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Benefits of Vine Leaf on Different Biological Systems

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Abstract

For centuries, the therapeutic benefits of grapes and other byproducts have been empirically used for medical purposes such as bleeding, pain, inflammation, nausea, diarrhea, gastroenteritis, or skin diseases. Moderated intake of the red wine improves parameters as blood lipids, endothelial dysfunction, platelet aggregation, and other risk factors for cardiovascular disease. However, few studies have been explored the potential benefits from vine byproducts. Vine leaves, a waste product from the vine, are also rich source of polyphenols and other therapeutic compounds. In this chapter, we explored the therapeutic properties from vine leaf in different biological systems.

Keywords: polyphenols, organic viticulture, grapevine, natural products, live, heart, kidney, brain

1. Introduction

The production of grapes is considered an economically important activity in many countries, mainly related to the wine production [1]. Beyond their lucrative potential, grapes and their byproducts show nutritional and functional properties [2–4]. Since centuries ago, grapes have been used for medical purposes, preventing or treating diseases as nausea, diarrhea, gastroenteritis, or skin disorders [5]. More recently, the therapeutic effect of red wine has been reported, and moderate intake has been related to improved blood lipid parameters, endothelial dysfunction, platelet aggregation, and other risk factors for cardiovascular disease [6, 7]. Apart from the grape or wine, studies have been shown that grape byproducts such as juice, or extracts from the skin, seed, or leaf also present therapeutic proprieties [8–12]. Grape

leaves, for example, have been popularly used to stop bleeding, relieve pain, inflammation, and diarrhea (**Figure 1**) [13, 14].

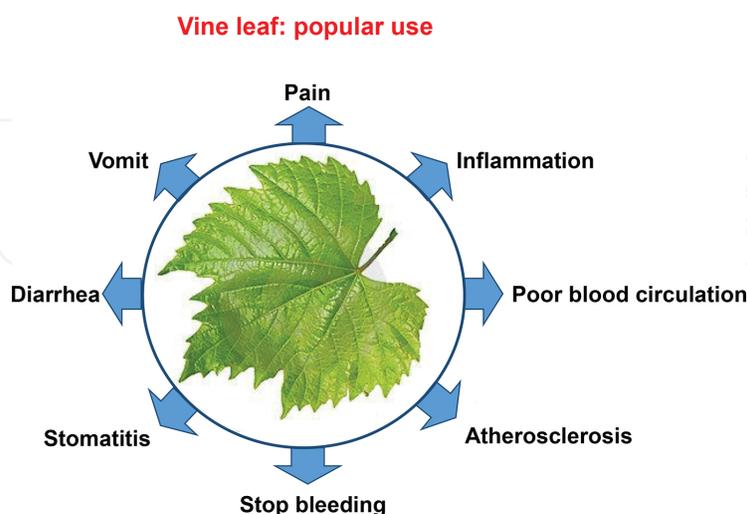


Figure 1. Popular use of vine leaf for health purpose.

Therapeutic proprieties by grapes, wine, or byproducts are mainly related to the polyphenolic compounds [7, 15]. Leaves, which are a waste product from the grapevine, usually discarded by grape farmers, are also rich source of polyphenols and other therapeutic compounds [16]. More recently, their therapeutic properties have been explored, mainly because grape juices are rich in carbohydrates and wine is an alcoholic beverage, nonrecommended to diabetic or alcoholics individuals, respectively.

2. Bioactive polyphenols in vine leaves

The grapevine (*Vitis* spp.) is cultivated across the world in different regions, mainly in temperate climate with adequate rain, warm and dry summers, and mild winters [17]. Climate, soil, conventional or organic cultivation method, and different cultivars are determinant to phytochemical constitution of grapevines [18]. These phytochemical compounds include a variety of bioactive organic acids (e.g., malic, oxalic, fumaric, ascorbic, citric, linoleic, and tartaric acids), vitamin E, terpenes, tannins, carotenoids, and polyphenols that have been highlighted for their beneficial effect on human health [19, 20]. The most important grape polyphenols as flavanols (e.g., epicatechin and galocatechin), flavonols (e.g., quercetin and myricetin), anthocyanins (e.g., pelargonidin and cyanidin), and resveratrol are secondary metabolites synthesized by plants and associated with growth, pigmentation, pollination, environmental stress, and resistance against pathogens and predators [13, 17].

