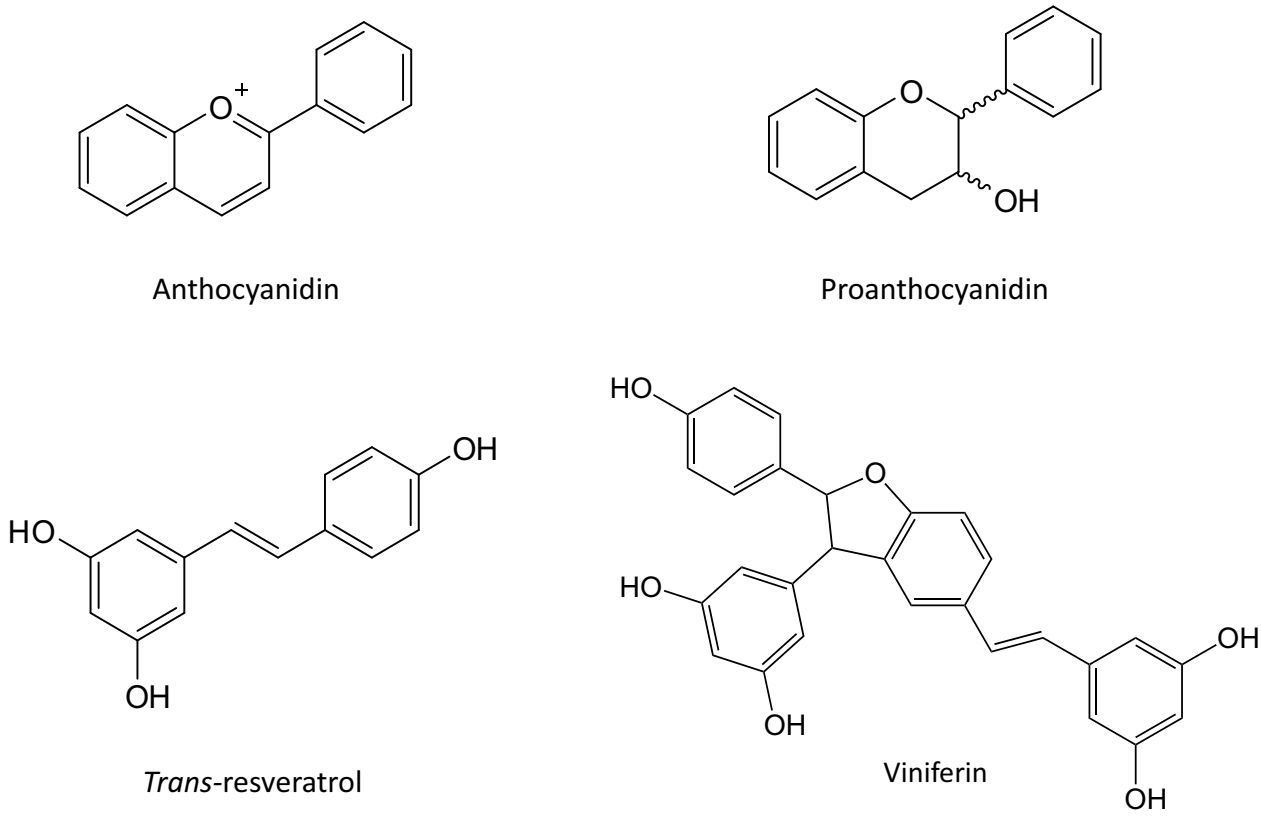


Figure 2. *Prominent compounds in Vitis vinifera L.*

2. OVERVIEW

2.1. Fruit

The phenolic proportion of *V. vinifera* L. fruits highly depend on the grape variety [7]. Previously, minor polar, nonvolatile constituents are identified from juices of *V. vinifera* using droplet countercurrent chromatography including monoterpenoids, C13 norisoprenoids, phenols, and other compounds (including astilbin, quercetin-3-O-β- glucopyranuronoside, roseoside, methyl vanillate, cinnamyl alcohol, and 3-phenylpropan-1-ol) [8]. Three main techniques (Hot-press, Cold-press, and Hot break) are used to extract the juices. Among them, the continuous hot-pressing process becomes more popular because the cold-pressing process results in a meager juice yield (18%). The total phenolic compounds content in grapes juices (400 to 3,000 mg/L) depends on the grape variety, grape maturity, geographical origin and soil type, sunlight exposure, and other factors [9]. Although the total anthocyanin content in the grape skins ranged from 1500 to 30,000 mg malvidin equivalents/kg dry weight of grape skin, the grape juice anthocyanins concentration depends on the factors to the raw material, the processing technology, and heat treatments. It is reported that the concentration of *trans*-resveratrol in grape juice ranged from 0.19 to 0.90 mg/L [10]. The compounds found in grape juice include simple phenolic, flavonoids (anthocyanins, flavanols, flavonols), phenolic acids, and stilbenes (resveratrol). They exhibit many health benefits linked to antioxidant activity by sequestering reactive oxygen species (ROS), such as hydroxyl radical and singlet oxygen. Besides, several studies are conducted to corroborate the benefits of juice like inhibiting human platelet aggregation and DMBA-induced tumorigenesis *in vivo* [11]. Notably, the glycoside forms of resveratrol and quercetin in grape juice are absorbed to a lesser extent than the aglycones.

2.2. Skin and flesh

