

A COMPREHENSIVE REVIEW, OF THE PHARMACOLOGICAL POTENTIAL OF *VITIS VINIFERA* (GRAPES): EXPLORING THE THERAPEUTIC PROPERTIES

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Abstract

Mankind has known the grape, *Vitis vinifera*, since ancient times. It is a common fruit with high nutritional content. This well-known grape species originated in western Asia and Southern Europe and are members of the *Vitis* genus within the *Vitaceae* family. Although grapes are mostly used to make wine, juice, dried fruit, and fresh fruit, they are also used to treat a variety of illnesses, including piles, hepatopathy, chronic bronchitis, iron deficiency anemia, and dyspepsia, because of their medicinal qualities. Grapes, or *Vitis vinifera*, are phenolic-rich fruits that are high in nutrients, minerals, and edible fibers. They also have a variety of biological activities that promote health. One of the most popular fruits in the world is *Vitis vinifera*, which is high in polyphenols and antioxidants. The *Vitis vinifera* grape is utilized in herbal medicine, its seeds and leaves are used as dietary supplements. This review covers the phytochemistry, pharmacological properties, medicinal applications, and traditional usage of *Vitis vinifera* (grapes) and their active ingredient.

Keywords: Antioxidants; Pharmacological activities; Traditional uses; *Vitis vinifera*

Introduction

There are many different kinds of therapeutic plants in the world. Numerous weeds that grow around us are actually very powerful medicinal plants that can help to treat a variety of significant health issues. India has long been recognized as one of the ancient civilizations with the largest stores of natural remedies (Parihar and Sharma, 2021). The grape, *Vitis vinifera*, is a member of the *Vitaceae* family. One of the most important agricultural commodities is grape. The farming of grapes is referred to as Viticulture. There are about 10,000 different types

of grapes in the globe. The variations are available in white, red, and green hues, as well as seedless and non-seedless types. 90% of all grape species are dominated by the *Vitis vinifera* species (Insanu *et al.*, 2021). Grapes have been utilized for their nutritional and therapeutic qualities for thousands of years. Sugars, flavonoids, proanthocyanins and anthocyanins, organic acids, tannin, mineral salts, and vitamins are abundant in these grapes (Kanagarla *et al.*, 2013). On the other hand, the majority of wines are produced in New Zealand,

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Canada, the USA, Germany, France, and Italy. Iran, Turkey, India, and the United States are among the nations that find great popularity in the manufacturing of raisins. With more than 750,000 hectares, China is the country with the largest agricultural land holdings. The total amount of wine produced in a year is 77.44 million metric tons. The majority of grapes, between 50% and 75% are used to make wine. The remaining grapes are used to make juice, dried fruits, and fresh fruits (Venkitasamy *et al.*, 2019).

As to Teixeira *et al.* (2014), there is a substantial prolonged agro-economic activity associated with the harvesting of grapes, with over 60 million tons being harvested worldwide. In 2012, 67 million grapes were produced worldwide, with about 23 million tons coming from European countries, according to FAOSTAT, the Food and Agriculture Organization of the United Nations. Its advantages, juice consumption, raisins, and other pharmacological qualities due to the numerous phytochemicals in it are the reasons for the fruit plant's widespread production of this fruit. Leaving out may be the most important and significant part of their importance in winemaking or vineyard management. Considered from these angles, the vine is a noteworthy and urgent medicinal plant.

A number of studies have demonstrated the pharmacological properties of the bioactive compounds in grapes, including their ability to act as an antioxidant, antidiabetic, anticancer, antibacterial, antifungal, anti-inflammatory, anti-acne, anti-aging, antihypertensive, protective effect, antiasthma, antiplatelet, antiviral, anticataract, antiobesity, anticholinergic, anti-sunburn, antihyperpigmentation, and properties that promote wound healing (Egea *et al.*, 2015).

Taxonomical Classification:

Kingdom: Plantae
 Clade: Tracheophytes
 Clade: Angiosperms
 Clade: Eudicots
 Clade: Rosids
 Order: Vitales
 Family: Vitaceae
 Genus: *Vitis vinifera*

History and Origin:

Early farmers and Neolithic foragers collected wild grapes. This fruit has been gathered for its nutritional and therapeutic properties for thousands of years, and its history is closely linked to that of

wine (Thurmond, 2016). Grapes have made a significant contribution to Western Civilization, as history has demonstrated. In Western Civilization, winemaking and grape farming have advanced significantly. Wine made artificially from grapes was regarded as a beverage by the ancient people. The ancient Egyptians had an odd and mystical belief regarding alcohol. Wine was regarded as a gift from the gods among them. Wine was attributed to Bacchus, Dionysus, and Osiris by the Greeks, Romans, and Egyptian tradition. Many associations with wine are found in the Old Testament. Following the Flood, Noah, according to Genesis, planted a vineyard and drank the wine the plant produced. Wine mythology and viticulture traditions make the grapevine special among cultivated plants. The berries of the wild vines that climbed on the forest trees are probably prehistoric humans. It's likely that wine was discovered by accident. Grape berries have a surface that is very conducive to yeast growth, and the fruit of the grapevine makes an ideal substrate for fermentation. The storage glove may have contributed to the unanticipated discovery of wine as a result of the growth of international wine trade (Mullins *et al.*, 1992).

