



ISSN (E): 2277-7695
ISSN (P): 2349-8242
NAAS Rating: 5.23
TPI 2022; SP-11(6): 2235-2243
© 2022 TPI

www.thepharmajournal.com

Received: 10-04-2022

Accepted: 16-05-2022

Anvi Rana

Department of Food Technology and Nutrition, School of Agriculture, Lovely Professional University, Phagwara, Punjab, India

Jaspreet Kaur

Department of Food Technology and Nutrition, School of Agriculture, Lovely Professional University, Phagwara, Punjab, India

Kartik Sharma

International Center of Excellence in Seafood Science and Innovation (ICE-SSI), Faculty of Agro-Industry, Prince of Songkla University, Hat Yai, Songkla 90110, Thailand

Jyoti Singh

Department of Food Technology and Nutrition, School of Agriculture, Lovely Professional University, Phagwara, Punjab, India

Vishesh Bhadariya

Department of Chemical and Petroleum Engineering, School of Chemical Engineering and Physical Sciences, Lovely Professional University, Phagwara, Punjab, India

Corresponding Author

Jaspreet Kaur

Department of Food Technology and Nutrition, School of Agriculture, Lovely Professional University, Phagwara, Punjab, India

A comprehensive review on the nutritional value and health benefits of grape leaves

Anvi Rana, Jaspreet Kaur, Kartik Sharma, Jyoti Singh and Vishesh Bhadariya

Abstract

For centuries, grape leaves, especially red grape leaves, have been employed in herbal medicines and are still in use today. While grape leaves have long been used to cure a variety of diseases, further research is still needed to determine their true effectiveness. Due to high polyphenol content (as enlisted in table 4), grape leaves are frequently used in food fortification due to their health advantages. As a result, a complete review of grape leaves extract polyphenols and their health advantages in functional foods are required. As a result, we highlighted how grape leaves are a rich source of nutrients for general health and wellness, as well as having a complex chemical composition that appears to contribute to their therapeutic potential, particularly antioxidant activity. Grape leaves also offer anti-inflammatory, reproductive, cardiovascular, diabetic, and anti-cholesterol qualities, among other physiological advantages. The bioactive polyphenols, health benefits, and biological activity of grape leaves have all been reviewed.

Keywords: Grape leaves, antioxidant properties, functional foods, biological polyphenols, health benefits

1. Introduction

Grape cultivation is considered as a profitable trade in many nations. In addition to their market worth, grapes and their by-products contain nutritional and functional characteristics. Grape leaves have long been used to control bleeding and help relieve discomfort, diarrhea and is also associated with better blood lipid parameters, endothelial dysfunction, and other cardiovascular disease markers (Dani *et al.*, 2007) ^[1]. The therapeutic properties of grapes and leaves are mostly due to the presence of bioactive flavonoids in them. Grapevine leaves, which are usually thrown out by grape producers, are high in antioxidants and other therapeutic components. Since grape juices are heavy in sugars and wine is an alcoholic beverage, both of which are not allowed for diabetics or alcoholics people, their medical effects have only lately been researched (Asami *et al.*, 2003) ^[2].

2. Morphology, description, taxonomical classification and uses

2.1 Morphology

Grape leaves are basic oval or circular ovate with sharp spines. They have lengthy spines and are 5-25 cm broad. The mature leaf segment consists of Petiole, lobes, lateral sinus, tooth as described in figure 1. They have harsh teeth and can be entire or lobed (3-5 lobes), with bristly or woolly hair. On the flower, tiny, fragrant yellow-green blooms bloom. (Xia *et al.*, 2010) ^[4]. The fruits are spheroid or ovate berries that range in size from 6 to 25 mm in length and color (from green to yellow to dark blue-purple). Fruits (grapes) come in a variety of flavors, including sour, sweet, and juicy. Each one has 3-4 seeds (Rockenbach *et al.*, 2011) ^[3]. A grown leaf may be described using the following identifiers which has been mentioned in table 1 and the taxonomical classification of the same has been enlisted in table 2.

2.2 Biological Explanation

The Vitaceae family includes grapes, which are woody vines. This genus has over 700 species, the majority of which are found in tropical and subtropical regions, while some do occur in colder areas. *Vitis* is a genus with around 50 species. Some grape cultivars are occasionally used in gardening. *Vitis vinifera* and *Vitis Coignetiae* are two species that are commonly used in horticulture (Singh *et al.*, 2004) ^[10].

2.3 Ecological Background

The grapevine is widely present in a region that stretches from northeast Afghanistan to the Black Sea and the southern borders of the Caspian Sea. It was cultivated there around 4000 BCE and spread over the Mediterranean Basin, Western Europe, India, China, and Japan (Devi *et al.*, 2011)^[11].

2.4 Ethnic and Cultural description

One of the most ancient and traditional culinary applications of the grape leaf is the Greek meal "Dolmathes." Dolmathes is a term that refers to the Ottoman Empire's dominance over Greece, the Middle East, and the Mediterranean. Avgolemono, a lemon-based sauce that may be served hot or cold, is served with dolmades stuffed with meat, rice, and herbs. In Greece, Dolmathes are exclusively eaten with Avgolemono, which gives the dish a creamy, salty, and sour flavor. Dolmathes are commonly served as a snack or as a side dish to the main dinner (Orhan *et al.*, 2007)^[17].

2.5 Uses

In vineyards, grape leaves and shoots are chopped after the grapes are gathered. These leftovers are either pulped and returned to the vineyard or burnt on-site. In Turkey, grape leaves are an important source of food for animals during the critical period when field quality and quantity are poor (Dani *et al.*, 2010)^[6]. Grape leaves have been suggested as a potential antioxidant and nutritional supplement (Pietta 2000). Grape leaves were first used as a container for a mixture of fillers. They've become increasingly popular, and they may now be found in sauces, rice and grain dishes, steamed fish, and a variety of other foods (Pari and Suresh, 2008)^[7].

3. Nutritional value and bioactive composition of grapeleaves

Grape leaves are high in fiber and low in calories (13 kcal), and they are high in vitamins A and K. They also contain a lot of antioxidants. According to studies, grape leaves contain ten times the antioxidant properties of grape juice or pulp (Gabler *et al.* 2003)^[36]. The nutritional composition (proximate as well as mineral content) of grapeleaves is enlisted in table 3.

3.1 Chemical composition and bioactive constituents

Many physio-chemical studies stated that there is the presence of phenolics, Stillbenoids, Anthocyanins, tannins, terpenoids, and proteins. It has been shown by the sources that the geography of phenolic content in VV varies (Gambuti *et al.*, 2004)^[37]. Catechins, flavonoids, tannins, malic, silicic, citric, tartaric, and succinic acids, as well as resveratrol, are the principal physiologically active components of the grape leaves (Garidini *et al.*, 2004).