Grape skin accumulates various phenolic compounds that protect against environmental stresses, including light and pathogens. Previously, polyphenols from grape skin extract were isolated using high-speed countercurrent chromatography [12]. Grapes possess an array of colors, ranging from the green/yellow to the dark blue tones caused by different amounts and composition of anthocyanin. The myeloblastosis (MYB) haplotypes influence the ratio of tri/dihydroxylated and methylated/nonmethylated anthocyanins modulating the structural genes. These genes are associated with anthocyanin biosynthesis, resulting in diverse colored tones. These findings can predict the color diver-sification in different grape cultivars [13]. Oligomeric anthocyanins are synthesized from monomeric anthocyanins such as anthocyanidin and proanthocyanidin originated from grape skin extract using *Aspergillus niger*, crude enzymes, and glucosidase to obtain higher antioxidant activity. Oligomeric anthocyanins are determined using Matrix-assisted laser desorption/ionization mass spectrometry (MALDI-MS) to identify their molecular weight [14]. Combining multi omic tools (genome-wide microarray, proteomics) indicates that ultraviolet-C irradiation induces the stilbene synthetic pathway, resveratrol in particular. Scientists establish an environmentally friendly extraction method for grape skin phenolics using deep eutectic solvents (DES) as a green alternative to conventional solvents coupled with highly efficient microwave-assisted (MAE) and ultrasound-assisted extraction (UAE) methods.

Polyphenols in the extracts of grape skin or flesh exert the radical scavenging properties *in vitro* and *in vivo* studies using male Wistar rats (16-18 week-old) [15]. Furthermore, these extracts also protect the rat brain against inflammation and histological alterations when consuming ethanol. Alpha-galactosidase activity, but not other glycosidases, in grape flesh significantly increases four weeks after fruit-bearing, and about 15-fold after 12 weeks [16]. Although grape skin and flesh are focused on discovering their potential in polyphenolic constituents, the study related to health benefits is con-ducted mostly in wine preparation.