Grapes are found practically everywhere in the world. It is grown in China, India, Iran, Egypt, Turkey, Brazil, Mexico, Central and Southern Europe, Western Asia, including Anatolia, the Caucasus, the Middle East, China, Africa, the Northern Mediterranean Coast, South Africa, North Africa, California, Michigan, New Mexico, New York, Oregon, Washington State, British Columbia, Ontario, Quebec, Chile, Argentina, Uruguay, and Peru. The countries that produce the most wine are New Zealand, Canada, France, Italy, and Germany. Iran, Turkey, India, and the United States are the most popular countries for producing raisins. India grows a variety of grape varieties, including Thompson seedless, Anab-e-Shahi, Dilkhush, Bangalore blue, and others (Parihar and Sharma, 2021).

Biological Description:

Figure 1 shows the parts of *Vitis vinifera*, it is a perennial woody climbing vine with stems that can reach 35 m in length, but in cultivation, annual pruning often reduces them to 1-3 m; Usually with persistent tomentum beneath, the leaves are thin, circular to circular-ovate, and measure 5-23 cm in width. The margins are dentate or jagged, the basal sinus is deep, and the lobes overlap frequently. The tendrils are branched and typically appear opposite two of the three leaves. The flowers are

numerous and arranged in dense panicles or thyrses opposite the leaves. Flower: calyx extremely small, five lobes; petals around 5 mm, pale green, sweetly perfumed; no clusters or tendrils at every third node; Fruit: huge, long clusters of soft, pulpy berries with ellipsoid to globose, oval or oblong, ellipsoid to globose, skin sticking to pulp; Seeds: 2-3, sometimes none, pyriform, with somewhat long beak (Kanagarla *et al.*, 2013).

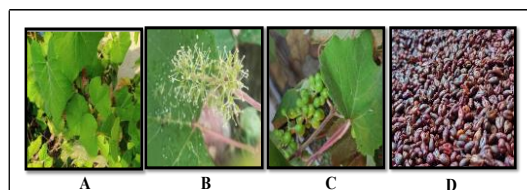


Figure 1. *Vitis vinifera* (A) Leafs (B) Flower (C) Fruit (D) Seeds

Vitis vinifera has a dark brown shrub, or less frequently a tree, with a solid trunk and many long, twisted, uneven straggling branches that are somewhat thickened at nodes (Bentley and Trimen, 2004) Flowers bloom in clusters and are fragrant and green (Kulkarni and Ansari, 2004) 3-5 lobed orbicular leaves (Pullaiah, 2006) Fruit: a berry, oblong or oval, occasionally spherical; 1.5-2.5 cm long and 0.5-2.5 cm wide; outer skin wrinkled irregularly, forming ridges and furrows; usually contains 1-4 seeds, 4-7 mm long, ovoid, rounded to triangular or simply ovoid, brown to black, odour, sweetish and pleasant (Chatterjee and Pakrashi, 1991) Table 1 represent the nutritional constituents of *Vitis vinifera* parts and its product.

Active Constituents:

Recent research indicates that consuming grapes and grape products has positive health impacts, which are linked to the special combination of polyphenolic chemicals (Georgiev *et al.*, 2014).

Fruit: A good source of dehydroascorbic acid, cholesterol, ergosterol, beta-sitosterol, malic acid, and tannic acid (bio flavonoids, or vitamin P).

Flavonoids: Approximately 5% of grape seeds contain flavonoids, such as myricetin, kaempferol-3-O-glucosides, and quercetin-3-O-glucosides.

Polyphenols: Grape seeds contain between 60 and 70 percent of the polyphenols found in grapes.

Grape polyphenols are derived from flavon-3-ol. The main ingredients include procyanidins dimer (B1, B5), procyanidin C1, procyanidin B5 - 32-gallate, (+)-catechins, (-)-epicatechins, and (-)-epicatechin-3-o-gallate.

Procyanidins and proanthocyanidins are also present in grape seeds: These are gallic acid esters. Nonetheless, there have also been reports of the presence of (+)-catechin, (-)-epicatechin, and (-)-epicatechin-3-O-gallate monomers.

Anthocyanins: 3, glucosides, 3, acetylglucosides, 3, coumaroylglucosides, 3, caffeoyl glucosides, 3,5-diglucosides, 3-acetyl-5-diglucosides, 3-coumaroyl-5-diglucosides, and 3-caffeoyl-5-diglucosides of cyanidin, delphinidin, peonidin, petunidin, and malvidin are among the anthocyanins that have been identified for *Vitis vinifera*.

Stilbene derivatives: Grapes have also been reported to contain trans-Resveratrol (trans-3,40-trihydroxystilbene) (Kanagarla *et al.*, 2013).