3.2 Bioactivepolyphenols in grape leaves

The *Vitis vinifera* s cultivated in a wide range of regions across the world, but mostly in temperate areas with plenty of precipitation, hot and dry summers, and chilly climes. The phytochemical development of grape leaves is influenced by climate, soil, traditional or organic farming techniques, and different cultivars. Phytochemical substances such as malic, oxalic, ascorbic, citric, linoleic, and tartaric acids, vitamin E, terpenes, tannins, carotenoids, and polyphenols have been identified for their beneficial effects on human health (Boccalandro *et al.*, 2011)^[39]. Flavanols (e.g., epicatechin and Gallo catechin), flavonols (e.g., quercetin and myricetin), anthocyanins (e.g., pelargonidin and cyanidin), and

resveratrol are secondary metabolites produced by plants. Antioxidants, anti-inflammatory, anticancer, antibacterial, cardio-protective, and anti-aging are some of the biochemical activities of polyphenols (Brown *et al.*, 2009)^[40]. According to a review, organic vine leaf extract contains greater resveratrol concentrations than regular vine leaf extract, even though total polyphenols are equivalent and catechin and quercetin are smaller. Due to variability in phytochemical substances, measurement of phenolic components can be applied to determine the quantity and therapeutic efficacy of vine leaves (Dinicola *et al.*, 2012)^[45].

In an analysis comparing 8 grape varieties cultivated in southern Georgia, the USA, the average content of phenolic compounds was greater in various extracts, demonstrating that the leaf (351.6mg/g) is a rich source of phenolic compounds. Grape leaves contain 10 times the antioxidant activity of grape juice or pulp, according to the antioxidant index evaluated by the Trolox comparable antioxidant potential (TEAC) assay. Agricultural operations such as organic or traditional viticulture, in addition to environmental conditions, may influence polyphenol production. In organic viticulture, grapevine cultivated without pesticides, additives, or genetic engineering changes is more resistant to external attacks from insets or bacteria, which can lead to greater creation of phytochemicals that defend the plant (Ding *et al.*, 2014)^[43].

4. Biological activities of grape leaves

The biological activity of phenolic compounds found in grape leaves has been linked to human health advantages such as antioxidant, cardio-protective anticancer, ant inflammation, anti-aging, gastrointestinal systems, and antibacterial capabilities (Cheah *et al.*, 2014)^[41].

4.1 Effects on Hepatic and gastrointestinal systems

Alcoholism and nonalcoholic liver disease have been related to chronic exposure to risk factors such as cigarette smoking, medicines, air pollutants, and irradiation. These lifestyle variables are well understood for encouraging the formation of excess oxygen and nitrogen reactive species in the liver, which can lead to oxidative stress. Despite the absence of clinical research, preclinical tests imply that natural antioxidants from products like grape leaves block or reduce the prevalence of liver disorders induced by oxidative pathways (Derry *et al.*, 2013)^[46]. Animals have been tested for morphological and biochemical changes produced by hepatotoxic chemicals, as well as the protective impact of grape leaf extracts. Biomarkers that indicate liver function, such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), glutamyl transferase (GGT), and alkaline phosphatase (ALP), were examined in these investigations (ALP). Chronic oral treatment of an aqueous extract of organic grape leaves (*Vitis labrusca*) reduced AST activity in a diabetic animal. The synergistic effects of different polyphenols in the grape leaf extract reduced oxidative stress, prevented lipid and protein injury, and increased enzymatic and non-enzymatic antioxidant defenses in the livers of diabetic rats, providing a possible therapeutic solution to hepatic complications caused by diabetes. After 3weeks of treatment, grape leaf extract (*Vitis labrusca*) lowers biliary enzyme leakage and liver fibrosis in a model of nonalcoholic steatohepatitis (Filip *et al.*, 2010)^[61]. By increasing plasma antioxidant capacity, lowering reactive species, and increasing NFB (Nuclear Factor B-cells) activity, a major mechanism linking oxidative stress and inflammation,

the extract alleviated or reduced the progression of hepatic fibrosis. The stability of hepatocyte membranes was preserved from *Vitis vinifera*, as evidenced by reduced plasma levels of AST, ALT, and GGT (Fontana *et al.*, 2013)^[48].

4.2 Effects on the cardiovascular system

Cardiovascular disease is the main cause of morbidity and mortality worldwide, with over 18 million deaths per year and a predicted increase to 23.6 million by 2030. Hypertension, dyslipidemia, obesity, and smoking are all important cardiovascular risk factors (Miura *et al.*, 2003)^[82]. By lowering the availability of nitric oxide and encouraging the formation of oxidized LDL cholesterol by activating oxidative and inflammatory peaks, these circumstances promote atherosclerosis, endothelial dysfunction, and cardiovascular damage (Cotoras *et al.*, 2014)^[52]. These factors have a deleterious effect on the vascular endothelium, reducing nitric oxide supply and encouraging the deposition of damaged LDL cholesterol by triggering oxidative and inflammatory cascades that lead to atherosclerosis, endothelial dysfunction, and cardiovascular damage. According to studies, the antioxidant, anti-inflammatory, and antithrombotic properties of grape polyphenols and compounds have been associated with a reduction in cardiovascular risk (Fraternali *et al.*, 2011)^[44]. Anthocyanins also help to improve vascular permeability and strength while also preventing platelet aggregation. Anti-inflammatory properties of flavonoids and other grape leaf components contribute to the cardiac protective system against ischemia/reperfusion injury (Berardi *et al.*, 2009)^[53]. The grape leaf extract was also tested in women who had plexopathy in their lower limbs and were on long-term hormone replacement treatment. Following 12 weeks, leaf extract treatment lowered calf and ankle circumference, as well as the diameter of the great saphenous vein (GSV), alleviating venous problems and enhancing the quality of life of users. Grape leaf extraction's antioxidant qualities have been connected to the generation of NO (nitric oxide) by endothelium and red blood cells, meaning that it modulates blood flow (Jagadeb *et al.*, 2014)^[50].

4.3 Effects on Anti-diabetic

Many studies on the anti-diabetic properties of grape leaves have been conducted. According to studies, a variety of proteins and enzymes are involved in these anti-diabetic actions. Potential glucose tolerance tests revealed that *V. vinifera* leaf extracts (100 mg/kg and 200 mg/kg, for 12 weeks) could protect a prediabetic person from peripheral alterations. It had no effect on glucose homeostasis over the 12-week treatment period and was unaffected by nerve fiber length (IENF) (in mm). Lipid profiles have changed as well (Mirmiran *et al.*, 2014)^[81].