2.3. Seed

Grape phytochemicals are rich in terpenoid (oleanolic acid), carotenoids (β-carotene, lutein), and flavonoids (flavon-3-ols (quercetin), flavan-3-ols (catechins), anthocyanins, oligomers and polymers (tannins and proanthocyanidins), and resveratrol) [17]. Due to the potential in the pharmaceutical, cosmetic, and food industry, grape seed oil and its chemical substances (phenolic compounds, fatty acids, and vitamins) have been intensively researched. Grape seeds extract (GSE) is a rich source of polyphenols which possess antioxidant, chemopreventive, and anticancer properties. Total GSE (50 - 400 μg/mL) suppresses the proliferation of oral cancer Ca9-22 cells in a dose-dependent manner via differential apoptosis, oxidative stress, and DNA damage [18]. The improvement of gap-junction-mediated cell-cell communications corroborates GSE's anti-proliferative and pro-apoptotic activities against the human breast cancer cell (MCF-7) model re-localization of Cx43 proteins and up-regulation of cx43 mRNA expression [19]. This finding contributes further insight into the herbal mechanisms and pivotal role of nutraceuticals. Procyanidin, which is rich in grape seed extract, can be considered an anti-neoplastic and chemo-preventive agent against non-small cell and small-cell lung cancer via alternations of prostacyclin and 15-HETE Eicosanoid pathways [20 - 21]. In a randomized, double-blinded, two-arm, parallel, placebo-controlled trial, grape seed extract (GSE) beverage

improve blood pressure in people with pre-hypertension (JNC8) [22]. Consistently, proanthocyanidin extract (400 mg/day), another flavonoid from grape seed, maintains vascular elasticity and normal blood pressure in a randomized, double-blind, placebocontrolled study 30 Japanese adults with prehypertension [23]. Grape seed proantho-cyanidin extract (500 mg/kg bw) elevates the activity of antioxidant enzymes. It decreases C-reactive proteins' levels in serum and the expression of tumor necrosis factor-α, monocyte chemoattractant protein-1 and intercellular adhesion molecule-1 in diabetic rats' kidneys. Monomeric and oligomeric flavan-3-ols from Masquelier's GSE were determined using high-performance liquid chromatography-mass spectrometry and proton nuclear magnetic resonance fingerprinting techniques. Then, the benefits in vasculature from this extract are elucidated in clinical data after eight weeks due to the alternations in the gene expression of inflammatory pathways [24]. Proantho-cyanidins (enriched in GSE) are indicated 12-week GSE supplementation ameliorates gut barrier function and colonic cell differentiation in the IL10-deficient mice through inhibiting Wnt/β-catenin pathway. It is also reported that proanthocyanidins (catechin, epicatechin and epicatechin gallate) extracted from GSE attenuate Aβ25-35 cytotoxicity, and lactate dehydrogenase leakage ratio, inhibited apoptosis and increased mitochondrial membrane potential Ψm on pheochromo-cytoma (PC12) cells. The *in vivo* data indicated a significant improvement in cognition and spatial memory ability, an improvement in amyloid precursor pathology, tau protein, and a decrease in presenilin-1 mRNA expression levels using APP/ PS-1 double transgenic mice [25]. Polyphenol-rich wine grape seed flour, a prebiotic with lactic acid bacteria (probiotics originated from Kefir), inhibited obesity and inflammation on high-fat diet-induced obese mice due to alterations an intestinal permeability and adipocyte gene expression [26]. The antioxidant activity of polyphenols extracted from GSE is indispensable to prevent calcium oxalate monohydrate papillary calculus formation induced by cytotoxic compounds using a renal lithiasis rat model [27]. When orally consuming volatile marjoram oil and grape seed extract for ten weeks, ethanol's deleterious effects on male fertility, liver, and brain tissues are alleviated on ethanol-treated rats [28]. Also, grape seed oil's beneficial properties are mainly determined by *in vitro* studies, such as anti-inflammatory, cardio-protective, antimicrobial, and anticancer properties. These effects have been associated with grape seed oil constituents, majorly tocopherol, linolenic acid, resveratrol, quercetin, procyanidins, carote-noids, and phytosterols.