Polyphenols present biological activities, such as antioxidant, anti-inflammatory, anticancer, antimicrobial, cardioprotective, and antiaging effects [9, 14]. Polyphenols therapeutic proprieties have been related to their chemical structure and ability to act as radical scavengers of the

lipid peroxidation chain reactions, donating electrons, and neutralizing free radicals [21]. Moreover, they are chelators of metals as iron (Fe²⁺) and copper (Cu²⁺), preventing oxidation caused by highly reactive hydroxyl radicals [21, 22]. They also inhibit the immune cell recruitment (T lymphocytes and natural killer cells) and decrease the nuclear factor kappa B (NFκB) expression [23, 24].

Species	Viticulture method	Preparation	Total phenolic mg/g gallic acid	Phytochemicals detected	Reference
<i>Vitis vinifera</i>	NI	Ethanollic extract	216.0 ± 5.1	Total flavonoids	[26]
<i>Vitis vinifera</i>	NI	Aqueous extract	149.93 ± 0.35	Total proanthocyanidin; total flavonoid	[27]
<i>Vitis vinifera</i>	NI	Aqueous extract	146.3 ± 4.2	Anthocyanin: cyanidin-3- <i>O</i> -glucoside > peonidin-3- <i>O</i> -glucoside Flavonols: quercetin-3- <i>O</i> -glucuronide Caffeic acid derivatives: caftaric acid	[28]
<i>Vitis vinifera</i>	NI	Ethanollic extract	98.84 ± 9.26	NI	[29]
<i>Vitis labrusca</i>	Organic	Aqueous extract	81.79 ± 2.68	Catechin; resveratrol	[30]
<i>Vitis vinifera</i>	NI	Ethanollic extract	60.4 ± 0.4	Flavonols; quercetin-3- <i>O</i> -glucuronide > kaempherol-3- <i>O</i> -glucoside Anthocyanin: peonidin-3- <i>O</i> -glucoside > cyanidin-3- <i>O</i> -glucoside Hydroxycinnamic acid: <i>trans</i> -caftaric acid	[10]
<i>Vitis labrusca</i>	Organic	Ethanollic extract	20.2 ± 1.8	Catechin; resveratrol; quercetin; rutin; kaempherol	[9]
<i>Vitis labrusca</i>	Conventional	Aqueous extract	19.83 ± 0.76	Catechin; resveratrol	[30]
<i>Vitis labrusca</i>	Conventional	Ethanollic extract	19.0 ± 1.8	Catechin; resveratrol; quercetin; rutin; kaempherol, naringin	[9]
<i>Vitis vinifera</i>	NI	Acetone/methanol extract		Anthocyanins: peonidin 3- <i>O</i> -glucoside > malvidin > cyaniding 3- <i>O</i> -glucoside; flavonols: quercetin 3- <i>O</i> -β- <i>D</i> -glucuronide > isoquercitrine quercetin 3- <i>O</i> -β- <i>D</i> -glucoside phenolic acids	[16]

NI: not informed.

Table 1. Phenolic compounds from different vine leaf extracts.

A study comparing 10 grape cultivars grown in southern Georgia, USA, showed that the total concentration of phenolic compounds was higher in seed (2178.8 mg/g gallic acid equivalent), followed by skin (374.6 mg/g), and leaf (351.6 mg/g) [25], evidencing that the leaf is also an important source of phenolic compounds. Although gallic acid was a dominant phenolic acid in the vine leaf, other constituents may contribute to the beneficial properties of its extract. **Table 1** shows the phenolic contend in different extracts from *V. vinifera* and *V. labrusca* leaves.

It reveals that ethanolic extracts show the highest extraction rate and the *V. labrusca* varietal shows the highest total phenolic concentration. Optimal or prolonged low-temperature exposure decreases the phenolic contents in *Vitis vinifera* leaves from 526 g/g to 458 mg/g of extract [31]. Antioxidant index, measured by trolox equivalent antioxidant capacity (TEAC) assay, showed that, similarly to grape seeds, leaves present 10 times higher antioxidant activity than grape juice or pulp [7]. Moreover, total phenolic levels in leaf are not affected by brining, a method assumed to preserve vine leaves for future use in the Turkish cuisine [32]. Resveratrol, a compound with therapeutic properties, accumulates in the surface of leaves at range of 40–400 $\mu\text{g/g}$ fresh weight in according to environmental conditions [33].