Table 1. Nutritional constituents of plant parts & products

References	Parts of plants & product	Nutritional constituents
(Mateo and Maicas, 2015; Romero <i>et al.</i> , 2010)	Leaf	Reducing and non-reducing sugars, lipids, vitamins, minerals, potassium, magnesium & zinc
(Mateo and Maicas, 2015)	Stem	Dietetic fibers
(Arora <i>et al.</i> , 2016)	Fruit	Proteins, fats, vitamin C, calcium, boron & phosphorus
(Esatbeyoglu <i>et al.</i> , 2016; Mateo and Maicas, 2015)	Seed	Minerals, proteins, lipids, carbohydrates, & fibers.
(Skinner and Matthews, 1989; Amiri and Fallahi, 2007)	Flower	Mineral, phosphorous, potassium and magnesium
(Di Lorenzo <i>et al.</i> , 2016)	Raisins	Sugars, insoluble fibers & minerals
(Chikwanha <i>et al.</i> , 2018)	Pomace	Crude proteins, neutral detergent fibers, acid detergent fibers, minerals, potassium, magnesium, sulfur, sodium, iron & aluminium
(Sousa <i>et al.</i> , 2014)	Pomace flour	Proteins, fibers, carbohydrates, pectin, iron, potassium, zinc, fructose & glucose
(Smolin and Grosvenor, 2020)	Seed oil	Nutritional quality & dietetic, rich source of edible oil used for salad, margarine, mayonnaise and canned foods.
(Li <i>et al.</i> , 2019)	Pulp	Fiber, vitamin B, vitamin C, potassium, calcium & magnesium.
(De Nisco <i>et al.</i> , 2013)	Grape wine	Carbohydrates, vitamin B6, minerals, polyphenols, calories.

Traditional Uses:

In certain parts of Turkey, including Malatya and Manisa, grapes are used as traditional medicinal plants. The Malatya region found that grapes helped develop blood vessels (Tetik *et al.*, 2013). According to Sargin *et al.* (2015), Manisa residents can treat a variety of conditions with grape products and parts include seeds, branches, fruit, dried fruit and leaves can help allergies, wound care, iron deficiency anemia, colds and flu, carminatives, and bronchitis. Grapes (*Vitis vinifera*) are commonly utilized in traditional medicine in Pakistan. The grapes are eaten as carminatives in the Northwest area of Pakistan (Adnan *et al.*, 2014). The leaves and entire grapes in the Sudhanoti district of Pakistan have been found to have anti-phlegm, blood-purifying, and thirst-quenching properties (Ishtiaq *et al.*, 2015).

Since ancient times, people have used the fruits of the *Vitis vinifera* plant for food and sustenance. The ripe fruit has long been used as a laxative, purgative, appetite enhancer, diuretic, aphrodisiac, and appetizer. It has also been used as a medicine for blood disorders, asthma, jaundice, and several other conditions. The stems ashes are used to treat piles, testicular enlargement, and joint pain. Grape flowers have been used as a bronchitis remedy, expectorant, and haematinic. *Vitis vinifera* leaves are utilized in traditional Iranian cuisine, as well as in the treatment of bleeding and diarrhea. Skin conditions can be treated with the sap of young grape branches. Dried fruits are used to treat coughs, body heat, thirst, and stomach-aches. They are also cooling, delicious, laxative, and soothing. The malagma of seed is used as a folk treatment for joint condylomata. Grape juice, prepared in different ways, has been traditionally used to cure different types of tumors (Kanagarla *et al.*, 2013).

Vitis vinifera Latex:

The plant-specific protein known as Major Latex Protein (MLP) was initially discovered in the latex of opium poppies and is extensively present in other plants (Nessler *et al.*, 1985; Nessler *et al.*, 1990). MLP-like proteins are proteins that have been discovered and extracted from grapes and encoded by genes that are homologous to MLP (Zhang *et al.*, 2018). In grapevines, little is known about the functions of MLP members. MLP is utilised to combat disease, and genes linked to stress responses encode MLP (Radauer *et al.*, 2008). According to a growing body of research on MLP activity in plants,

these molecules may be crucial for how plants react to biotic and abiotic stressors. Still unknown, though, are the MLP family's genome-wide identification and functional analysis in *Vitis vinifera*. Since the publication of the grape genome sequence (Jaillon *et al.*, 2007), a multi-omics data analytics platform was created.

The most often grown grape variety worldwide is *Vitis vinifera* Cabernet Sauvignon, one of the most well-known red wine grapes. 14 MLP genes from *Vitis vinifera* have been fully discovered, and the recently published assemble sequence of the Cabernet Sauvignon genome (Chin *et al.*, 2016) provides a chance to find and examine MLP gene families in this species.

Nutritional Properties:

There are two types of nutrients: macronutrients, which are required in relatively large quantities, and micronutrients, which are required in smaller amounts. Minerals and vitamins are considered micronutrients, whereas carbohydrates, lipids, fiber, proteins, and water are considered macronutrients. Chemicals found in food samples that have been linked to human harm include cyanogenic glycosides (Vetter, 2000), hemoglutiin (Wisser *et al.*, 2006), and aflatoxin. Three components interact to produce toxicity: the kind of organism, the amount of toxin present, and the length of exposure (Savage *et al.*, 2000).

Anti-nutrients are unhealthy compounds that include lead, calcium, and mercury. The body needs a lot of zinc, calcium, vitamins, and other antioxidants to counteract the effects of these substances. An anti-nutrient that hinders the body's ability to absorb minerals from food is phytotic acid. Flavonoids, a class of polyphenolic chemicals that includes tannins, are another very common type of anti-nutrient (Beecher, 2003). These substances limit the absorption of these nutrients by chelating metals like iron and zinc. Tannins, one type of polyphenol, have anticancer characteristics, therefore even though they are antinutrients, certain people may benefit from drinking green tea or other beverages high in these components (Chung *et al.*, 1998).