4.4 Effects on Inflammatory diseases

An aqueous extract from grape leaves (*V. vinifera*) inhibited TNF-induced IL-8 production and transcription in human gastric epithelial cells by altering the NF- κ B pathway; this might be useful in lowering gastric inflammation. This anti-inflammatory effect is considered to be mediated by quercetin glycosides rather than anthocyanin, and it is most noticeable after stomach digestion (Aguirre *et al.*, 2014)^[83].

4.5 Effects on Hepatoprotective activity

To investigate how *V. Vinifera* affects various hepatotoxic models, it was mixed with other herbal medications. The

antioxidant, free radical scavenging, and anti-inflammatory activities of grapes leaves and other plants appear to be responsible for their hepatoprotective effects (Bagchi *et al.*, 2000)^[84]. In one study, participants were given a meal containing 15% grape leaf powder, which protected numerous tissues, including the liver, from oxidative stress produced by 20% ethanol (Charradi *et al.*, 2014)^[85].

4.6 Effects on Reproductive system

Male rats were administered grape leaves extract (2 g/kg) during their sexual maturation phase and until the completion of one spermatogenic cycle in maturity, which protected testicular anatomy from cadmium poisoning, which has been linked to male infertility (Dallasta *et al.*, 2012).

4.7 Effects on Anti-hypercholesterolemic

Vitis vinifera was reported to lower cholesterol levels and increase HDL levels in rats with clinically caused atherosclerosis. Moreover, extract administration in experimental mice lowers endothelial lining rupture and blood vessel lining thickness. For 21 days, the rats were given substantial quantities of cholesterol (2 percent by weight) and cholic acid (0.5 percent by weight) along with a portion of the ordinary diet, resulting in hypocholesteremia. Rats were given either aqueous or methanolic grape leaf extract (100 mg/kg, 200 mg/kg, or 400 mg/kg) or simvastatin (10 mg/kg) or none (cholesterol control group) (Devi and Singh, 2017)^[87].

4.8 Effects on Chronic venous insufficiency

Plant extracts from grapevine leaves, as per a 2010 study done by the Department of Dermatology at the University of Freiburg, decrease edema in patients with chronic venous insufficiency. This is a disorder in which the veins in the legs have trouble delivering blood to the heart. When blood cannot return to the heart, edema develops in the legs. Edema elimination will not only make the person more comfortable by lowering swelling but will also reduce the load on the vascular system (Reuter *et al.*, 2010)^[88].

4.9 Antioxidant activity

Grapevine leaves contain polyphenols and phenolic chemicals, which suggests that they might be an antioxidant source. Numerous antioxidant chemicals were found in the metabolic profile of 'Pinot noir' leaves, suggesting that they have substantial antioxidant potential. Pinot noir leaves have a strong antioxidant capacity (2402 198 mol TE per 100 g fresh weight) (Muresan *et al.*, 2010)^[61].

5. Bioactive nutraceutical components

Plants are major source of natural bioactive chemicals, which are employed in the pharmaceutical, dairy, and cosmetic sectors. Even yet, there are a number of disadvantages to using plants as a source of natural goods, the most notable of which is the restricted availability of the compounds of interest, as well as the quantity of beginning content, that is not always sufficient for chemical extract purposes. One strategy for resolving these difficulties is to transform agricultural waste into a useful resource by selecting numerous plant materials with greater phytochemical composition and nutritional value (Yanni *et al.*, 2015)^[56]. Grapevine bioactive chemicals have mostly been investigated at the grape level, although the vegetative parts of the plant, particularly the leaves, remain a neglected by-product of the

business. Grape leaves are a common plant material that contains antioxidants and have long been used in herbal therapy to treat leaks, inflammation, diarrhea and vomiting, and diabetes-related liver issues (Tiwari *et al.*, 2009)^[57].

6. Metabolic Profile

6.1 Fatty acids

According to fatty acid measurement, alpha-linolenic acid is the highest concentrated fatty acid in the leaves of 'Pinot Noir.' Linoleic acid and palmitic acid were the second and third most concentrated FAs, respectively accounting for 25% and 22% of total FAs (Fatty acids). Omega-6 and omega-3 polyunsaturated fatty acids (PUFAs) are not produced by human cells. Long-chain PUFAs like arachidonic and eicosatetraenoic acids, on the other hand, are predicted to be produced. These two PUFAs were allegedly discovered in 'Pinot Noir' leaves by mass spectrometry (MS), most likely from a microbiological source, and are conserved signaling molecules linked to immunological responses. The levels of 'Pinot noir' leaves used by the Implementing Agency (IA) are small, at 0.32 and 0.17, respectively, indicating that they might be part of a balanced diet (Veskoukis *et al.*, 2012).

6.2 Sterols

Plant sterols (also known as phytosterols) are a type of secondary lipid that can block cholesterol absorption and can be present in a range of meals. In the leaves of 'Pinot Noir,' we identified 22S-hydroxysterol, stysterol B, 16, 17-estriol 17-(d-glucuronide), 1-hydroxyvitamin D3 3-d-glucopyranoside, and various additional vitamin D3 derivatives (Sun *et al.*, 2012)^[59].

6.3 Polyketides

The most significant Polyketides subclasses are flavonoids and phenolic lipids. Caffeic acid, as well as its 3-glucoside and phenethyl ester forms, is a potent antioxidant phenolic acid that is thought to be found in *V. vinifera* 'Pinot noir.' Grape seeds have also yielded a number of polyphenols for application in the dairy, cosmetics, and pharmaceutical sectors. Flavonoids were detected in all *V. Vinifera* tissues and organs. In 'Pinot noir' leaves, the most common glycosylated forms and isoforms of kaempferol and quercetin, notably glucoside, galactosidase, and glucuronide conjugate forms, epicatechin, and epigallocatechin, were all putatively characterized flavonoids. Plant catechins (flavan-3-ols) are particularly fascinating and have been widely exploited in the pharmaceutical industry as nutraceutical products. The acylated anthocyanin peonidin 3-(6''- acetylglucoside) was putatively discovered for the first time in 'Pinot noir.' These acylated pigments have excellent antioxidant capabilities and increased durability, making them more desirable for usage as supplements in commercial foods. The bioactive chemicals found in 'Pinot noir' leaves included ascorbic and dehydroascorbic acid, as well as alpha-tocopherol (Singha and Das 2014)^[60].