In addition to environmental influences, farming practices, as organic or conventional viticulture, also interfere with the production of polyphenols [34]. In the organic viticulture, grapevine grown in the absence of pesticides, chemicals, or genetic engineering modification, and it is more vulnerable to external attacks from insects or microorganisms, which may contribute to the higher production of phytochemicals, responsible for plant defenses [35]. A study showed that organic vine leaf extract presents higher concentrations of resveratrol than conventional vine extract, although total polyphenols were similar and catechin and quercetin were lower [9, 30] (**Table 1**). Given the variability in the phenolic composition of the vine leaf, the quantification of the phenolic constituents may estimate the quality and therapeutic potential in vine leaves [16].

3. Effect of vine leaf extract on hepatic and gastrointestinal systems

Alcoholic and nonalcoholic liver diseases have been related to chronic exposition to risk factors as alcohol, tobacco smoking, drugs, environmental pollutants, and irradiation. It is well known that these risk factors promote excessive formation of oxygen and nitrogen reactive species and may lead to oxidative damage in the liver [36]. Although clinical studies are scarce, preclinical studies show that natural antioxidants from products as vine leaves prevent or attenuate the severity of liver diseases induced by oxidative mechanisms. Animal studies have explored some morphological and biochemistry changes by hepatotoxic substances and the protective effect of vine leaf extracts. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ -glutamyl transferase (GGT), and alkaline phosphatase (ALP) are some biomarkers that predict liver function and explored in these studies. Aqueous extract from *Vitis coignetiae Pulliat* leaves shows hepatoprotective effect after chronic oral administration in an animal model of nonalcoholic steatohepatitis (NASH), evidenced by decreasing on AST and ALP activity, confirmed by increasing in plasma antioxidants and delaying in the progression of liver fibrosis [37] (**Table 2**). Similarly, alcoholic or butanolic extract of vine leaves (*Vitis vinifera*) decreased AST and ALT activity after acute hepatotoxicity induced by carbon tetrachloride (CCl_4) in rats [26]. Vine leaves extract also decreased AST, ALT, ALP, and GGT activity after chronic alcohol administration [29]. For both, CCl_4 and alcohol-induced hepatotoxicity models, vine leaves extract decreased biomarkers of serum oxidative stress as malondialdehyde (MDA), superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase

(GPx) enzyme, as well decreased histopathological lesions [26, 29]. Preincubation with organic and conventional vine leaf (*Vitis labrusca*) extracts also prevents both lipid and protein oxidative damage in the rat liver after oxidative stress induced by hydrogen peroxide [39]. Moreover, the organic vine leaves extract restored SOD and the conventional vine leaves extract restored CAT activity, both decreased by hydrogen peroxide-induced stress and related to different phenolic content in each extract [39] (Table 2). The liver of diabetic individual is also subject to damage due to exposure to self-oxidation of free glucose and deficiency of antioxidant system [41]. Indeed, chronic oral administration of aqueous extract of organic grape leaves (*Vitis labrusca*) reduced the AST activity in an experimental model of diabetes in rats [38]. The synergistic effects of different polyphenols in the vine leaf extract reduced the oxidative stress, preventing lipid and protein damage and increasing enzymatic and nonenzymatic antioxidant defenses in the liver of diabetic rats, suggesting a promising therapeutic approach to hepatic complications induced by diabetes [38].

Species	Culture method	Treatment	Condition	Results	Reference
<i>Vitis labrusca</i>	Organic	Aqueous extract Orally	Diabetes (rats)	↓ Lipid peroxidation ↓ Protein damage ↑ Nonenzymatic antioxidant defenses ↑ SOD activity ↓ CAT activity ↓ AST	[38]
<i>Vitis labrusca</i> <i>Vitis labrusca</i>	Organic Conventional	Aqueous extract preincubation	H ₂ O ₂ -induced stress (<i>in vitro</i>)	↓ Lipid peroxidation ↓ Protein damage ↑ SOD activity ↓ Lipid peroxidation ↓ Protein damage ↑ CAT activity	[39]
<i>Vitis vinifera</i>	NI	<i>n</i> -BuOH extract Orally	Cirrhosis (rats)	↓ Lipid peroxidation ↑ GSH content ↓ Histopathological injury ↓ AST, ALT	[26]
<i>Vitis vinifera</i>	NI	Ethanol extract Orally	Alcohol induced oxicity (rats)	↓ AST, ALT, ALP, GGT ↓ Lipid peroxidation ↓ Hydroperoxides ↑ Vitamin E ↑ Vitamin C ↑ GSH ↑ SOD activity ↑ CAT activity ↑ GPx activity ↑ GST activity	[29]
<i>Vitis coignetiae</i>	NI	Aqueous extract Orally	Nonalcoholic steatohepatitis (rats)	↓ ALT ↓ Fibrosis area ↓ MPO activity ↓ Mitochondrial ROS ↓ NFκB expression	[40]
<i>Vitis coignetiae</i>	NI	Aqueous extract Orally	Nonalcoholic steatohepatitis (rats)	↓ AST and ALP ↓ CYP2E1 induction ↓ Fibrosis	[37]

