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Vitis vinifera: Brief overview of pharmacognostic and pharmacological studies

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Abstract
Vitis vinifera L. (Family: Vitaceae), popularly known grape species, come from western Asia and southern Europe. *V. vinifera* contains flavonoids, anthocyanidins, phenolic compounds and stilbenoids. Each portion of the grapevine contained varying amounts of phytochemical substances. Different parts of this plant show Anti-inflammatory, Hepatoprotective, Antioxidant, Antidiabetic, Antiasthmatic, Antihypertensive, Anti-ischemic, Antimicrobial, Anti-aging, Anti-cancer, Anticataract, Antipyretic, Antinociceptive, Protection against bone loss, Anticholinergic, CNS protective, Anti-alzheimer, Anti-acne, Anti-sunburn, Antiplatelet, Wound healing, Antispasmodic, Anti-viral activity in SARS-CoV-2. Each pharmacological activity is determined by the phytochemical substances found in the grapevine, the components employed, and the extraction method used. This review covers different types, chemical constituents, and pharmacological actions of different parts of *V. vinifera*.

Keywords: anthocyanidins, flavonoids, grapevine, stilbenoid, *Vitis vinifera*

Introduction
In 2016, the EU produced 55 million tonnes of agricultural and forestry wood waste [1]. These residues may serve as a source of bio-based goods (such as animal feed, biopesticides, and bioplastics) or used as a source of high-value compounds [2, 3]. Plant extracts and natural remedies have been used for thousands of years. Even though the tremendous progress of synthetic pharmaceuticals is happening, interest in plant-based medicine and cosmetic formulations from various plant fractions and extracts has gradually increased since last decade. [2].
Grapes are one in all the foremost delicious, refreshing, and wholesome fruits. They are considered as refreshing fruit with taste, nutrient content, composition, and with less calorie value. It is the largest produced fruit in the world. It's thought-about the fruit of the temperate region however has been with success accustomed in many semitropical countries of wines. Grapes also are used for the preparation of alternative merchandise corresponding to raisins, contemporary juices, and jams, etc. Sugar content, mainly hexoses, of grapes are high, and are easily digested. Grapes also contain iron and vitamins B1 and B2. The juice may function as a mild laxative as well as a kidney stimulant. In India, it is grown on a total area of 116000 hectares, yielding 22, 21, 00 tons. The industrial grape varieties full-grown in the Asian nation belong to the dicot genus *V. vinifera* (European grape variety), which originates from the Mediterranean region. Yankee grapes belong to *V. rotundifolia*, the skin separates from the pulp after ripening. The most commercially grown varieties are Metropolis blue, Gulabi, Anabe Shahi, Dilkush, Patcha Draksha, Puas seedless, Thompson Seedless, Beauty Seedless, and Perlette.
The wine-making process produces huge quantities of by-products, which include skins, seeds, and stems in various proportions [4]. The use of circular economy ideas in this sector has resulted in an evolution of activities aimed at reusing these by-products with beneficial economic implications [4].
The grape seed market has been tracked recently by Technavio, a global market research firm, and they are forecasting accordingly. According to a survey, the grapeseed oil market is predicted to increase by $ 73.8 million from 2020 to 2024, with a compound annual growth rate (CAGR) of 4% throughout that time [5]. Vendors operating in the global grape seed market done detailed study and recognized therapeutic use of these parts of the grape as the leading reason for the market environment in this sector, primarily through cosmetics.
Many studies in recent years have focused on new natural sources of actives, primarily antioxidants and antimicrobials, which are used in cosmetics and food items [2]. Furthermore, the selective extraction of specific phytochemicals from natural products is being investigated as a potential replacement for synthetic chemicals currently utilised in the cosmetics sector.
The principal phenolic components in grapes that are found in human diet include flavonols, anthocyanidins, hydroxybenzoic acids, and stilbenes [6]. They are useful in the treatment of acne, other minor skin issues, and treatment of more serious skin disorders like cancer. Due to their availability and chemical diversity, they offer excellent prospects as cosmetic additives as a result of processes in the wine business. Depending on the

qualities of the extracts utilised in their manufacturing procedures, the bioactive chemicals found in so-called natural cosmetic products may have a distinct profile [7]. Cosmetics containing natural substances having active skin functions are preferred by consumers, and they are willing to pay more for a cosmetic that offers skin advantages [8]. Topical administration and transport of bioactive chemicals through the skin can take a variety of paths, and the solubility, polarity, molecular weight, and other properties of these compounds influence their diffusion through distinct layers [9]. Since the second half of the twentieth century, the word "cosmeceuticals" has been used to describe topical products that impact both the overall look and feel of the skin. These substances are both cosmetic and pharmaceutical in nature, and have a long-lasting effect due to physiological and/or pharmacological action [10].