7. Health benefits and Nutritive value

Grape leaves are plentiful in iron, a mineral that is thought to aid in the prevention of anemia. It is necessary for red blood cell hemoglobin synthesis. Vitamin C also helps, as it promotes iron absorption and so prevents anemia (Bezier *et al.*, 2002)^[25]. With 1.5 grams of fiber per cup, the leaves are rich in fiber. This ensures that grape leaves, despite their modest calorie content, can make you feel complete. Grape

leaves' fiber helps to fill your stomach while also delaying digestion, resulting in a steady release of sugar into your bloodstream rather than a spike and crash that leaves you starving (Boido *et al.*, 2006)^[26]. Grape leaves are modestly anti-inflammatory, according to a grading scale that measures the inflammatory potential of foods and dietary combinations (Borie *et al.*, 2004)^[27]. Grape leaves are particularly abundant in vitamin C, as well as fat-soluble vitamins A and K, making them an excellent source of these nutrients. Vitamin A helps your cells grow by guiding them from immature, non-functional cells to specialized cell types, which then become a part of your functioning tissue (Boselli *et al.*, 2004)^[28]. Grape leaves also contain calcium and iron, two essential minerals. Grape leaves include 51 mg of calcium per cup, which is around 5% of your daily calcium need. Iron in grape leaves allows the blood to transfer oxygen throughout the body and promotes normal circulation (Downey *et al.*, 2003)^[29]. Grape leaves have a low glycemic index. It also has a lot of dietary fiber, which helps to keep blood sugar levels in check (Downie *et al.*, 2004)^[30]. Zinc, found in grape leaves, assists in the healing and preservation of intestinal mucosa. When the mucosa of the intestine is injured, such as when diarrhea develops, it aids in the rapid healing of the gut (Duxbury *et al.*, 2004)^[31]. Grape leaves also contain calcium, which is essential for bone development. It helps to improve and maintain bone integrity (Elmer and Reglinski, 2006)^[32]. Magnesium, which is present in grape leaves, can help to relieve muscle cramps. It works as a pain reliever in all areas of the body (Flechtner *et al.*, 2004)^[33]. Vitamin B in grape leaves strengthens the nervous system. It guards each nerve's end against harm. It alleviates the symptom of numbness or tingling (Flots, 2002)^[34]. Vitamin B6 is found in grape leaves and plays an important function in the central nervous system. It strengthens the brain and improves cognitive function. It lowers the risk of dementia (Fournand *et al.*, 2006)^[35]. The nutraceuticals composition of grapeleaves is enlisted in table

8. Dietary supplements with medication effect

The grape leaf is used to treat attention deficit hyperactivity disorder (ADHD), chronic fatigue syndrome (CFS), diarrhea, heavy menstrual flow, uterine hemorrhage, and canker sores. Leg edema can be caused by poor circulation (chronic venous insufficiency). When taken orally, grape leaf extract appears to relieve symptoms of chronic venous insufficiency such as aching or heavy legs, tension, tingling, and discomfort. Eye strain is a typical occurrence, however, a person may lessen glare tension on their skin by consuming grape leaf extract capsules by mouth (Nassiri and Hosseinzadeh, 2009)^[62].

8.1 Grape supplement's functioning mode

Grapes contain flavonoids, which have antioxidant characteristics that help lessen the risk of coronary heart disease by decreasing low-density lipoproteins (LDLs, or "bad cholesterol"), relaxing blood vessels, and reducing the risk of coronary artery disease (Aghbali *et al.*, 2013)^[67]. Antioxidants found in grapes may help prevent heart disease and provide other health advantages. Red grape types have more antioxidants than white or red grape varieties (Mukherjee *et al.*, 2012)^[63]. The anti-inflammatory and astringent effects of the grape leaf are well-known. To put it another way, the grape leaf appears to have the potential to draw tissue together, which might help with bleeding and diarrhea prevention. The crimson leaves have most of these characteristics (Patel *et al.*, 2010)^[66].

8.2 Safety concerns

When consumed in average dietary proportions, the grape is likely to be healthy. The grape is perhaps healthful when consumed orally in medical proportions. Grape leaf extracts have been used for up to 24 weeks in clinical studies with no negative side effects. People could experience diarrhea if they consume a lot of grapes, especially dried grapes. Some people are allergic to grapes and grape-based products. Side effects include stomach upset, indigestion, nausea, vomiting, cough, dry mouth, sore throat, infections, headaches, and muscular pain (Parekh *et al.* 2011) [65].

9. Conclusion

Grape leaves, have been applied in herbal remedies for ages and are still in use today. Grape leaves are also used to treat diarrhea, heavy menstrual flow, uterine hemorrhage, canker sores, and excessive vaginal discharge, among other ailments. For diarrhea, hepatitis, stomach aches and pains, and thrush, Native Americans brewed a tea from grape leaves. Sore breasts, rheumatism, headaches, and fevers were treated with wilted grape leaves. Although grape leaves have been used for a long time to treat a number of ailments, further study is needed to evaluate their genuine usefulness. Grape leaves are absolutely packed with antioxidants. Their remarkable health advantages include antioxidant safety, anti-diabetic, anti-cholesterol, and anti-platelet components. Grape leaves' polyphenols' bioactivities are thought to be the principal source of grape leaves' medicinal advantages. The possible health effects of dietary polyphenols on big chronic non-communicable illnesses have been revealed in a few meta-analyses. As a consequence, more study into specific polyphenol components in grape leaves with health effects is required. Furthermore, in order to establish the benefits of integrating these beneficial polyphenol elements from grape

seeds into food systems employing new technology, much study is necessary. More study is needed to understand the efficacy of grape seed extract in the food environment and its role as an antibacterial agent in food security. Grape leaf consumption is high in nutrients, and it may contribute to a Mediterranean diet by lowering the risk of major illnesses. It appears to be a considerable source of nutrients and useful chemicals, according to the research. Grape leaf extracts are a source of bioactive components because they include more insoluble fibers than the soluble fraction, as well as considerable amounts of vitamin C and anthocyanin. However, additional research on this residue is necessary, for example, to determine the identity of other bioactive substances and to investigate the antioxidant impact of phenolic compounds and plant fatty acid content.