NI: not informed; AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT: γ -glutamyl transferase; ALP: alkaline phosphatase; SOD: superoxide dismutase, CAT: catalase; GPx: glutathione peroxidase; GSH: reduced glutathione; GST: glutathione-S-transferase; ROS: reactive oxygen species; MPO: myeloperoxidase; NFκB; factor nuclear kappa B.

Table 2. Hepatoprotective effects of vine leaf.

Vine leaves extract (*Vitis coignetiae Pulliat*) decreases the leakage of biliary enzymes and attenuates liver fibrosis after 3 weeks of treatment in a model of nonalcoholic steatohepatitis in rats [40]. Improving on hepatic fibroses or suppression of its progression by the extract was associated to increasing on plasma antioxidant activity, decreasing on reactive species and NF κ B activity, a key pathway linking oxidative stress and inflammation [40]. Vine leaves extract from *Vitis vinifera* preserved the integrity of the membrane of hepatocytes in CCl₄-intoxicated rats, evidenced by the reduction in plasma levels of AST, ALT, and GGT [27]. Additionally, the extract reduced the concentration of bilirubin, lipoproteins, lipid oxidation and, in parallel, preserved histological injuries of the liver [27].

Among the gastrointestinal diseases, the prevalence and incidence of gastritis, peptic ulcers, and inflammatory bowel disease have increased in recent years, associated to the consumption of processed foods and lifestyle [42]. The activation of inflammatory pathways is the common pathological mechanism of these diseases and initiates by the activation of NF κ B, which is related with transcriptional control of multiple proinflammatory mediators as IL-1 β , TNF- α , and IL-8 in the gastrointestinal tissue [43].

In this context, the biological activity of the aqueous extract of vine leaves (*Vitis vinifera*) was assessed *in vitro* in a model of gastric inflammation (human gastric and intestinal epithelial cell) [28]. Vine leaf extracts impaired the NF κ B pathway and, consequently, reduced the TNF- α and IL-8 secretion and expression by gastric epithelial cells. The anti-inflammatory effect of the extract decreased significantly after simulation of intestinal digestion, explained by the poor stability and high rate of degradation of anthocyanins and flavonoids present in the aqueous extract of vine leaves in an alkaline pH [28].

4. Effect of vine leaf extract on the cardiovascular system

Cardiovascular diseases are the most common causes of morbidity and mortality worldwide, currently responsible for over 17 million deaths, with growth forecast to 23.6 million per year to 2030 [44]. Hypertension, dyslipidemia, obesity, and smoking are considered the main cardiovascular risk factors [45]. These factors adversely affect the vascular endothelium, reducing the availability of nitric oxide, facilitating the deposition of oxidized LDL cholesterol by activating oxidative and inflammatory cascades leading to atherosclerosis, endothelial dysfunction, and cardiovascular damage [46].

Studies suggest that consumption of grape polyphenols and its derivatives is associated with reduction in cardiovascular risk related to their antioxidant, anti-inflammatory, and antithrombotic properties [6]. It is well known that there is a correlation between moderate consumption of red wine and the lowest risk of death associated with heart disease [47, 48]. Indeed, the daily consumption of low to moderate doses of wine reduces by half the risk of death compared to individuals who did not drink wine [49]. Aqueous extract of grape leaves has been tested in rodents and evidenced also an antioxidant effect, decreasing lipid and protein damage, as well increasing SOD and CAT activity in a heart homogenates injured by H₂O₂ in

rats [39]. These antioxidant effects were more significant compared to those extracts prepared from organic grape leaves [39] (Table 3).