In addition to being low in calories (13 kcal) and high in vitamins A and K, grape leaves also have a high fiber content. They are also rich in antioxidants. Studies have shown that the antioxidant content of grape leaves is ten times higher than that of grape juice or pulp (Gabler *et al.*, 2003).

Therapeutic Uses:

Numerous studies on grapes have concentrated on some of its bioactive components, such as phenolic acids, flavonoids, and stilbenes are seen in Table 2 illustrates the therapeutic profile, parts of *Vitis vinifera*, and the types of its extracts. According to Yadav *et al.* (2009), researchers have found that the fruit has anti-tumor, immune-modulatory, antidiabetic, anti-atherogenic, anti-infectious, and neuroprotective qualities.

According to Keser *et al.* (2013), antioxidants derived from different grape extracts demonstrated superior or equal efficacy in radical scavenging, metal chelating, and lipid peroxidation inhibition when compared to butylated hydroxytoluene (BHT), tocopherol, and trolox in an in vitro investigation. Of all the extracts utilized in the study, the aqueous and ethanolic extracts of the seed exhibited the highest concentration of phenolic chemicals.

Cardiovascular Disease: It has been discovered that polyphenols shield the body against inflammation, which is frequently present in heart disease patients (Yadav *et al.*, 2009). The acute effects of polyphenols on the endothelium, or inner

lining of blood arteries, were examined in a 2013 meta-analysis of clinical trials. According to the investigation, in the first two hours following grape polyphenol consumption, blood vessel function in healthy people improved dramatically (Li *et al.*, 2013). The polyphenols in the grape's fruit, peel, and seed all demonstrated cardioprotective benefits, according to another analysis (Leifert and Abeywardena, 2008). Grapes have demonstrated protective effects against oxidative stress, atherosclerosis (plaque build-up in arteries), high blood pressure, and ventricular arrhythmia (irregular heartbeat) in animal, in vitro, and limited human trials.

Cancer Chemopreventive Effects: Researchers have looked at the chemopreventive properties of polyphenols in relation to cancer, as the disease's origins and treatments are intricate and varied (Waffo-Teguo *et al.*, 2001). These antioxidants show promise in defending the body against agents that cause cancer as well as in stopping the formation of tumor cells by safeguarding DNA and controlling programmed cell death (Lila, 2004). Grape extracts from two fruit kinds showed inhibitory effect against human colon cancer cells in an in vitro investigation. According to

Table 2. Shows that the therapeutic profile, parts of *Vitis vinifera* and its extract type

Reference	Parts of <i>Vitis vinifera</i>	Extract type	Pharmacological attributes
(Moldovan <i>et al.</i> , 2020; Balea <i>et al.</i> , 2020)	Leaf	Leaf extract	Anti-inflammatory
(Sangiovanni <i>et al.</i> , 2019)		Aqueous leaf extract	Anti-inflammatory
(Leal <i>et al.</i> , 2020; Esparza <i>et al.</i> , 2021)	Stem	Stem extract	Antibacterial, anti-aging, Antimicrobial activity,
(Zeghad <i>et al.</i> , 2019)	Fruit	Hydroalcoholic fruit extract	Antioxidant
(Sochorova <i>et al.</i> , 2020; Felhi <i>et al.</i> , 2016)	Seed	Ethanol extract	Antioxidant
(Cádiz-Gurrea <i>et al.</i> , 2017; Simonetti <i>et al.</i> , 2017; Radulescu <i>et al.</i> , 2020; Manipal <i>et al.</i> , 2019; Tkacz <i>et al.</i> , 2019; Lucarini <i>et al.</i> , 2019)		Seed extract	Anti-inflammatory, Antibacterial, Antidiabetic, anti-cancer, Anti-platelet & anti-coagulant activity
(Di Lorenzo <i>et al.</i> , 2016)	Raisins	Hydroalcoholic raisins extract	Anti-inflammatory
(Yilmaz <i>et al.</i> , 2015; Liu <i>et al.</i> , 2018; Tkacz <i>et al.</i> , 2019)	Pulp	Pulp extract	Antioxidant & Antidiabetic activity
(Yilmaz <i>et al.</i> , 2015; Pavić <i>et al.</i> , 2019; Radulescu <i>et al.</i> , 2020; Felhi <i>et al.</i> , 2016; Tkacz <i>et al.</i> , 2019; Santos <i>et al.</i> , 2017; da Costa <i>et al.</i> , 2017)	Skin	Skin extract	Antioxidant, Antibacterial, Antidiabetic & Antiobesity activity
(da Costa <i>et al.</i> , 2020)		Aqueous skin extract	Antihypertensive

Georgiev *et al.* (2014), Grape seed extract has also demonstrated the capacity to cause pancreatic cancer cells to undergo apoptosis, or normal, pre-programmed cell death, as well as to stop their proliferation. It is believed that PACs' anti-inflammatory and antioxidant properties are the cause of these effects. Also, research on animals and in vitro has demonstrated that resveratrol has cancer chemopreventive properties that impact all phases of carcinogenesis (Jang *et al.*, 1997).