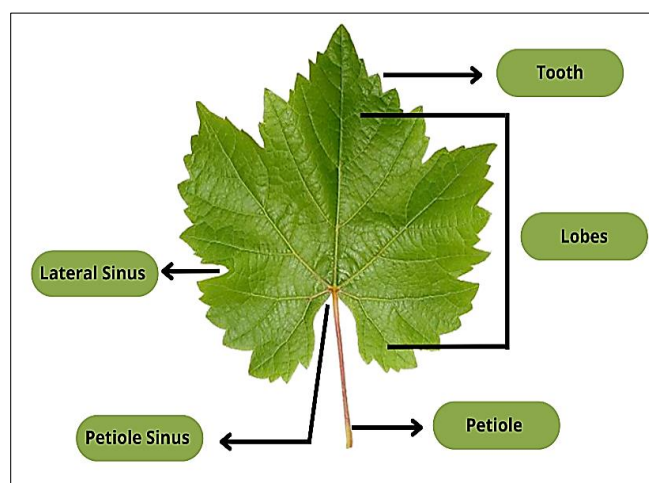


Fig 1: Mature leaf segments of *Vitis vinifera*

Table 1: Description of Grape Leaf

Parts of grape leaf	Description
1. Hair	The hair on the leaf seems to be spikes or shaggy, and the number of hairs on the leaf varies from zero to numerous
2. Size and shape of the tooth	It can be concave, pointed, or convex
3. Lobe number	It might be completely entire, or it can contain three or more four lobes
4. Shape of leaf	Oval, wedge-shaped, or pentagonal leaves are all possible
5. Color of leaf	The color of the leaf is light, dark, neutral, and toad green and red
6. Leaf contour	It's strappy, curved, or flat
7. Surface of leaf	The surface of the leaf is either rough or smooth

Source: Oliboni *et al.*, 2011 [5]

Table 2: Taxonomic classification of Grape leaves

Kingdom	Plantae
1. Scientific name	<i>Vitis vinifera</i>
2. Division	Magnoliophyta
3. Class	Magnoliopsida
4. Subclass	Rosidae
5. Order	Rhamnales
6. Family	Vitaceae
7. Sub-family	Vitoideae
8. Genus	<i>Vitis</i>
9. Species	<i>V. Vinifera</i>

Sources: Rodrigues *et al.*, 2012 [12].

Table 3: Nutritional content of grape leaves

Nutritional components	Amount (30g)
Proximate composition	
Moisture(g)	10.26
Energy (kcal)	13 cal
Carbohydrates(g)	2.42
Protein (g)	0.78
Dietary fiber (g)	1.5g
Total sugar (g)	0.88g
Minerals	
Calcium (mg)	51 g
Iron(mg)	0.37g
Magnesium(mg)	13 g
Potassium (mg)	38 g
Vitamin A(IU)	3853
Vitamin (mg)	2.6 mg
Vitamin K(ug)	15.2 ug
Vitamin E(ug)	0.28 mg

Sources: Gaberl *et al.*, 2003 ^[36].

Table 4: Polyphenolic component of grape leaf

Polyphenolic Compound of Grape vine leaf	Description
1. Anthocyanins	They are found in every higher plant and are responsible for the leaves' color. The red-colored leaf has a high concentration of anthocyanins.
2. Resveratrol	Resveratrol, a phytoalexin that belongs to the stilbenes (phenolic subgroup), is a stress-induced plant metabolic resveratrol that can only be found in stressed leaves due to stress causes such as fungal infection and damage.
3. Catechins	Catechins are abundant in a red vine leaf. The content of catechins is affected by the leaf's location on the plant and its stage of growth.

Sources: Lardo and Kreute 2000 ^[90].

10. References

- Dani C, Oliboni LS, Vanderlinde R, Bonatto D, Salvador M, Henriques JAP *et al.* Phenolic content and antioxidant activities of white and purple juices manufactured with organically-or conventionally-produced grapes. *Foo Chem Toxi.* 2007;45(12):2574-2580.
- Asami DK, Hong YJ, Barrett DM, Mitchell AE, *et al.* Comparison of the total phenolic and ascorbic acid content of freeze-dried and air-dried marionberry, strawberry, and corn grown using conventional, organic, and sustainable agricultural practices. *J Agr Foo Chem.* 2003;51(5):1237-1241.
- Rockenbach II, Gonzaga LV, Rizelio VM, Gonçalves AEDSS, Genovese MI, Fett R, *et al.* Phenolic compounds and antioxidant activity of seed and skin extracts of red grape (*Vitis vinifera* and *Vitis labrusca*) pomace from Brazilian winemaking. *Foo Res Int.* 2011;44(4):897-901.
- Xia EQ, Deng GF, Guo YJ, Li HB, *et al.* Biological activities of polyphenols from grapes. *Int J Mol Sci.* 2010;11(2):622-646.
- Oliboni LS, Dani C, Funchal C, Henriques JA, Salvador M, *et al.* Hepatoprotective, cardioprotective, and renal-protective effects of organic and conventional grapevine leaf extracts (*Vitis labrusca* var. Bordo) on Wistar rat tissues. *Anais da Academia Brasileira de Ciencias.* 2011;83(4):1403-1411.
- Dani C, Oliboni LS, Agostini F, Funchal C, Serafini L, Henriques JA, Salvador M, *et al.* Phenolic content of grapevine leaves (*Vitis labrusca* var. Bordo) and its neuroprotective effect against peroxide damage. *Toxi Vit.* 2010;24(1):148-153.
- Pari L, Suresh A, *et al.* Effect of grape (*Vitis vinifera* L.) leaf extract on alcohol induced oxidative stress in rats. *Foo Chem Toxi.* 2008;46(5):1627-1634.
- Pietta PG. Flavonoids as antioxidants. *J Nat Pro.* 2000;63(7):1035-1042.
- Halliwell B, *et al.* Role of free radicals in the neurodegenerative diseases. *Drug Agi.* 2001;18(9):685-716.
- Singh RP, Sharad S, Kapur S, *et al.* Free radicals and oxidative stress in neurodegenerative diseases: relevance of dietary antioxidants. *J Indian Acad Clin Med.* 2004;5(3):218-225.
- Devi SA, Chandrasekar BS, Manjula K, Ishii N, *et al.* Grape seed proanthocyanidin lowers brain oxidative stress in adult and middle-aged rats. *Exp Gero.* 2011;46(11):958-964.
- Rodrigues AD, Scheffel TB, Scola G, Dos Santos MT, Fank B, de Freitas SCV, *et al.* Neuroprotective and anticonvulsant effects of organic and conventional purple grape juices on seizures in Wistar rats induced by pentylentetrazol. *Neuro Int.* 2012;60(8):799-805.
- Scola G, Scheffel T, Gambato G, Freitas S, Dani C, Funchal C, Salvador M, *et al.* Flavan-3-ol compounds prevent pentylentetrazol-induced oxidative damage in rats without producing mutations and genotoxicity. *Neuro Let.* 2013; 534:145-149.
- Jayakumar T, Sakthivel M, Thomas PA, Geraldine P, *et al.* Pleurotus ostreatus, an oyster mushroom, decreases the oxidative stress induced by carbon tetrachloride in rat kidneys, heart and brain. *Chemico-Biological Interactions.* 2008;176(2-3):108-120.
- Saucier C, Mirabel M, Daviaud F, Longieras A, Glories Y, *et al.* Rapid fractionation of grape seed proanthocyanidins. *J Agri Foo Chem.* 2001;49(12):5732-5735.
- Dani C, Pasquali MA, Oliveira MR, Umezu FM, Salvador M, Henriques JA, *et al.* Protective effects of