2.4. Pomace

Pomace or marc is the substantial remains of grapes, olives, or other fruits after pressing for juice or oil. It contains the skins of the fruits, pulp, seeds, and stems. Flavanols like (+)-catechin and (-)-epicatechin and malvidin-3-glucoside, an anthocyanin, are the most abundant substances extracted from red grape pomace (*V. vinifera* L. cv. Malbec). Moreover, this is the first time piceatannol, a stilbene analog to resveratrol has been determined and quantified in grape pomace [29]. Ethanolic extract of grape pomace from four red varieties, which contains phenolic compounds (catechin, epicatechin, and quercetin) and fatty acids such as linoleic acid (C18:2n6), linolenic acid (C18:3n3), and palmitic acid (C16:0), can exert platelets aggregation inhibition in a wide range of agonist concentrations and cardioprotective properties [30]. A herbal combination consisting of propolis, pomegranate peel, and Aglianico grape pomace (PPP) extracts (4:1:1) delay the disease's onset. It alleviates the severity of the clinical symptoms using *in vivo* collagen-induced arthritis models. Besides, PPP treatment is connected to reducing in serum levels of IL-17, IL-1b, and IL-17-triggering

cytokines [31]. A seven-day pretreatment with grape pomace extracts on the isoprenaline-induced an infarct-like lesion in rats significantly enhances cardiac and oxidative stress parameters like ECG monitoring, serum levels of creatine kinase, aspartate transaminase, alanine transaminase, total serum oxidative status, total the antioxidant response, oxidative stress index, malondialdehyde, total thiols, and nitric oxide.

Interestingly, higher phenolic content and antioxidant activity were identified in fermented pomace extracts compared to fresh pomace extracts [32]. A randomized, placebo-controlled, cross-over trial indicates that grape pomace polyphenolic extract results in a significant increase of resveratrol (RSV) in serum and a decrease in Trimethylamine N-oxide (TMAO) of the treatment group compared to placebo (63.6% vs. 0.54%, respectively, $P < 0.0001$) after a 4-week treatment [33]. The flavonol and flavan-3-ols subfractions, rather than the anthocyanin subfraction in grape pomace and grape seed extracts, perform antiproliferative and cytotoxic effects on colon cancer cells (Caco-2, HT-29) owing to the downregulation of Myc gene expression in HT-29 and upregulation of Ptg2 [34]. In a piglet model, a diet with 5% grape pomace elevates the total antioxidant status (TAS) and reduces lipid peroxidation (TBARS) in both the duodenum and colon, and increased SOD activity in duodenum and CAT and GPx activity in the colon [35]. Also, three out of six different extracts from grape pomace presented a rebound effect on systolic blood pressure during six weeks with spontaneously hypertensive rats [36]. In terms of obesity, grape pomace extract induced beige cells in both white adipose tissue from rats and 3T3-L1 adipocytes [37]. As a result, grape pomace decreases obesity, diabetes, and steatosis due to gut microbiota changes and markers of gut barrier [38]. The hydrophilic low molecular weight polyphenols containing the free phenolic acids from crude grape pomace extract exhibits a dose-dependent inhibitory activity against both collagenase and elastase activity with IC50-values of 20.3µg/mL and 14.7µg/mL, respectively. Altogether, the by-product of winemaking is a sustainable source for the plethora of health benefits.

2.5. Leaf and tendril

V. vinifera leaves (grape leaves) are common in Mediterranean cuisine and rich in vitamins and minerals. Traditionally, grape leaves used to deal with plenty of health problems such as stomach aches, diarrhea, canker sores, heavy menstrual bleeding, arthritis, and liver inflammation. In healthy grapevine leaves, anthocyanins, dihydromyricetin-rhamnoside, hexosides of dihydroquercetin, and dihydrokaempferol exclusively accumulate in veins. Astilbin is the only flavanonol detected in blades and the prevalent flavanonol in veins [39]. In order to determine sustainable sources of high-quality pharmaceutical material, a comparative study of 135 distinct samples of red leaves is conducted to evaluate the contents of flavonol (0.6 - 3.5%), anthocyanin (0.2 - 1.45%), and polyphenol (4.6 - 18.9%) using HPLC. The abundant substances (glycosylated flavonoids, ellagic, and chlorogenic acids) and average bioactivities are confirmed using LC-MS/MS and *in vitro* antioxidant, neuro-protective, and cytotoxic assays [40]. The effects of leaf extract (GLE) exhibit on anti-oxidant *in vitro* (DPPH* and ABTS*(+) (cation radical)) and lipid peroxidation states when treating alcohol in the liver and kidney. The dose-dependent decrease of GLE in the activity of liver marker enzymes (AST, ALT, ALP, and GGT), and lipid peroxidation markers (TBARS, lipid hydroperoxides) in liver and kidney as compared with control rats demonstrate a protective effect on alcohol-induced oxidative stress. The hepatoprotective effect of n-BuOH fraction (83 mg/kg) from ethanolic extract of *V. vinifera* leaves possesses remarkable anti-oxidant and hepatoprotective activities against