Specie	Viticulture method	Treatment	Condition	Target tissue	Results	Reference
<i>Vitis labrusca</i>	Organic and conventional	Aqueous extract Preincubation	H ₂ O ₂ -induced stress (<i>in vitro</i>)	Heart	↓ Lipid peroxidation ↓ Damage protein ↑ CAT activity	[39]
<i>Vitis vinifera</i>	NI	Aqueous extract Orally	Diabetic (rats)	Heart	↑ GSH content	[50]
<i>Vitis vinifera</i>	NI	Ethanollic extract Orally	Alcohol-induced toxicity (rats)	Kidney	↓ TBARS ↓ Hydroperoxides ↑ Vitamin E and vitamin C ↑ GSH ↑ SOD activity ↑ CAT activity ↑ GPx activity ↑ GST activity	[29]
<i>Vitis labrusca</i>	Organic	Aqueous extract preincubation	H ₂ O ₂ -induced stress (<i>in vitro</i>)	Kidney	↓ Lipid peroxidation ↓ Damage protein ↑ SOD activity	[39]
<i>Vitis vinifera</i>	NI	Aqueous extract Orally	Toxicity-induced by CCl ₄ (rats)	Kidney	↓ Creatinine, uric acid, and calcium levels ↓ MDA ↑ NP-SH	[27]
<i>Vitis labrusca</i>	Organic and conventional	Aqueous extract preincubation	H ₂ O ₂ -induced stress (<i>in vitro</i>)	Cerebral cortex, cerebellum and hippocampus	↓ Lipid peroxidation: cerebellum, hippocampus ↓ Damage protein: cerebral cortex, cerebellum, hippocampus ↓ Lipid peroxidation: cerebellum ↓ Damage protein: cerebral cortex	[9]
<i>Vitis labrusca</i>	Organic	Aqueous extract pretreatment (intraperitoneally)	CCl ₄ -induced stress (in rats)	Cerebral cortex, cerebellum and hippocampus	↓ Damage protein: cerebral cortex, cerebellum, hippocampus ↓ SOD activity: cerebral cortex, hippocampus ↑ SOD activity: cerebellum ↑ SOD/CAT ratio: cerebral cortex, cerebellum	[30]

NI: not informed; CCl₄: carbon tetrachloride; MDA: malondialdehyde; NP-SH: nonprotein sulfhydryl; SOD: superoxide dismutase; CAT: catalase; GPx: glutathione peroxidase; GSH: reduced glutathione; GST: glutathione-S-transferase.

Table 3. Therapeutic effects of vine leaf in different tissues.

Aqueous extract of grape leaves also presents an *in vivo* antioxidant effect, increasing the GSH levels in the heart of streptozotocin-induced diabetic rats, at doses of 500 mg/kg [50], although it did not change MDA levels (Table 3).

Vine leaves are rich in polyphenols such as flavonoids and anthocyanins (Table 1). Beside antioxidant activities, polyphenols inhibit pro-oxidant enzymes (e.g., xanthine oxidase,

NADPH oxidase, lipoxygenases), chelate transient metals, interact with some ion channels, reduce platelet aggregation and leukocyte adhesion, and promote vasodilatation, decreasing the resistance to blood flow [51, 52]. Anthocyanins are also responsible for increasing in the strength and vascular permeability, as well as the inhibition of platelet aggregation [53]. Studies suggest that they promote vasorelaxation by increasing nitric oxide levels and by inhibiting the action of phosphodiesterase-5 enzyme, which metabolizes the cyclic guanosine monophosphate (cGMP), an important vasodilator, reducing the risk of cardiovascular disease [54].

Anti-inflammatory properties from flavonoids and other grapevine constituents also contribute to the cardioprotective mechanism against injury caused by ischemia-reperfusion [51, 52]. Flavonoids inhibit phospholipase A2 and cyclooxygenase enzymes, decreasing prostaglandins synthesis and, indirectly, all inflammatory cascade [55]. Studies show that flavonoids inhibit the TNF- α , IL1- β , and interferon- γ synthesis [51]. All these mechanisms contribute to LDL cholesterol reduction and increasing on HDL cholesterol, useful to protect against cardiovascular disease [56].