- purple grape juice on carbon tetrachloride-induced oxidative stress in brains of adult Wistar rats. *J Med Foo*. 2008;11(1):55-61.
17. Orhan DD, Orhan N, Ergun E, Ergun F, *et al.* Hepatoprotective effect of *Vitis vinifera* L. leaves on carbon tetrachloride-induced acute liver damage in rats. *J Ethno*. 2007;112(1):145-151.
 18. Kalus U, Koscielny J, Grigorov A, Schaefer E, Peil H, Kiesewetter H, *et al.* Improvement of cutaneous microcirculation and oxygen supply in patients with chronic venous insufficiency by orally administered extract of red vine leaves AS 195. *Drugs in R & D*. 2004;5(2):63-71.
 19. Barka EA, Eullaffroy P, Clément C, Vernet G, *et al.* Chitosan improves development, and protects *Vitis vinifera* L. against *Botrytis cinerea*. *Plant Cell Reports*. 2004; 22(8):608-614.
 20. Alcalde-Eon C, Escribano-Bailón MT, Santos-Buelga C, Rivas-Gonzalo JC, *et al.* Changes in the detailed pigment composition of red wine during maturity and ageing: A comprehensive study. *Analytica Chimica Acta*. 2006;563(1-2):238-254.
 21. Asenstorfer RE, Markides AJ, Iland PG, Jones GP, *et al.* Formation of vitisin A during red wine fermentation and maturation. *Aust J of Grape Wine Res*. 2003;9(1):40-46.
 22. Aziz A, Poinssot B, Daire X, Adrian M, Bézier A, Lambert B, *et al.* Laminarin elicits defense responses in grapevine and induces protection against *Botrytis cinerea* and *Plasmopara viticola*. *Mol Pla- Micro Int*, 2003;16(12):1118-1128.
 23. Belhadj A, Saïgne C, Telef N, Cluzet S, Bouscaut J, Corio-Costet MF, *et al.* Methyl jasmonate induces defense responses in grapevine and triggers protection against *Erysiphe necator*. *J Agr Foo Chem*. 2006;54(24):9119-9125.
 24. Matthäus B. Virgin grape seed oil: Is it really a nutritional highlight. *Euro J Lipid Sci Techno*. 2008;110(7):645-650.
 25. Bézier A, Lambert B, Baillieux F, *et al.* Study of defense-related gene expression in grapevine leaves and berries infected with *Botrytis cinerea*. *Euro J Plan Patho*. 2002;108(2):111-120.
 26. Boido E, Alcalde-Eon C, Carrau F, Dellacassa E, Rivas-Gonzalo JC, *et al.* Aging effect on the pigment composition and color of *Vitis vinifera* L. cv. Tannat wines. Contribution of the main pigment families to wine color. *J Agr Foo Chem*. 2006;54(18):6692-6704.
 27. Borie B, Jeandet P, Parize A, Bessis R, Adrian M, *et al.* Resveratrol and stilbene synthase mRNA production in grapevine leaves treated with biotic and abiotic phytoalexin elicitors. *Amer J Eno Viti*. 2004;55(1):60-64.
 28. Boselli E, Boulton RB, Thorngate JH, Frega NG *et al.* Chemical and sensory characterization of DOC red wines from Marche (Italy) related to vintage and grape cultivars. *J Agr Foo Chem*. 2004;52(12):3843-3854.
 29. Downey MO, Harvey JS, Robinson SP, *et al.* Synthesis of flavonols and expression of flavonol synthase genes in the developing grape berries of Shiraz and Chardonnay (*Vitis vinifera* L.). *Aust J Grape Wine Res*. 2003;9(2):110-121.
 30. Downie A, Miyazaki S, Bohnert H, John P, Coleman J, Parry M, *et al.* Expression profiling of the response of *Arabidopsis thaliana* to methanol stimulation. *Phytochemistry*. 2004;65(16):2305-2316.
 31. Duxbury M, Hotter G, Reglinski T, Sharpe N, *et al.* Effect of chitosan and 5-chlorosalicylic acid on total phenolic content of grapes and wine. *Amer J Eno Viti*. 2004;55(2):191-194.
 32. Elmer PAG, Reglinski T, *et al.* Bio suppression of *Botrytis cinerea* in grapes. *Plant Pathology*. 2006;55(2):155-177.
 33. Flechtner-Mors M, Biesalski HK, Jenkinson CP, Adler G, Ditschuneit HH, *et al.* Effects of moderate consumption of white wine on weight loss in overweight and obese subjects. *Int J Obes*. 2004;28(11):1420-1426.
 34. Folts JD. Potential health benefits from the flavonoids in grape products on vascular disease. *Flavonoids in cell function*, 2002, 95-111.
 35. Fournand D, Vicens A, Sidhoum L, Souquet JM, Moutounet M, Cheynier V, *et al.* Accumulation and extractability of grape skin tannins and anthocyanins at different advanced physiological stages. *J Agr Foo Chem*. 2006;54(19):7331-7338.
 36. Gabler FM, Smilanick JL, Mansour M, Ramming DW, Mackey BE, *et al.* Correlations of morphological, anatomical, and chemical features of grape berries with resistance to *Botrytis cinerea*. *Phytopathology*. 2003;93(10):1263-1273.
 37. Gambuti A, Strollo D, Ugliano M, Lecce L, Moio L, *et al.* trans-Resveratrol, quercetin, (+)-catechin, and (-)-epicatechin content in south Italian monovarietal wines: relationship with maceration time and marc pressing during winemaking. *J Agr Foo Chem*. 2004;52(18):5747-5751.
 38. Gardini F, Zaccarelli A, Belletti N, Faustini F, Cavazza A, Martuscelli M, *et al.* Factors influencing biogenic amine production by a strain of *Oenococcus oeni* in a model system. *Food Control*. 2005;16(7):609-616.
 39. Boccalandro HE, González CV, Wunderlin DA, Silva MF, *et al.* Melatonin levels, determined by LC-ESI-MS/MS, fluctuate during the day/night cycle in *Vitis vinifera* cv Malbec: evidence of its antioxidant role in fruits. *J Pin Res*, 2011;51(2):226-232.
 40. Brown JC, Huang G, Haley-Zitlin V, Jiang X, *et al.* Antibacterial effects of grape extracts on *Helicobacter pylori*. *App Env Micro*, 2009;75(3):848-852.
 41. Cheah KY, Howarth GS, Bastian SEP, *et al.* Grape seed extract dose-responsively decreases disease severity in a rat model of mucositis; concomitantly enhancing chemotherapeutic effectiveness in colon cancer cells. *PloS one*. 2014;9(1):e85184.
 42. Gharib A, Fahezadeh Z, Godarzee M, *et al.* Treatment of diabetes in the mouse model by delphinidin and cyanidin hydrochloride in free and liposomal forms. *Planta medica*. 2013;79(17):1599-1604.
 43. Ding Y, Dai X, Jiang Y, Zhang Z, Li Y, *et al.* Functional and morphological effects of grape seed proanthocyanidins on peripheral neuropathy in rats with type 2 diabetes mellitus. *Phytother Res*. 2014;28(7):1082-1087.
 44. Fraternali D, Sosa S, Ricci D, Genovese S, Messina F, Tomasini S, *et al.* Anti-inflammatory, antioxidant and antifungal furan sesquiterpenoids isolated from *Commiphora erythraea* (Ehrenb.) Engl. resin. *Fitoterapia*. 2011;82(4):654-661.
 45. Dinicola S, Cucina A, Pasqualato A, D'Anselmi F, Proietti S, Lisi E, *et al.* Antiproliferative and apoptotic effects triggered by grape seed extract (GSE) versus