Diabetes: To offset a high-fructose diet, healthy overweight or obese patients with a family history of type 2 diabetes were administered grape polyphenols in a randomized, double-blind controlled clinical research. All individuals showed protection from fructose-induced insulin resistance after nine weeks of treatment from grape polyphenols (Hokayem *et al.*, 2013). In another study, diabetic patients fasting insulin levels were lowered when they drank dealcoholized Muscadine grape wine (Banini *et al.*, 2006). Clinical trials on patients with type 2 diabetes have shown that both Grape seed extract and grape juice supplementation are related with lower blood sugar levels (Rasines-Perea and Teissedre, 2017).

Antihypertension Effect: Using the tail-cuff method, skin grape aqueous extract may be able to stop spontaneously hypertensive rats systolic blood pressure from rising. The findings showed that hypertensive rats treated with grape skin extract had blood pressure < 150 mmHg, while hypertensive rats had blood pressure > 200 mmHg (da costa *et al.*, 2020). According to Godse *et al.* (2010), the myricetin concentration of grape raisins may lower systolic blood pressure in rats given fructose as well as in rats given deoxy cortisone acetate (DOCA) and salt (Borde *et al.*, 2011).

Anti-MERS-CoV Effect: Resveratrol, also known as trans-3,5, 4-trihydroxystilbene, is a chemical found in *Vitis vinifera* that reduces MERS-CoV cell death. Additionally, neutral red uptake (NRU) tests using 250-125 µM resveratrol doses. Additionally, at high dosages, resveratrol inhibited MERS-CoV RNA replication. It has been demonstrated that administering resveratrol concurrently with MERS-CoV or afterward can prevent MERS-CoV infection (Lin *et al.*, 2017a).

Anticholinergic Effect: Seeds, skins, and flesh from *Vitis vinifera* Seyval Blanc, Hibernel, Pinot Gris, Freiminer, Roter Taminer, Regent, and Rondo can suppress acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE), according to research by Tkacz *et al.* (2019). At 55.33%, grape skin variety Rondo exhibits the highest AChE-inhibition activity. Freiminer grape seeds had the highest BuChE-inhibition activity, measuring

36.84%. Rondo skin exhibited the strongest anticholinergic action overall.

Anti-hyperpigmentation and skin lightening Effect: Tyrosinase, which is responsible for skin pigmentation, was inhibited by the anti-hyperpigmentation activity of red vine leaf extract of *Vitis vinifera* which contained flavonoids, resveratrol, gallic acid, chlorogenic acid, and epicatechin (IC₅₀ 3.84 mg/ml) (Lin *et al.*, 2017b). According to the Yucatan swine test, black skin treated with a topical solution containing 1% resveratrol five days a week and twice a day for eight weeks showed skin lightening activity without causing any irritation (Boo, 2019).

Wound-healing Effect: The hydroxyproline found in grape oil (20.10 ± 0.02 mg/g) has a wound-healing effect, as demonstrated by the 84.6% reduction in wound area on the thirteenth day following grape oil administration (Shivananda Nayak *et al.*, 2011). In earlier studies, Nayak *et al.* (2010) demonstrated that grape skin had wound-healing properties as well, as evidenced by the closure of the wound region on the thirteenth day.

Pharmacological Activities:

Antioxidant Effect:

It has been demonstrated that consuming dietary flavonoids derived from grapes in the form of grape seed powder and grape extract can effectively regulate oxidative stress and prevent oxidative damage in vivo. Grape flavonoids roles as metal-chelating and free radical-scavengers are responsible for these properties of grapes (Georgiev *et al.*, 2014). The presence of polyphenols and phenolic compounds in grapevine leaves raises the possibility that they are a source of antioxidants. The metabolic profile of "Pinot noir" leaves revealed a number of antioxidant compounds, indicating a high level of antioxidant capacity. Strong antioxidant activity can be found in pinot noir leaves (2402 198 mol TE per 100 g fresh howeight) (Muresan *et al.*, 2010).

Table 3 displays the pharmacological activity studies of *Vitis vinifera* plant parts. It's been shown that grapes especially grape seeds have a lot of antioxidant activity. Various grapes have demonstrated a relationship between the density of phenolics in the system and their antioxidant potential. The seeds of a Petite Syrah wine were used to extract procyanidin dimers, trimers, and catechin oligomers, which were reported to have antioxidant inhibitory action against LDL oxidation in vitro (Teissedre *et al.*, 1996). Procyanidin dimers B2 and B8, trimer C1, and the monomers

epicatechin, myricetin, and catechin all have high levels of antioxidant activity (Teissedre *et al.*, 1996; Yang and Xiao, 2013).

Trolox-equivalent antioxidant capacity (TEAC), ferric reducing antioxidant power (FRAP), and oxygen radical absorbance capacity (ORAC) were used to test the antioxidant activity of grape seed extracts. The results show that the extracts had TE/g values of 6.1 ± 0.8 mmol, 6.5 ± 0.5 mmol, and 8.6 ± 0.7 mmol (Cadiz-Gurrea *et al.*, 2017).