A commercial standardized red vine leaf aqueous extract (Antistax[®], Boehringer Ingelheim Pharma GmbH & Co, Ingelheim am Rhein, Germany) from *Vitis vinifera Folium* is available for chronic venous insufficiency, improving the cutaneous microcirculation and oxygen supply in humans [57]. A randomized, double blind study showed that this vine leaf extract decreased the lower leg edema and circumference in chronic venous insufficiency patients [58]. Additionally, the vine leaf extract was investigated in women in long-term hormone replacement therapy with phlebopathy of the lower limbs [59]. After 3 months, leaf extract treatment decreased the calf and ankle circumference, besides the diameter of the great saphenous vein (GSV), relieving venous symptoms, and improving the quality of life of users [59]. Regulation of blood flow by vine leaf extract has been positively associated to NO (nitric oxide) synthesis by endothelial and red blood cells, adding to its antioxidant properties [60].

5. Effect of vine leaf extract on the renal system

Diseases that affect the renal system are related to progressive and irreversible loss of kidney function, and inability of the kidney to adequately clean waste products from the blood. This condition is characterized by a reduction in glomerular filtration rate, decreased urine output, proteinuria and microalbuminuria, common in diabetes, and hypertensive patients [61, 62].

Oxidative stress is considered an important pathogenic mechanism in renal diseases [61]. In diabetic individuals, particularly, high levels of final advanced glycation end products (AGEs), reactive species, and oxidative stress promote protein oxidation, DNA damage, and apoptosis [62, 63]. Glomerular hypertrophy and tubulointerstitial fibrosis in the kidney in diabetic individuals may progress to nephropathy [63]. Buffering the generation of oxidative pathway may represent a nephroprotective effect against oxidative damage by diabetes [62].

In this context, unpublished results from our group (**Figure 2**) showed the beneficial effects of an organic aqueous vine leaves extract on the kidney of diabetes rats, agreeing with the results

from others [62]. In our experimental protocol, nondiabetic (C) and streptozotocin-induced diabetic (D) rats were daily administered with 50, 100, and 200 mg/kg of an organic vine leaf extract, by oral gavage, for 30 days (design details showed at [38]). The kidney was collected for analysis of oxidative stress parameters and the blood, for urea and creatinine determination. A two-way ANOVA showed that diabetes significantly increased protein oxidation (carbonyl), and SOD activity ($P < 0.05$) and decreased the total sulfhydryl levels ($P < 0.001$) in the kidney of diabetic rats. All three doses prevented the protein carbonylation ($P < 0.05$) increased by diabetes, but only the dose of 50 mg/kg restored sulfhydryl levels ($P < 0.05$) and decreased the SOD activity ($P < 0.05$) (Figure 2).

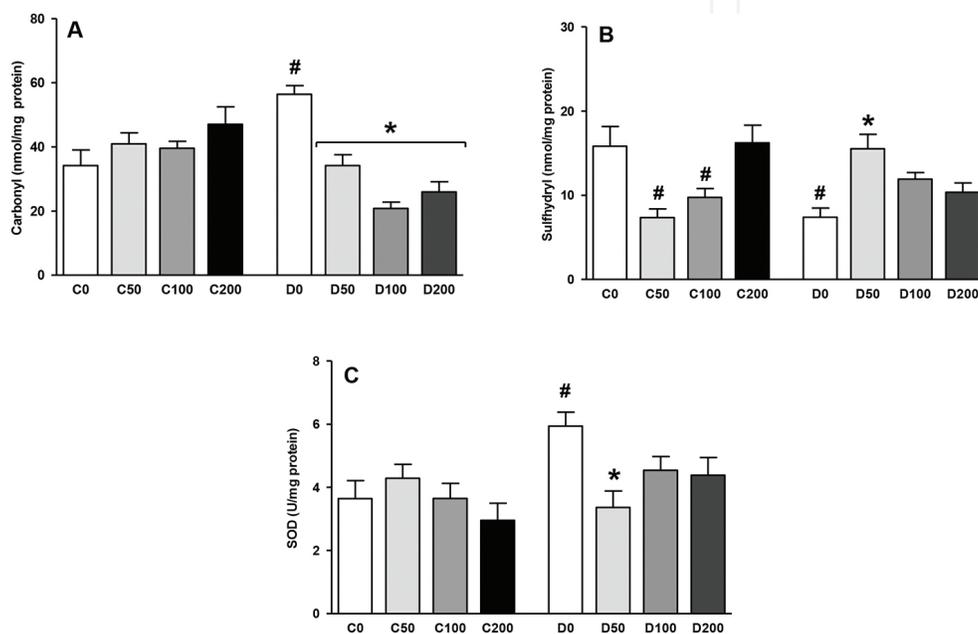


Figure 2. Effect of different doses (50, 100, and 200 mg/kg) of an organic aqueous vine leaf extract in the (A) carbonyl levels, (B) total sulfhydryl levels, and (C) SOD activity in the kidney of nondiabetic (C) and diabetic (D) rats. Values were represented as mean ± standard error; $n = 10$ /group; ANOVA two-way + Bonferroni. (#) Different from C0 group, $P < 0.05$; (*) different from D0 group, $P < 0.001$.