Parts of Grape vine plant

1. **Trunk:** Vertical main stem of the vine
2. **Arms/Cordons (Primary):** The major branches coming from the trunk or expansions of the trunk normally grow vertically.
3. **Arms/Cordons (Secondary):** Secondary arms or cordons that arise from primary arms or extensions of primary arms.
4. **Head:** The part of the trunk from which the arms or canes emerge.
5. **Shoot:** The current season's new growth (herbaceous) that emerges from a bud on the arm or trunk.
6. **Cane:** The past season's matured shoot.
7. **Spur:** A shorter cane or a portion of a cane that remains after pruning.
8. **Fruiting spur:** The spurs have a few buds, some of which sprout and grow into fruiting branches (typically the apical ones) [1].

Types of *Vitis Vinifera*

The grape is a member of the *Vitaceae* family, which includes 12 genera and over 600 species that are found across the tropics and subtropics, with a range that extends into temperate regions. *Vitis* is the only genus that contains food plants, making it extremely valuable economically. The genus *Vitis* is subdivided into two subgenera *Muscandinia* and *Euvitis*. The genus *Vitis* consists of about 60 species and there are only three species in the *Muscandinia*. While studying the origin and World distribution of *Vitis*, De Lathin in 1939 grouped many species of *Euvitis* in the following 9 sections. *Muscandinia* and *Euvitis* are the two subgenera of the *Vitis* genus. There are around 60 species in the genus *Vitis*, but only three species in the *Muscandinia*.

When exploring the origin and global spread of *Vitis* in 1939, De Lathin grouped diverse species of *Euvitis* into the 9 categories: 1. Labruscae 2. Cinerascentes 3. Ripariae 4. Muscandinia 5. Aestivales 6. Rupstress 7. Incertae 8. Viniferae 9. Labruscoides [1]

More than 90% of the world's total grape production comes from pure *V. vinifera*, often known as old-world grape, European grape, or Californian grape in the United States [2]. Pure vinifera grapes or vinifera hybrids with one or more American species are grown in Europe and other significant grape-growing locations. The majority of hybrids were created by crossing vinifera with native American species, particularly *V. labrusca* [11].

Types According to Their Use

1. **Table grapes**

1. White grapes: Thompson seedless, tas-a-Ganesh, Sonaka, Manik Chaman, Superior seedless.
2. Colored grapes: Sharad seedless, flame seedless, Crimson seedless, fantasy seedless, red globe, etc

2. **Juice grapes:** Bangalore purple, Pusa Navrang, etc
3. **Raisin grapes:** Thomson seedless, tas a Ganesh, Sonaka, arkavathi
4. **Wine grapes**

1. Coloured grapes: Ruby Cabernet, Cabernet Sauvignon, Pinot noir, Merlot.
2. White grapes: Chardonnay, Sauvignon Blanc.

5. **Seeded grapes:** Anab-e-shahi, Bangalore blue, Banqui abyad, Cheema Sahib, A pearl of Csaba, Cardina, black Champa, Gulabi, etc.

1. Thompson seedless

It was first farmed by William Thompson of Yuba City in California, and it originated in Asia Minor. In the Eastern Mediterranean region, it's known as oval Kishmish, while in Australia and South Africa, it's known as Sultana. It is a versatile cultivar that is mostly used for raisin production, with one cultivar accounting for more than half of all raisins produced worldwide. It's also employed in the production of White Desert wines. In Peninsular India, Thompson seedless is the most popular table grape. It is adaptable, and clones such as Tas a Ganesh, Manik Chaman, and Sonaka have done well in Maharashtra, Karnataka, Andhra Pradesh, and Tamilnadu. it is a mild-season variety and fruit ripens uniformly. The small and elongated berries are yellowish-green to Golden when fully ripe [11].

2. Perlette

This cultivar is a cross between sultanina Marble and scolokertekhiralyonje (sultanina Marble x scolokertekhiralyonje). Dr. H. P. Olmo of the University of California, USA, developed it. The mature fruit's

translucence is the most noticeable feature. This aspect is vividly explained by the French word 'Perlette,' which means 'tiny pearl.' Berries are medium in size, with pale, spherical flesh that is delicate and mildly flavored with Muscat. In North India, this cultivar is commercially successful [11].