Anti-Inflammatory Effect:

Research has demonstrated that by altering the inflammatory pathways or lowering ROS levels, grape polyphenols reduce chronic inflammation. Grapefruit flavonoids and proanthocyanidins have been shown to be more effective than manufactured mono-targeted anti-inflammatory medications because they target numerous pathways to reduce chronic inflammation. It has been discovered that proanthocyanidins isolated from grape seeds play an

Table 3. Shows that pharmacological activity studies in plant parts

Reference	Activity	Compound with plant parts	Studies	Effect
(Olchowik <i>et al.</i> , 2012)	Antioxidant	Condensed tannins from grape seeds	Incubation of erythrocyte with oxidant	Prevented oxidative damage to erythrocytes
(Kedzierska <i>et al.</i> , 2011)		Phenolic extract from grape seed	H ₂ O ₂ treated platelets	Increased glutathione depletion in human platelets
(Orhan <i>et al.</i> , 2006)		Aqueous extract of leaf	Hyperglycaemic and STZ-induced diabetic rats	Oxidative stress plays a key role in the pathogenesis of both microvascular and macrovascular complications.
(Sahpazidou <i>et al.</i> , 2014)	Anti-cancer	Stem extract (polyphenols)	Caki-1, K1, HT29 cell lines	Inhibited cell proliferation
(Sun <i>et al.</i> , 2012)		Skin extract (Polyphenols)	4 T1 cells	Inhibited the PI3k/Akt and MAPK pathways, as well as cell migration and viability.
(Micheli <i>et al.</i> , 2018)		Hydroalcoholic leaf extract	Apoptosis induced by oxaliplatin and neurotoxicity	Protect against oxaliplatin-induced oxidative damage and neuropathy
(Yanni <i>et al.</i> , 2015)	Cardio protective	Currants	0.5% w/w cholesterol diet	Lowered the development of atherosclerotic lesions, reduced oxidative stress in plasma, and maintained normal levels of AST
(Chis <i>et al.</i> , 2009)	Antidiabetic	Seed extract	STZ-induced diabetics in rats	Demonstrated protective effects on liver cells and antioxidant properties against ROS production.
(Soares de Moura <i>et al.</i> , 2012)		Skin Aqueous extract	Alloxan-induced diabetics mice	Increased glucose transporter-4, glucose did not change
(Ahmed <i>et al.</i> , 2015)	Hepato protective	Leaf aqueous extract	CCl ₄ -induced toxicity	Histological evidence and biochemical markers supported this hepatorenal protection.
(Downing <i>et al.</i> , 2015)		Grape seed procyanidin extract	Fructose induced hypertriglyceridemia	Reduced cholesterol and hepatic lipid droplet accumulation may thus reduce fructose-induced steatosis. Reduced production of TG and elevated excretion of total faecal lipids

immune modulatory effect in conditions when there is an excess of prostaglandin E2 and nitric oxide (Li *et al.*, 2001)

Grapes contain compounds called anthocyanins, which have anti-inflammatory properties. Additionally, they might lower the chance of developing a number of illnesses, such as diabetes, obesity, heart disease, Alzheimer's, and vision issues. Studies have also demonstrated that resveratrol shields the heart against inflammation. One study found that taking 250 mg of resveratrol capsules daily for three months decreased the levels of inflammatory gene markers such as interleukin 6 (IL-6), which is present in 60 individuals with heart disease. A 2012 study found that adults who regularly drank grape extract had higher levels of adiponectin. Reduced levels of this hormone are associated with an increased risk of cancer and obesity (Balea *et al.*, 2020).

High dosages of *Vitis vinifera* leaf extract exhibited strong anti-inflammatory effect, as evidenced by edema reduction by carrageenan-induced hind paw edema test at 400 mg/kg (50.02%) after 4 hours. Quercetin, kaempferol, resveratrol, and quinic acid were among the ingredients that had anti-inflammatory properties (Aouey *et al.*, 2016). In human umbilical vein endothelial cells (HUVECs), Cadiz-Gurrea *et al.* (2017) demonstrated that grape seed extracts at concentrations exceeding 50 and 60 mg/ml exhibited anti-inflammatory effect by lowering the mRNA expression of monocyte chemoattractant protein-1 (MCP-1).

According to Esatbeyoglu *et al.* (2016), grape root extract (20 µg/mL) possesses anti-inflammatory properties by reducing the expression of the Nf-kb target genes IL-1β and inducible nitric oxide synthase (iNOS) in lipopolysaccharide induced macrophages.

Anticancer Effect:

The abundance of grapes in the diet and their antioxidant qualities have drawn research teams and food producers attention to polyphenolic chemicals from grapes in recent years. Research conducted in vitro and in vivo has demonstrated the strong antioxidant activity of grape plants, which also reduces cholesterol and prevents the growth of cancer cells and platelets from aggregating (Yang and Xiao, 2013). According to Raja *et al.* (2020), they may prevent a number of illnesses linked to oxidative stress and cancer.

Certain cancers, including breast and colon cancer, may be less common in those who consume grape components, according to certain research. The anti-inflammatory, anti-proliferative, and antioxidant qualities of grape antioxidants

contribute significantly to their anticancer efficacy. Antioxidants found in grapes have been demonstrated in study models to inhibit carcinogenesis and cancer growth as well as to cause cell cycle arrest and apoptosis in cancer cells. Their impact on many cellular processes linked to tumor start, development, and advancement accounts for part of their anti-cancer action mechanism (Sun *et al.*, 2012).

The growth inhibition of A431 skin cancer cells is increased by the high concentration of *Vitis vinifera* skin and seed extract. By inducing cytotoxicity, the mechanism of its suppression may be observed. The cytotoxic effect of the two extracts was assessed using the MTT test on A431 cells and the human keratinocyte cell line (HaCaT). Using a fluorescent microscope, the IC50 values of grape seeds and skin extract on A431 cells were found to be 111.11 µg/ml and 319.14 µg/ml, respectively. This was followed by an increase in the generation of reactive oxygen species (ROS), which caused the cells to undergo apoptosis (Grace Nirmala *et al.*, 2018).