- epigallocatechin and procyanidins on colon cancer cell lines. *Int J Mol Sci.* 2012;13(1):651-664.
46. Derry M, Raina K, Agarwal R, Agarwal C, *et al.* Differential effects of grape seed extract against human colorectal cancer cell lines: the intricate role of death receptors and mitochondria. *Cancer letters*, 2013;334(1):69-78.
47. Filip A, Clichici S, Daicoviciu D, Catoi C, Bolfa P, Postescu ID, Muresan A, *et al.* Chemo preventive effects of *Calluna vulgaris* and *Vitis vinifera* extracts on UVB-induced skin damage in SKH-1 hairless mice. *J Physio Pharma.* 2011;62(3):385.
48. Fontana AR, Antonioli A, Bottini, R *et al.* Grape pomace as a sustainable source of bioactive compounds: extraction, characterization, and biotechnological applications of phenolics. *J Agr Foo Chem.* 2013;61(38):8987-9003.
49. Fraternali D, De Bellis R, Calcabrini C, Potenza L, Cucchiari L, Mancini U, Ricci D, *et al.* Aqueous extract from *Vitis vinifera* tendrils is able to enrich keratinocyte antioxidant defenses. *Natural product communications.* 2011;6(9):458-698.
50. Jagadeb M, Konkimalla VB, Rath SN, Das RP, *et al.* Elucidation of the inhibitory effect of phytochemicals with Kir6. 2 wild-type and mutant models associated in type-1 diabetes through molecular docking approach. *Genomics & informatics.* 2014;12(4):283-458.
51. Dai J, Wang G, Li W, Zhang L, Yang J, Zhao X, *et al.* High-Throughput Screening for Anti-Influenza A Virus Drugs and Study of the Mechanism of Procyanidin on Influenza A Virus-Induced Autophagy. *J Biomol Screen.* 2012;17(5):605-617.
52. Cotoras M, Vivanco H, Melo R, Aguirre M, Silva E, Mendoza L, *et al.* *In vitro* and *in vivo* evaluation of the antioxidant and prooxidant activity of phenolic compounds obtained from grape (*Vitis vinifera*) pomace. *Molecules*, 2014;19(12):21154-21167.
53. Berardi V, Ricci F, Castelli M, Galati G, Risuleo G, *et al.* Resveratrol exhibits a strong cytotoxic activity in cultured cells and has an antiviral action against polyomavirus: potential clinical use. *J Exper Clin Cancer Res.* 2009;28(1):1-7.
54. Liang Z, Cheng L, Zhong GY, Liu RH, *et al.* Antioxidant and antiproliferative activities of twenty-four *Vitis vinifera* grapes. *PloS one.* 2014;9(8):105-146.
55. Tang YL, Chan SW, *et al.* A review of the pharmacological effects of piceatannol on cardiovascular diseases. *Phytotherapy Research.* 2014;28(11):1581-1588.
56. Yanni AE, Efthymiou V, Lelovas P, Agrogiannis G, Kostomitsopoulos N, Karathanos VT, *et al.* Effects of dietary Corinthian currants (*Vitis vinifera* L., var. *Apyrena*) on atherosclerosis and plasma phenolic compounds during prolonged hypercholesterolemia in New Zealand White rabbits. *Food & function.* 2015;6(3):963-971.
57. Tiwari R, Mohan M, Kasture S, Maxia A, Ballero M, *et al.* Cardioprotective potential of myricetin in isoproterenol-induced myocardial infarction in Wistar rats. *Phyto Research: Int J Dev Pharma Toxic Eval Nat Pro Deri.* 2009;23(10):1361-1366.
58. Veskokis AS, Kyparos A, Nikolaidis MG, Stagos D, Aliagianis N, Halabalaki M, *et al.* The antioxidant effects of a polyphenol-rich grape pomace extract *in vitro* do not correspond *in vivo* using exercise as an oxidant stimulus. *Oxidative medicine and cellular longevity.* 2016;8(2):15-28.
59. Sun T, Chen QY, Wu LJ, Yao XM, Sun XJ, *et al.* Antitumor and antimetastatic activities of grape skin polyphenols in a murine model of breast cancer. *Food and chemical toxicology.* 2012;50(10):3462-3467.
60. Singha I, Das SK, *et al.* Antioxidant potential of different grape cultivars against Fenton-like reagent-induced liver damage *ex-vivo*. 2014;20(15):256-389.
61. Mureşan A, Alb C, Suciuc S, Clichici S, Filip A, Login C, *et al.* Studies on antioxidant effects of the red grapes seed extract from *Vitis vinifera*, Burgund Mare, Reçaş in pregnant rats. *Acta Physiological Hungarica.* 2010;97(2):240-246.
62. Nassiri-Asl M, Hosseinzadeh H, *et al.* Review of the pharmacological effects of *Vitis vinifera* (Grape) and its bioactive compounds. *Phytotherapy Research: Int J Dev Pharma Toxi Eva Nat Prod Deri.* 2009;23(9):1197- 1204.
63. Mukherjee S, Das SK, Vasudevan DM, *et al.* Dietary grapes (*Vitis vinifera*) feeding attenuates ethanol-induced oxidative stress in blood and modulates immune functions in mice. 2012;35(10):125-250.
64. Moyano-Mendez JR, Fabbrocini G, De Stefano D, Mazzella C, Mayol L, Scognamiglio I, *et al.* Enhanced antioxidant effect of trans-resveratrol: potential of binary systems with polyethylene glycol and cyclodextrin. *Drug development and industrial pharmacy.* 2014;40(10):1300-1307.
65. Parekh P, Motiwale L, Naik N, Patel Rao KVK, *et al.* Downregulation of cyclin D1 is associated with decreased levels of p38 MAP kinases, Akt/PKB and Pak1 during chemopreventive effects of resveratrol in liver cancer cells. *Experimental and Toxicologic Pathology.* 2011;63(1-2):167-173.
66. Patel KR, Brown VA, Jones DJ, Britton RG, Hemingway D, Miller AS, *et al.* Clinical pharmacology of resveratrol and its metabolites in colorectal cancer patients. *Cancer research.* 2010;70(19):7392-7399.
67. Aghbali A, Hosseini SV, Delazar A, Gharavi NK, Shahneh FZ, Orangi M, *et al.* Induction of apoptosis by grape seed extract (*Vitis vinifera*) in oral squamous cell carcinoma. *Bosnian journal of basic medical sciences.* 2013;13(3):186.
68. Downes FP, Ito K, *et al.* *Compendium of Methods for the Microbiological Examination of Foods.* Washington DC, USA: American Public Health Association. 2001;69(11):14-30.
69. Bussmann RW, Malca G, Glenn A, Sharon D, Nilsen B, Parris B, *et al.* Toxicity of medicinal plants used in traditional medicine in Northern Peru. *J Ethnopharma.* 2011;137(1):121-140.
70. Camargo UA, Tonietto J, Hoffmann A, *et al.* Progressos na viticultura brasileira. *Revista Brasileira de Fruticultura.* 2011;33(SPE1):144-149.
71. Lachumy SJT, Sasidharan S, Sumathy V, Zuraini Z, *et al.* Pharmacological activity, phytochemical analysis and toxicity of methanol extract of *Etingera elatior* (torch ginger) flowers. *Asia Paci J Trop Med.* 2010;3(10):769-774.
72. Yilmaz Y, Toledo RT, *et al.* Health aspects of functional grape seed constituents. *Trends in food science & technology.* 2004;15(9):422-433.
73. Pastrana-Bonilla E, Akoh CC, Sellappan S, Krewer G, *et*