3. Kishmish chorni

The vitality of the vines is average. the bunches are medium to large in size, conical in shape, shouldered, and densely packed. The berry is medium to large, brick red, and slightly elongated. The berries have a sweet flavor and a long shelf life. It is becoming quite popular in Maharashtra under the name Sharad seedless, however, under Maharashtra's agro-climatic conditions, it produces a dark purple color. Due to the high day temperature in North India, color development is weak [11].

4. Delight

This is a 'Perlette' sister seedling created by Dr. H. P. Olmo at the University of California in the United States. In 1936, a cross between Skolokertek Hiralaynoje 26 (Hungarian) and Sultanina Marble (Russian) was created. This is a Muscat variety that ripens early and has a distinct flavor. The berries are green, tiny, and almost round, and the bunch is medium in size, compact, conical, and appealing. It is suitable for both eating and shipping [11].

5. Himrod

E. Snyder created this cultivar in 1928 by crossing Ontario (American type) with Thompson seedless. It is a prolific bearer that ripens in the middle of the season, has good quality, and is resistant to insect pests and illnesses. The vine is strong and produces a lot of fruit. Yellow-green berries abound in the bunches. The disadvantage of this cultivar is that the Berry skin is quite thick and difficult to eat [11].

6. Pusa seedless

It is a selection made at IARI New Delhi from an unknown origin introduction. In many ways, though, it resembles Thompson seedless. Only the shape of the berries, which are slightly more elongated, distinguishes it from the well-known Thompson seedless. Due to its superior fruit quality, it commands a higher market price than Perlette. The vine is robust and yields a medium amount of fruit. It can also be used to make good quality raisins in addition to being used for table purposes. It has a good shelf life [11].

7. Arkavati

Long conical well-filled clusters of yellowish-green medium-sized spherical to ellipsoidal seedless berries characterize this strong variety. It was developed from a hybrid between Black Champa and Thompson seedless and was first introduced in 1980. It can produce up to three times as much as Thompson seedless varieties. This type is ideal for raisin and white dry wine production due to its thin peel and good-quality berries [11].

8. Flame seedless

This purple-hued Complex hybrid was developed in the United States. The vines are vigorous, fruitful, and adapt to a variety of training systems. In North India, it ripens about 10 days after Perlette. The berries are round and larger than perlette, and the clusters are elongated. It has a low quality of juice. Due to its higher yield than Thompson seedless, this variety is gaining popularity in Maharashtra. It develops a dark purple color in low day temperatures in Maharashtra but fails to do so in higher temperatures in North India [11].

9. Beauty seedless

The bunches are medium to large, long-shouldered, and compact with blue-black, medium-sized, spherical berries [31].

Seeded Cultivares

1. Anab-e-shahi

This is a robust cultivar that requires a lot of structure. It was brought to India by Haj pilgrims from the Middle East and is widely planted in Andhra Pradesh and Karnataka, but Thompson seedless has surpassed it in terms of seedlessness and fruit quality. The fruit is round and thin-skinned, and the bunches are appealing [11].

2. Bangalore Blue

A popular cultivar in Karnataka that produces many crops per year. It was identified as a Vitis vinifera x *Vitis labrusca* hybrid by Chatterjee and Randhawa (1952). It is used for juice and wine in addition to being used for table purposes.

The berry clusters are tiny and densely packed with little to medium-sized fruit [11].

3. Cheema sahibi

Dr. G. S. Cheema of Pune made this selection from open-pollinated seedlings of Pandhari Sahibi. The vine is strong and produces a lot of fruit. Long, conical, and shouldered with medium-sized oval berries, the bunches are long, conical, and shouldered. It's a variety that ripens late [11].

4. **Black Champa** It is a selection from the Indian Institute of Horticultural Research (IIHR) Bangalore and has been extensively employed in the institute's breeding programme. It's a high-quality purple grape. It can be juiced after being processed. The pulp has a slight Muscat flavor and is delicate and sweet. Because of its low yield and small bunches, it is not commercially viable, but it is an important parent in hybridization [11].

5. **Gulabi:** Karachi, Paneer draksha, and Muscat are some of the other names for it. The berries are deep purple, round, and modest in size, and the bunches are small and loose. The Berry skin is thick and has good shipping quality. Aside from the above-mentioned varieties Almeria types in Spain, Dattier in Spain, and South Africa are also worth mentioning. Emperor, Malaga, and Concord are popular grape varieties in the United States, Delaware and Kyoho in Japan, Italia and Muscat Hamburg in Central Europe, and Tengnian in China [11].