We also showed that diabetes increased the relative kidney weight ($P < 0.001$) and urea ($P < 0.05$) and decreased creatinine levels (Table 4). The organic vine leaf extract did not change kidney weight, but the dose of 50 mg/kg significantly decreased urea levels in diabetic rats. Moreover, the organic extract decreased creatinine at doses of 50 and 100 mg/kg in diabetic rats and at dose of 50 mg/kg in nondiabetic rats.

The nephroprotective effect of our vine leaf extract is related to its ability to inhibit *in vivo* oxidative stress. Our results replayed *in vitro* assays that showed that the organic and conventional vine leaf extracts prevent both lipids and proteins oxidative damages in the kidney after hydrogen peroxide or alcohol-induced stress [29, 39]. Polyphenols are the main antioxidants from vine leaf, since these compounds undergo redox reactions and hydrogen atoms transfer from the phenolic hydroxyl group to the free radicals, stabilizing them [29, 64]. Bioactive phytochemicals in our extract showed a remarkable antioxidant activity as evidenced by the

reduction of protein oxidation and increase in nonenzymatic antioxidants in the renal tissue of diabetic rats. Resveratrol, one of these bioactive compounds, restores the nonenzymatic levels of antioxidants in the kidney of diabetic rats by reducing the availability of reactive species and improving antioxidant status in this tissue [65]. Indeed, flavonoids increase the expression of enzyme γ -glutamylcysteine synthetase, a rate-limiting enzyme in the synthesis of glutathione, a potent antioxidant [66].

Groups	Kidney weight (g)	Urea (mg/dl)	Creatinine (mg/dl)
C0	0.32 ± 0.03	31.01 ± 12.58	0.29 ± 0.04
C50	0.31 ± 0.03	29.20 ± 3.70	0.25 ± 0.03**
C100	0.31 ± 0.03	28.05 ± 7.59	0.28 ± 0.03
C200	0.33 ± 0.08	27.80 ± 4.08	0.28 ± 0.07
D0	0.53 ± 0.08*	77.03 ± 25.52*	0.29 ± 0.08
D50	0.52 ± 0.07*	40.71 ± 16.78#	0.20 ± 0.03*#
D100	0.52 ± 0.04*	56.02 ± 16.39	0.25 ± 0.07#
D200	0.50 ± 0.06*	59.80 ± 22.32	0.31 ± 0.09
<i>P</i>	<0.001	<0.05	<0.05

Values are represented as mean ± standard deviation, $n = 10$ /group; ANOVA two-way + Bonferroni; (*) different from C groups; (**) different from C0 group, (#) different from D0 group.

Table 4. Relative weights of kidney (g/% body weight), as well as urea and creatinine levels, after 30 days of daily oral administration from an organic aqueous vine (*Vitis labrusca*, L.) leaf extract, in different doses (50, 100, or 200 mg/kg), in diabetic (D) and nondiabetic (C) rats.

Regarding the antioxidant enzymes, we found that only the dose of 50 mg/kg prevented the increasing on SOD activity in the kidney by the chronic hyperglycemia. Because SOD catalyzes the dismutation of superoxide to H_2O_2 and water, we may infer that this was the main reactive species produced in this tissue in our diabetic rats, prevented by polyphenols present in the organic vine leaf extract [38]. We do not discard that diverse effect would be found after chronic treatment with conventional vine leaf extract, since a study showed that only the organic extract from vine leaf (*Vitis labrusca*) restored SOD activity after *in vitro* alcohol-induced stress in the kidney of rats [39].