Hepatoprotective Effect:

By altering lipogenesis and β-oxidation genes through mRNA expression regulation, the polyphenol chemicals included in grape skin extract have the potential to ameliorate hepatic steatosis and obesity in mice on high-fat diets (Park *et al.*, 2013). Extract from grape seeds was able to prevent alcohol-induced liver damage. Rats given grape seed extract after being given 20% ethanol were shown to have lower levels of AST and LDH (Dogan and Celik, 2012). ALP levels may be lowered in rats given grape dried seed after they were given paracetamol (Almajwal and Elsadek, 2015).

Because of their antioxidant and anti-inflammatory qualities, grape polyphenols have been linked to hepatoprotective activity (Nassiri-Asl and Hosseinzadeh, 2009). It was shown that the grape skin extract high in polyphenols prevented diet-induced obesity and hepatic steatosis while also improving liver steatosis itself. The regulation of mRNA expression of enzymes involved in the regulation of lipogenesis and fatty acid oxidation, as well as the suppression of lipogenic enzymes in adipose and liver tissues, are likely the causes of the effect (Park *et al.*, 2013).

Antibacterial And Antimicrobial Effect:

Compounds that either kill bacteria and viruses selectively or inhibit their growth without severely damaging tissue are associated with antibacterial activity in molecules. Antibacterial drugs have a critical role in the battle against infections. *Vitis*

vinifera has a wide range of applications as antibacterial agents. Clearly, the most important component is seeds. Studies on a wide range of microorganisms have demonstrated the antibacterial properties of Grape Seed Extract (GSE). The GSE is more effective than other methods at combating both Gram-positive and Gram-negative bacteria. It inhibits a multitude of important clinical viruses and fungi (Felhi *et al.*, 2016).

Research indicates that grape catechins have the ability to suppress the growth of harmful germs. Moreover, GC, EGC, and EGCg have bacteriostatic properties. Research has been done on the antibacterial properties of catechins against bacteria and pathogens, and the findings are consistent with what was found for *C. albicans* (Fukai *et al.*, 1991; Ikigai *et al.*, 1993; Hirasawa and Takada, 2004).

According to Rauha *et al.* (2000), flavanols, trans-resveratrol, gallic acid, hydroxycinnamic acids, and tannins have all been shown to have antimicrobial activity. It has also been claimed that 1% grape seed extract has antilisterial action. Within 10 minutes, the amount of *L. monocytogenes* in the skin and seed of Ribier grapes dropped from 106 ± 107 CFU/ml to undetectable colonies.

Antimicrobial, antifungal, and antiviral properties have been shown for plant polyphenols. The antimicrobial qualities of *Vitis vinifera* various phenolic compound-containing components varied. Studies show that the antimicrobial properties of GSE are greater than those of other grape components. Grape anti-microbial activity increases with the following: meat, whole fruit grape extract, fermented pomace, skin, leaves, and seed (Georgiev *et al.*, 2014).

Antidiabetic Effect:

Diabetes is a chronic condition that alters our bodies' ability to use food as fuel. The majority of the food we eat is transformed into glucose, or sugar, and then absorbed into our circulation (Broumand, 2006). Despite the lack of knowledge on the functional protein alterations, GSE has been found to be beneficial in the treatment of diabetic nephropathy. Only nine kidney proteins were reported to restore to normal levels in diabetic rats following GSE therapy. These proteins have been demonstrated to be involved in amino acid metabolism, glycosylation damage, and oxidative stress. In diabetic rats, glycation-associated heart injury was similarly lessened by GSE (250 mg/kg body weight/d) (Cheng *et al.*, 2007).

According to Tkacz *et al.* (2019), grape seeds, skins, and flesh from *Vitis vinifera* var Seyval Blanc, Hibernial, Pinot Gris, Freiminer, Roter Taminer, Regent, and Rondo showed antidiabetic potential by inhibiting α -amylase and α -glycosidase with

an IC50 ranging from 0.27 to 1.13 mg dry sample/ml. Ostberg-Potthoff *et al.* (2019) also revealed the activity concentration of red grape juice in α -amylase and α -glycosidase; the anthocyanin fraction and co-pigment fraction red grape juice concentrate had the best actions. Grape seeds, skins, and stems from the varieties Pusa Navrang and Merlot were found to boost insulin release in isolated mice's pancreatic islets by 2-8 times compared to usual (Doshi *et al.*, 2015). Gharib *et al.* (2013) revealed that *Vitis vinifera* contained chemicals called cyanidin and delphinidin that lowered the rate of albumin and HbA1c assessed both in vitro (using the ELISA assay) and in vivo (in diabetic mice). Moreover, mice with diabetes caused by alloxan and given grape skin extract showed increased insulin secretion (Soares de Moura *et al.*, 2012).