Major Chemical Constituents of *Vitis Vinifera*

Many phenolic chemicals are produced by *V. vinifera*. On the relative composition, there is a varietal effect. Flavonoids are mostly found in the stems, seeds, and skins of plants. Flavonoids account for about 90% of the phenolic component of wines. These substances add to the wine's astringency, color, and mouthfeel. Flavonoids have some antioxidant and chemopreventive effects [12].

Flavonols

Flavonols are a subcategory of flavonoids containing yellow pigment quercetin. Exposure to sunlight increases flavonols content in the grape berries.

Flavonoids

Flavan-3-ols

Catechines play crucial role in the grape berry's microbial defence. Catechine content in the grapes varies with the variety, high quantities found in pinot noir and low amounts seen in merlot and notably Syrah [13]. On average, flavonol quercetin is the most abundant flavonol in red grapes, followed by isorhamnetin, kaempferol, lacitrin, myricetin. Quercetin is the most abundant in white grapes, followed by kaempferol and isorhamnetin. All white grape types lack the delphinidin-like flavonols myricetin, laricitrin, indicating absence of the enzyme flavonoid 3', 5'- hydroxylase in white grape varieties. [14] Flavanols myricetin, laricetin [15], and syringes [16] are uniquely found in red grape types.

Anthocyanins

Anthocyanins are present throughout the plant kingdom. In fruits, flowers and wine grapes, they are responsible for the blue to red colors. They appear during the Veraison stage of ripening, when the skin of a red wine grape changes colour from green to red to black as the sugar content of the grape rises. Anthocyanins are exclusively found in the outer cell layer of skin in most grapes. Wine grapes contain a variety of Anthocyanins glycosides, which are responsible for a wide array of colors from Ruby red to deep black. They develop during the Veraison stage when the skin of a red wine grape changes color from green to red to black as the sugar in the grape increases during ripening. Anthocyanins are only found in the outer cell layer of skin in most grapes. There are numerous forms of Anthocyanins glycoside discovered in wine grapes that are responsible for the wide range of coloration from Ruby red to dark black. This finding can be used by ampellographers to help identify different grape varietals. Anthocyanins in *V. vinifera* are made up of only one molecule of glucose, whereas anthocyanins in non-vinifera wines, such as hybrids and American *V. labrusca*, are made up of two molecules of glucose. The phenomenon is caused by a twofold mutation in *V. vinifera's* anthocyanin 5-o-glucosyltransferase gene [17]. Also, unlike other grape types, red-berried pinot grape cultivars do not synthesise paracoumaroylated or acitylated anthocyanins. [18] Anthocyanins react with other acids and compounds in the wine, such as tannins, pyruvic acid, and acetaldehyde, as the wine ages, resulting in more brick red shades. [14] Piranoanthocyanins are chemical compounds formed during the fermentation of red wines by yeast. [19]

Tannins

Wine grape skins, stems, and seeds contain these compounds. Proanthocyanidins are the natural tannins present in grapes. Grape seed extract contains procyanidin oligomers as well as three monomers viz., catechin, epicatechin and epicatechin gallate. [13] Content of tannins in grapes varies according to the variety. The four most tannic grape varieties are Cabernet Sauvignon, Nebbiolo, Syrah, and Tannat. Proanthocyanidins, have a promising effect on vascular health. Tannins inhibit production of the peptide causing stiffening. These regions generate inhabitants with longer lifespans. [20]

Non-flavonoids

Hydroxycinnamic acids: These are the most common non-flavonoids phenols in wine, with the tartaric acid esters trans-caftaric, cis- and trans-coutaric, and trans-fetaric acids being the four most frequent. [21]

Stillbenoids

Stilbenoids are also produced by V. vinifera. The skins of wine grapes have the highest concentration of resveratrol. Both red and white wine grape varieties contain resveratrol, but red wines often have 10 times more

than white wines due to more frequent skin contact and maceration. Resveratrol produced by grapevines provides defense against microorganisms. Different grape types have different levels of resveratrol, with high content in Muscandines and the pinot family and lower levels in the cabernet family.
Piceatannol is also found in grapes which may be extracted and used to make red wine. [22]

Phenolic acids
Trace amounts of Vanillin, a Phenolic aldehyde, are found naturally in grapes but lignin structure of oak barrels have maximum content.