Lower urea and creatinine in diabetic rats treated with vine leaf extract at the dose of 50 and 100 mg/kg suggested a dose-related nephroprotective effect and consequently, improving on renal function. These results agree with another study that showed that polyphenols extracts from *Hibiscus sabdariffa* improved renal function in an experimental model of diabetes [67]. Resveratrol also decreased creatinine and urea levels, protecting against kidney damage caused by chronic hyperglycemia [65]. In nondiabetic rats, our extract decreased creatinine levels at dose of 50 mg/kg, suggesting an improvement on renal function by hemodynamic mechanisms, already evidenced by regulation of blood flow from polyphenols [57]. Indeed, acute aqueous extracts of *Vitis indica* leaves increased the urine volume, sodium and potassium

chloride excretion in rats [68]. Moreover, the pretreatment with epicatechin in rats exposed to an animal model of nephrolithiasis increased creatinine excretion and urine volume, reducing renal calcium and preventing papillary renal tissue from subepithelial calcification [69]. Pretreatment with vine leaf (*Vitis vinifera*) extract also restored the renal function, evidenced by decreasing on creatinine, urea, uric acid, and calcium plasma levels, associate to lower histopathologic injuries (Table 3) [27]. In addition, all these parameters were related to lower lipid oxidation and restoring on nonenzymatic antioxidant defenses in the kidney. Such nephroprotective effects were attributed to the antioxidant properties of proanthocyanidins and other flavonoids present in vine leaf [27].

6. Effect of vine leaf extracts on the central nervous system

The brain is susceptible to the oxidative damage and shows high oxygen consumption rate and abundant lipid content. Indeed, evidence shows that oxidative stress and inflammation are associated with Parkinson, Alzheimer, and other neurodegenerative diseases [70–72].

Bioactive compounds as flavonols, flavan-3-ols, anthocyanins, phenolic acids, or resveratrol, in red wine and other grapevine byproducts have been extensively studied by their central effect. Conventional and organic vines leaf extracts decrease lipid and protein oxidative damage induced by hydrogen peroxide (H_2O_2) in the rat brain, reestablishing the SOD and CAT activity [9]. The same neuroprotective effect was found after treatment with both conventional and organic vines leaf extracts in the cortex, hippocampus, and cerebellum after carbon tetrachloride-induced stress in rats [30].

Although poor central bioavailability, resveratrol is effective for the treatment of aging-related learning and memory deficits [73]. A recent study showed that oral resveratrol (20 and 40 mg/kg) ameliorated learning and memory impairment and prevented memory extinction in mice in an *in vivo* animal model of Alzheimer disease [74]. Agreeing with these results, resveratrol also improve learning and memory in old mice, related to increasing on CREB (cAMP response element-binding) and BDNF (brain-derived neurotrophic factor) proteins in the hippocampus [75]. Adding to these neurochemical mechanisms, the beneficial effect of resveratrol have been related to its anti-inflammatory and antioxidant properties in different brain areas as in the hippocampus, and frontal cortex of diabetic and nondiabetic rats [76]. Natural products, rich in anthocyanin, as purple sweet potato extracts also exhibit antioxidant properties and memory enhancing effects in rats [77].

Methanolic *Vitis amurensis* leaf extract (25–100 mg/kg, oral gavage) prevented oxidative stress after cerebral ischemic in rats indicated by increasing on GSH and decreasing on lipid peroxidation, beyond inhibition of cyclooxygenase-2, and phosphorylated mitogen-activated protein kinases (MAPKs) [78]. Moreover, that extract inhibited the glutamate-induced neuronal death *in vitro*, and changed the apoptosis-related proteins, suggesting that the neuroprotective effect of this extract is related to its antioxidant, anti-inflammatory, and anti-excitotoxic properties, preventing the neurodegeneration in stroke [78]. Glutamate-induced neural cytotoxicity *in vitro* was prevented by a *V. vinifera* seed extract [79]. Grape seed extract

also inhibited DNA damage in the CA1 region of gerbil hippocampus after transient forebrain ischemia, evidencing a neuroprotective effect [80].

7. Conclusion

For centuries, the therapeutic benefits of grapevines and other byproducts have been empirically explored. Recently, it has grown the interest in the health benefits from vine leaves. Leaves remain a waste product from many vine farming, although they show 10 times higher antioxidant activity than grape juice or pulp. Vine leaf extracts, for medical use, or freshly/cooked, for eating as a supplement, are devoid of alcohol (as wine) or sugar (as juice) providing an additional advantage from other vine byproducts. Here, we showed the effect of vine leaf extract in different tissues and point the needed of increase the researchers in the area to explore clinical use of this natural product.

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