CCl_4-induced acute hepatotoxicity in rats by ameliorating biochemical parameters (plasma and liver tissue MDA [malondialdehyde], transaminase enzyme levels in plasma [AST-aspartate transaminase, ALT-alanine transferase], and liver GSH [glutathione] levels) and histopathology. In gastric lesions induced by alcohol in a rat model, GLE exerts gastroprotective action by reducing gastric volume, gastric mucosal damage, and raising significantly gastric juice pH compared with the negative control group [41]. Also, ethyl acetate fraction (25 mg/kg) of the leaf is rich in polyphenolics and possesses a significant antihyperglycaemic and antioxidant activity compared with the tolbutamide (100 mg/kg) in diabetic rats. The *V. vinifera* leaf hydroalcoholic extract's antoxidant properties are depicted in primary rat astrocyte cells treated with oxaliplatin (100 µM). This extract (50 µg/mL) significantly attenuates the superoxide anion and lipid peroxidation in oxaliplatin-treated rat astrocytes without changes in the mortality by oxaliplatin in HT-29 cancer cells. These findings ameliorate oxaliplatin-induced neuropathy as a valuable therapeutic opportunity [42]. Aqueous extract (100 µg/mL) from *V. vinifera* leaves containing high polyphenols levels protect human keratinocytes cells against UV-A and UV-B radiation via the antioxidant and the DNA protective activity in Comet and ɣH2AX assays [43]. When conducting metabolite content of *V. vinifera* cv Falanghina leaves using NMR, kaempferol-3-O-*β*-d-glucuronide is identified as moderate anti-proliferative bioactivity against metastatic melanoma cells [44]. The ethanolic extract, which is rich in anthocyanins, shows the antileishmanial activity against Leishmania ainfantum promastigotes through the destruction of cytoplasmic and nuclear membranes Leishmania infantum promastigotes and the alternation of the cellular shape. Additionally, the biological activity of *V. vinifera* L. water extract from dried leaves validated by HPLC-DAD is investigated in two *in vitro* models of gastric and intestinal inflammation. This extract represses both IL-8 secretion and expression induced by TNFα in human gastric epithelial cells and maintains after gastric digestion. On the other hand, the effect after intestinal digestion is sharply decreased due to the degradation of the gut's active constituents [45]. It is reported that a leaf extract contains gallic acid (1.03 mg/g), chlorogenic acid (0.2 mg/g), epicatechin (18.55 mg/g), rutin (6.45 mg/g), and resveratrol (0.48 mg/g) which are effective for skin hyperpigmentation. This leaf extract is considered as an effective tyrosinase inhibitory activity with an IC50 value of 3.84 mg/mL for tyrosinase inhibition. Hence, the leaf extract will be potential as a whitening agent for the cosmetic industry [46]. The antioxidant activity of aqueous extracts of *V. vinifera* tendrils plays a vital role in the antioxidant defenses of keratinocytes exposed to oxidative stress and need. Fraternal et al. determine the antifungal activities of the ethanolic extract of *V. vinifera* tendrils against *Fusarium* species with MIC values of 250 - 300 ppm [47].