Chemical Structures

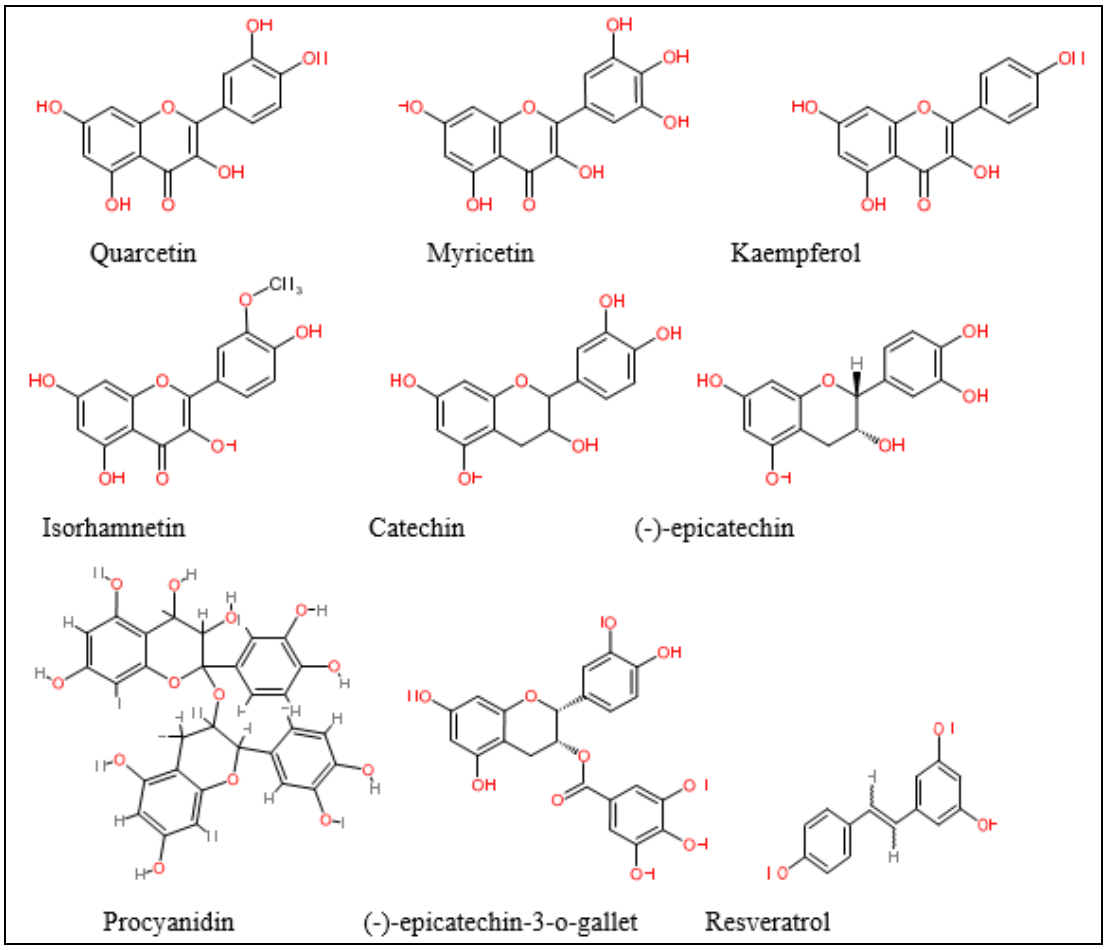

Fig 1

Pharmacological Activities of Vitis Vinifera

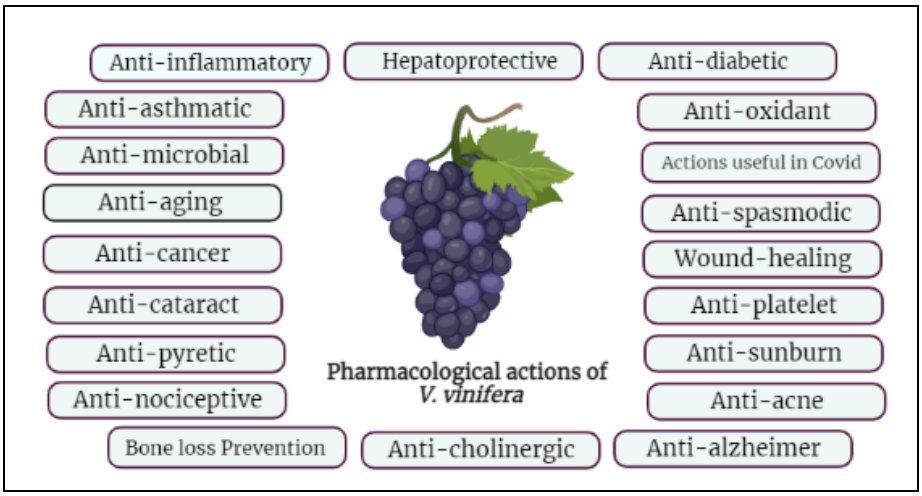

Fig 2: Pharmacological activities of *V. vinifera*

Anti-inflammatory activity: The anti-inflammatory properties of the phenol and proanthocyanidin chemicals present in Turkish and Portuguese raisin were discovered. Hydroalcoholic extracts of Turkish and Portuguese raisins inhibited IL-8 release in human gastric epithelial cells induced by TNF, indicating an anti-inflammatory mechanism. The Nf-kB pathway was inhibited by Turkish raisin extracts [23]. The anti-inflammatory efficacy of *V. vinifera* leaf extract at high dose of 400 mg/kg was confirmed by reduction in edema to 50.02 percent after four hours in a carrageen-produced hind paw edema test. Quercetin, kaempferol, resveratrol, and quinic acid were found to have anti-inflammatory properties [24]. Vitisin A, a resveratrol tetramer derived from *V. vinifera* roots, inhibited the ERK1/2 pathway, p38 phosphorylation, and NF-kB activation, which could limit lipopolysaccharide-induced NO generation. [25] Quercetin glycosides, rather than anthocyanins, may show this anti-inflammatory effect, which is less observed after gastric digestion. However, after intestinal digestion, its anti-inflammatory effect was reduced; may be due to breakdown and lack of biological activity in the gut. [23]

Hepatoprotective activity: Hepatoprotective effects of grape and other herb's are attributed to anti-oxidant, free radical scavenging, and anti-inflammatory properties [26]. After bile duct ligation, grape seed extract (50 mg/kg orally for 28 days) protected the liver from oxidative damage in rats. [27] Rats with hepatic ischemia/reperfusion injury were given grapeseed extract (50 mg/kg/day orally) for 15 days before the ischemia/reperfusion injury and then again before the reperfusion period exhibited protective role in hepatic damage. Rats fed a diet containing 15% grape seed powder were protected from oxidative stress generated by 20% ethanol in several organs, including the liver. Functional diets can aid in the prevention of chronic degenerative liver disease [28]. Proanthocyanidin containing grape skin extract of *V. vinifera* protected NAFLD mice against fatty liver high-fat-diet-induced. [29]. In diabetic rats, ethanolic grape seed extract from the Muscat variety reduced blood serum levels. [30].