- al.* Phenolic content and antioxidant capacity of muscadine grapes. *J Agr Foo Chem.* 2003;51(18):5497-5503.
74. Udonne JD, Ajani OO, Akinyemi O, *et al.* A comparative study of extraction of pectin from wet and dried peels using water based and microwave methods. *Int J Sci Eng Res.* 2016;7(3):416-432.
75. Yildirim Ö, Büyükbingöl Z, *et al.* Effects of supplementation with a combination of cobalt and ascorbic acid on antioxidant enzymes and lipid peroxidation levels in streptozocin-diabetic rat liver. *Biological trace element research.* 2002;90(1):143-154.
76. Bitsch R, Netzel M, Frank T, Strass G, Bitsch I, *et al.* Bioavailability and biokinetics of anthocyanins from red grape juice and red wine. *J Biomed Biotech.* 2004;24(5):293.
77. Kafkas E, Koşar M, Türemiş N, Başer KHC, *et al.* Analysis of sugars, organic acids and vitamin C contents of blackberry genotypes from Turkey. *Food chemistry.* 2006;97(4):732-736.
78. Krstic M, Moulds G, Panagiotopoulos B, West S, *et al.* Growing quality grapes to winery specifications- quality measurement and management options for growers (Winetitles: Adelaide). 2003;80(9):874-989.
79. EFSA P. Panel (EFSA Panel on Plant Health). Scientific opinion on the risk of *Phyllosticta citricarpa* (*Guignardia citricarpa*) for the EU territory with identification and evaluation of risk reduction options. *EFSA Journal.* 2014;12(2):7854-9854.
80. IAL. Institute Adolfo Lutz *et al.* Methods for Chemical and Physical Analysis of Food. 4th Edition, Analytical Standards of the Institute Adolfo Lutz, Sao Paulo. 2008;45(2):645-856.
81. Mirmiran P, Bahadoran Z, Azizi F, *et al.* Functional foods-based diet as a novel dietary approach for management of type 2 diabetes and its complications: A review. *World journal of diabetes.* 2014;5(3):267-456.
82. Miura D, Miura Y, Yagasaki K, *et al.* Hypolipidemic action of dietary resveratrol, a phytoalexin in grapes and red wine, in hepatoma-bearing rats. *Life sciences.* 2003;73(11):1393-1400.
83. Aguirre L, Fernández-Quintela A, Arias N, Portillo MP, *et al.* Resveratrol: anti-obesity mechanisms of action. *Molecules.* 2014;19(11):18632-18655.
84. Bagchi D, Bagchi M, Stohs SJ, Das DK, Ray SD, Kuszynski CA, *et al.* Free radicals and grape seed proanthocyanidin extract: importance in human health and disease prevention. *Toxicology.* 2000;148(2-3):187-197.
85. Charradi K, Elkahoui S, Karkouch I, Limam F, Hassine FB, El May MV, *et al.* Protective effect of grape seed and skin extract against high-fat diet-induced liver steatosis and zinc depletion in rat. *Digestive diseases and sciences.* 2014;59(8):1768-1778.
86. Dall'Asta M, Calani L, Tedeschi M, Jechiu L, Brighenti F, Del Rio D, *et al.* Identification of microbial metabolites derived from *in vitro* fecal fermentation of different polyphenolic food sources. *Nutrition.* 2012;28(2):197-203.
87. Devi S, Singh R, *et al.* Evaluation of antioxidant and anti-hypercholesterolemic potential of *Vitis vinifera* leaves. *Food Science and Human Wellness.* 2017;6(3):131-136.
88. Reuter J, Wölfl U, Korting HC, Schempp C, *et al.* Which plant for which skin disease? Part 2: Dermatophytes, chronic venous insufficiency, photoprotection, actinic keratoses, vitiligo, hair loss, cosmetic indications. *JDDG: Journal der Deutschen Dermatologischen Gesellschaft.* 2010;8(11):866-873.
89. Natarajan SB, Hwang JW, Kim YS, Kim EK, Park PJ, *et al.* Ocular promoting activity of grape polyphenols—A review. *Environmental toxicology and pharmacology.* 2017;150(50):83-90.
90. Lardo A, Kreute MH. Red vine leaf. 2000;40(2):58-79.
91. Borai IH, Ezz MK, Rizk MZ, Aly HF, El-Sherbiny M, Matloub AA, *et al.* Therapeutic impact of grape leaves polyphenols on certain biochemical and neurological markers in AIC13-induced Alzheimer's disease. *Biomedicine & Pharmacotherapy.* 2017;93(15):837-851.
92. Orhan N, Aslan M, Orhan DD, Ergun F, Yeşilada E, *et al.* In-vivo assessment of antidiabetic and antioxidant activities of grapevine leaves (*Vitis vinifera*) in diabetic rats. *Journal of ethnopharmacology.* 2006;108(2):280-286.