2.6. Root

The root extract of *V. vinifera* contains seven stilbenoids, including two monomeric (resveratrol and piceatannol), two dimeric (trans-ε-viniferin and ampelopsin A), one trimeric (miyabenol C), and two tetrameric (r-2-viniferin = vitisin A and r-viniferin = vitisin B) compounds using HPLC-ESI-MS/MS analyses [48]. Electron spin resonance and spin trapping experiments demonstrate that this root extract scavenged 2,2-diphenyl-1-picrylhydrazyl, hydroxyl, galvinoxyl, and superoxide free radicals. Besides, the root extract prevents hydrogen peroxide-induced DNA damage by inducing Nrf2 and its target genes (heme oxygenase-1 and γ-glutamylcysteine synthetase) using a cell-based model. Moreover, the root extract exerts the anti-inflammatory activity by inducing the antiatherogenic hepatic enzyme paraoxonase 1

and down-regulating pro-inflammatory gene expression (i.e., interleukin 1β and inducible nitric oxide synthase) in macrophages [48]. Stilbenes are protective molecules derived from grapevine in response to stresses like several elicitors and signal molecules. Interestingly, stilbenes are indispensable due to their pharmaceutical properties. To achieve high yield, cost-effective, and high purity production of resveratrol derivatives, three *Agrobacterium* rhizogenes strains, Ar318, ArA4, and LBA9402, are used induce hairy roots [49] or establishes from *Vitis vinifera* cv Pinot Noir 40024. The ethanolic extract (200 mg/kg) of the *V. vinifera* root possesses hepatoprotective activity in rats with carbon tetrachloride-induced liver damage by reducing the serum levels of SGPT, SGOT, alkaline phosphatase, and total bilirubin. Seven stilbenoids (Wilsonol C, heyneanol A, ampelopsin A, pallidol A, *cis*-piceid, *trans*-piceid and *trans*-resveratrol) are isolated from the aqueous methanolic extract of *V. vinifera* roots and structurally interpreted using bioassay-guided isolation and spectroscopy (NMR, MS), respectively. Notably, Wilsonol C exerts an inhibitory effect on pancreatic lipase with IC_{50} values of 6.7 ± 0.7 μM (Orlistat 0.7 ± 0.2 used as a positive control).

3. FUTURE PERSPECTIVE

In this review, various bioactive constituents in different *V. vinifera* extracts (i.e., pomace, skin, seed, leaf, root, fruit, and tendril) and several pharmacological effects, including antioxidant, anticancer, antibacterial, antidiabetic, cardioprotective, hepatoprotective, and neuroprotective effects were summarized.

The extraction methods and grape varieties have essential impacts on the pharmacological effects of grape extracts. Further studies need to consider the solvent to extract and fractionate into the rich's fractions in targeting compounds. Besides, agricultural by-products of grape-like pomace, seed, leaf, and tendril are an immense source for pharmaceuticals and neutraceuticals due to their health benefits. Further toxicological studies should be finished to determine effective doses of different grape products before conducting clinical studies.

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Tổng quan về thành phần hóa học và tác dụng dược lý của các bộ phận của cây nho *Vitis vinifera* L. (vitaceae)

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TÓM TẮT

Quả nho Vitis vinifera L. chứa các hợp chất phenolic, flavonoid và stilbene. Gần đây, những hoạt chất được tìm thấy trong các bộ phận khác của cây Nho. Trong bài này, chúng tôi sẽ khái quát thành phần có hoạt tính và hoạt tính dược lý trong các bộ phận dùng của Nho bao gồm chống oxy hóa, kháng ung thư, kháng viêm, kháng tiểu đường, và tác dụng bảo vệ gan, tim mạch, và thần kinh. Đáng lưu ý là yếu tố giống loài và phương pháp chiết xuất đóng vai trò then chốt trong xác định hoạt tính sinh học của các dịch chiết.

Từ khóa: *Vitis vinifera, bã nho, hạt nho, resveratrol*

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