Antioxidant Activity: Seven different Trolox standards were prepared in methanol in concentrations ranging from 0.05 to 0.73 mM for the calibration curve. To prepare the sample, 50.0 0.1 to 72.0 0.1 mg of extract were dissolved in 10 mL of methanol, and the resulting mixture was diluted ten times with methanol. [31] When a *V. vinifera* shoot extract was added to cultured normal human keratinocytes, it demonstrated in vitro antioxidant properties that were stronger than Vitamin E and Vitamin C. The fluorometric analysis of *in vivo* studies revealed a decrease in the level of ROS compared to controls and a decrease in the level of oxidative stress. After four weeks of application, the dermatologic evaluation revealed improvements in the main clinical signs of skin that is photoaged. [32] The grape seed extract is an antioxidant and free radical scavenger. Procyanidins from *V. vinifera* seeds were found to have a sparing/recycling impact on alpha-tocopherol in phosphatidylcholine liposomes and red blood cells. Procyanidins strongly and non-competitively inhibit xanthine oxidase activity, the enzyme that initiates the oxy-radical cascade. [33] The IC50 value of hydroalcoholic fruit extract of *V. vinifera* using DPPH method was 0.270 0.001 mg/ml, and 0.040 0.003 mg/ml using the ABTS method. [34] The Grape skin extracts from *V. vinifera* L. var. Blaufrankisch and Merlot exhibited antioxidant activity in DPPH method. The most extensive DPPH radical is found in Blaufränkisch. Scavenging activity enhanced following defoliation treatment before blooming, from 57.06 0.08 percent to 57.50 0.63 percent after defoliation treatment before blooming [35]. The antioxidant activity of white and red grape pulp extract (*V. vinifera*) using the FRAP method shows FRAP values of 7.880 mol Fe (II) / g FW > for seedless red grape (California), Victoria seedless red grape and Victoria seedless green grape [36].