Antiobesity Effect:

When weight gain increases the risk of obesity and fatty liver, grape skin extract may be able to stop the weight gain (Santos *et al.*, 2017; Costa *et al.*, 2017). According to Fan *et al.* (2019), proanthocyanidins found in grape skin extract of *Vitis vinifera* may have anti-fatty liver effects in mice with non-alcoholic fatty liver disease (NAFLD) caused by a high-fat diet. In addition to weight loss, lowering the levels of alanine transaminase (ALT), alkaline phosphatase (ALP), aspartate transaminase (AST), total protein (TP), total cholesterol (TC), low-density lipoproteins (LDL), and triglycerides (TG) as well as lowering the quantity of abnormal cells (lesion area) were also steps in the prevention of fatty liver. In diabetic rats, ethanolic grape seed extract from the Muscat variety may also lower blood serum levels (Giribabu *et al.*, 2015).

Cardiovascular Effect:

Several studies have indicated that consuming grapes and grape products on a daily basis may help to safeguard cardiovascular health. Improved vascular and endothelial function, lessened low-density lipoprotein (LDL) oxidation, favorable changes in blood lipid concentrations, and modulation of the inflammatory process are the causes of this protective action (Nassiri-Asl and Hosseinzadeh, 2009; Vislocky and Fernandez, 2013).

Antiacne Effect:

Propionibacterium acnes is the causative agent of acne vulgaris, the most prevalent skin condition. According to certain studies, the extract from grape leaves has anti-acne properties against *P. acnes* (Nelson *et al.*, 2016).

In addition to being particularly efficient against fungal infections and illnesses, grape seed skin, stem, berries, and other unidentified or even known components of *Vitis vinifera* are also useful. Biologically active substances with antifungal effects against a variety of diseases are stilbenes and pterostilbenes. On the other hand, grape pomace and leaves contain pterostilbene, which has strong antifungal qualities. Due to their strong antifungal activity, stilbenes are thought to be able to counteract the fungal diseases that grapevines are resistant to, and they may even be employed as factors of disease resistance in the future (Jeandet *et al.*, 2002).

Recent research has also shown that, under certain circumstances, the combination of antimycotics and EGCg has extraordinarily powerful antifungal efficacy against *Candida albicans*. In grape (*Vitis vinifera*) canes, the chemicals 3,5- and 3,4'-dimethoxy-resveratrol are present. Both compounds have also been shown to have antifungal activity at low minimum inhibitory concentrations. Additionally antifungal are the properties of grape resveratrol (Insanul *et al.*, 2021; Iriti and Faoro, 2006; Jeandet *et al.*, 2002).

Antiplatelet Effect:

For thousands of years, people have utilized grapes as a remedy for a wide range of conditions, including hypertension, hyperlipidemia, heart and blood vessel disease, and skin issues. Grape seeds have far more potent polyphenols with anticoagulant/antiplatelet and antithrombotic effects than other fruits and vegetables. Blood-thinning effects have also been demonstrated for grape (*Vitis vinifera*) seed preparations. There is a chance that it will cause more bleeding when combined with other blood thinners like warfarin (Coumadin), clopidogrel (Plavix), or aspirin.

It has also been demonstrated that grape skin extracts, such as polyflavan-3-ol, function as antiplatelet agents by stopping human platelets from clumping together (Insanu *et al.*, 2021).

Anticataract Effect:

Citronellol, which inhibits the action of glucose toxicity via an aldose reductase pathway and delays the development of diabetic cataracts, is present in grapes (*Vitis vinifera*) (Kaur *et al.*, 2017). Furthermore, Higashi *et al.* (2018) reported that resveratrol from grapes may also have anti-cataract properties based on tests conducted on 7-week-old Wistar rats with type 1 diabetes induced lens protein oxidative damage prevention.

Anti-Aging Effect:

Pollution and radiation can both contribute to skin aging. According to Cronin and Draelos, (2010) research, the t-resveratrol-containing grape seed extract from *Vitis vinifera* may be able to delay the onset of aging and may find use as an ingredient in anti-aging products. However, because *Vitis vinifera* Muscat Hamburg seed extract is rich in antioxidants and improves skin suppleness, it may find usage as an ingredient in anti-aging products (Sharif *et al.*, 2015).

Conclusion

In conclusion, *Vitis vinifera* emphasises its important function in winemaking, viticulture, and health advantages. In addition to being a vital component of the world's wine production, this species exhibits considerable medicinal promise due to its wide range of bioactive chemicals, especially resveratrol, polyphenols, flavonoids, and stilbene. These pharmacological characteristics, which include cardioprotective, anti-inflammatory, antioxidant, antidiabetic, anticancer, antibacterial, antifungal, anti-acne, anti-aging, anticataract, antihypertensive, antiplatelet, antiviral, and anti-obesity effect support a number of health advantages, including better cardiovascular health, increased cognitive function, and possible anticancer effects. The diverse therapeutic potential of grapes underscores their significance in preventive and integrative medicine. Numerous studies have been conducted on the potential benefits of *Vitis vinifera* bioactive components, especially resveratrol, for extending life expectancy and preventing chronic illnesses. When everything is considered, *Vitis vinifera* pharmacological functions provides confidence to its usage in traditional medicine and presents encouraging possibilities for other therapeutic uses. The potential benefits of products made from grapes are utilised in the management and prevention of chronic illnesses including cancer and heart disease. As a result of its rich cultural and historical relevance, *Vitis vinifera* continues to be an essential plant for ecological and economic sustainability. Further research is essential to fully elucidate their mechanisms of action and to explore the clinical applications of *Vitis vinifera* in modern medicine.

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