Antidiabetic effect: Grape seed proanthocyanidin extract (GSPE) (250 mg/kg body weight) is effective in reversing nine kidney proteins to normal levels in diabetic nephropathy in diabetic rats. These proteins have been proven to have anti-cancer properties. Oxidative stress, glycosylation damage, and amino acid metabolism are all affected by these proteins. [37].

Antiasthmatic activity: Alcoholic extract of the dried fruits of *V. vinifera* containing gallic acid shows antiasthmatic action. The alcoholic extract of dried fruits *V. vinifera* (concentration 31 mg/kg and 42.5 mg/kg) inhibits histamine release and reduces cytokine production (IL-4, IL-5, TNF, IL-1). Another mechanism is that it improves lung function by increasing lumen size, decreasing cellular infiltration, and lowering the number of leukocytes and white blood cells [38].

Cardiovascular system: Myricetin content of grape raisin can lower systolic blood pressure in fructose-induced rats as well as deoxycortisone acetate-induced (DOCA) -hypertensive rats with a high salt intake [39]. Adult male rats fed a high-fat diet (24 percent fat) and grape skin extract (ACH09) (100 mg/kg) during lactation were protected from hypertension later in life. Adiposity, plasma triglyceride levels, glucose levels, insulin resistance, and oxidative stress could all be reversed by ACH09 [40]. Procyanidin supplementation reduced ischemia/reperfusion damage in the heart in rats and rabbits, which was associated to an increase in plasma antioxidant activity. It was also able to block a peroxynitrite attack on vascular cells by stacking on the surface of coronary endothelial cells and increasing endothelial NO-synthase-mediated relaxation in human internal mammary aortic rings. However, it was discovered that the modest vascular relaxations observed with catechin and epicatechin are not endothelium-dependent, but that the relaxing effects of grape seed procyanidin and anthocyanins are both linked to endothelium integrity and nitric oxide production and release (NO) [27].

Antimicrobial Activity: Ointments and cosmetic therapies containing grape/wine polyphenols have been used to treat and prevent skin disorders since ancient times. Grapes produce many phenolic compounds as organic chemicals responsible for defense against phytopathogens [41]. Extracts also demonstrated bacteriostatic effect at 0.5-1%. It demonstrated a bactericidal effect against E. coli O157:H7 at a concentration of 2.5-5% [42]. The anti-inflammatory properties of grape seed extracts on biofilm formation are dose dependent, and the effect differs between different types of biofilms bacteria. The extract's poor efficiency was responsible for the lower efficiencies seen at increasing concentrations [43]. Products made from seedless wine pomace had bactericidal effects on total aerobic mesophilic bacteria and lactic acid bacteria, as well as inhibiting Enterobacteriaceae. Entire winery products had bacteriostatic activity on these bacteria (n.d.). Grapeseed extracts inhibited *Alicyclobacillus acidoterrestris* vegetative growth spores and cells, as well as *Listeria monocytogenes* [44]. Wine extracts and extracts that are alcohol-free *Candida albicans* have been proven to be inhibited by pomace, fermented seeds, and skin. Grape products were attractive for being integrated because of their antifungal action [45]. A grape seed extract has been recommended for periodontal disease prevention and therapy. The efficacy of red grape seed extracts to suppress bacterial growth and plaque formation has been proven. The combination of red wine and *F. nucleatum*, *S. oralis*, and *A. oris* were all resistant to dealcoholized wine [46].

Anti-aging activity: *V. vinifera* extract was once regarded to be one of the most effective anti-aging plant medicines. One grams of trans-resveratrol (0.1 percent w/v) mixed with water-in-oil (W/O) cream (10 g) alone or with -cyclodextrin was utilised in a single-blinded experiment with eight women (ages 45-70) in each group (-CD) [47]. Radiation and pollution can cause premature aging of the skin. *V. vinifera* seeds extract containing t-resveratrol could delay the onset of aging and [48]. Seed extract *of V. vinifera* L. var. Muscat Hamburg, which is high in antioxidants and increases skin suppleness, could be used as an anti-aging component [49].

Anticancer effects: Grape seed extract demonstrated anticancer effects and induced apoptosis in colon cancer cell lines. The growth inhibition induced by Italia and Palieri grape seed extracts was much stronger than that induced by epigallocatechin and procyanidins before [50]. The anticancer action of proanthocyanidin (the structure of epicatechin octamer) found in grape stems has been linked. The presence of cell growth inhibition from prostate cancer cells demonstrated anti-prostate cancer activity. Another anticancer effect of proanthocyanidin is to increase apoptosis in prostate cancer cells and reduce the mRNA and protein expression of the prostate cancer promoter fatty acid-binding protein five [51]. Grape seed extract is a chemopreventive drug increasing temporary gap-junction intercellular communications (GJIC), increases connexin-43 gene (cx34) expression in MCF-7 cells, relocalizes connexin-43 protein (Cx43), and suppresses oestrogen [52]. Stilbenoid chemicals in grape extract shows antiproliferative action on breast cancer cells [53].
Grape seeds extract with IC50 of 245.984 µg/ml could induce apoptosis in oral squamous cell carcinoma (KB cell) as measured by cell death detection ELISA plus kit. The apoptotic effect was given by grape seeds extract was the highest at 69.56%. Also, grape seed extract enhanced DNA fragmentation [54].

Anticataract activity: Citronellol, present in grapes (*V. vinifera*), protects against glucose toxicity via an aldose reductase inhibitor mechanism, preventing diabetic cataract [55]. The resveratrol in grapes may serve as an anti-cataract by decreasing oxidative degradation of lens protein in type 1 diabetes-induced in 7-week-old male Wistar rats. [56]

Antipyretic activity: In yeast-induced pyrexia paradigm, After 22 hours following yeast injection, the efficacy of V. vinifera leaf extract was reported to lower rectal temperature at doses of 100, 200 and 400 mg/kg. After 23 hours of injection, there was a substantial decrease at dosages of 200 and 400 mg/kg. [57]

Antinociceptive activity: Through acetic acid induced writhing and formalin testing, an aqueous ethanol extract of V. vinifera L. revealed antinociceptive efficacy. The extract had a 65.5 percent inhibitory impact on acetic acid-induced writhing in mice. The formalin test (chronic pain model) on the other hand, has been shown to lower licking time and suppress licking response. [58]

Bone loss Prevention activity: Bone loss was prevented by proanthocyanidins present in seed extract of red grape by reducing inflammatory osteolysis, inhibiting osteoclast differentiation, apoptosis and promoting proliferation in mice induced by lipopolysaccharide (LPS). [59].

Anticholinergic activity: Acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) were inhibited by different varieties of grape seeds, skins, and flesh. Maximum AChE-inhibition of 55.33% was observed with Rondo var while BuChE-inhibition of 36.84% was observed with Freiminer variety. In general, Rondo skin had the most potent anticholinergic activity [59].

Central Nervous System (CNS): Grape seed extract (50 mg/kg) decreased free-radical-induced lipid peroxidation in the CNS of old rats and prevented hypoxic-ischemic brain injury in neonates. Grape seed extract (60 mg/kg) had neuroprotective properties as well. After treatment with grape seed extract, DNA damage was inhibited in the hippocampus region of gerbil in neuronal injury induced by transient forebrain ischemia. The

extract (100 mg/ kg, 30 days) could reduce the buildup of age associated oxidative DNA damage in the spinal cord and in different areas of brain. Extract treatment (100mg/kg, 30 days) to aged rats enhanced memory performance and reduced ROS production, which may be associated to elevation of the antioxidant status in the CNS [27].

Anti-Alzheimer activity: Grape skin, seeds, and fruit shows anti-Alzheimer's activity by different mechanisms. Grape powder and ethanolic extract restored memory deficits and enhanced remembrance in Alzheimer's rats. It reduces mRNA expression of amyloid precursor protein and removes tau tangles [60].

Anti-acne activity: Grape leaf extracts demonstrated anti-acne action against acne vulgaris caused by *Propionibacterium acnes*, with MIC50 and MIC90 values of 64 g/ml [61].

Anti-Sunburn activity: Resveratrol from *V. vinifera* L. exhibited anti-sunburn activity by decreasing degrees of lightness from 64.20 to 59.3 and an increasing degree of green to red from 7.51 to 13.43 in the test group after treatment with resveratrol on skin exposed to UV irradiation for 4 days. [62].

Antiplatelet activity: Grape skin extract containing poliflavan-3-ol act as an antiplatelet by inhibiting human platelet aggregation [63]. Grape seeds extract was tested using the vasodilator-stimulated phosphoprotein (VASP) assay, it could reduce adenosine diphosphate (ADP)-induced aggregation in white blood [64].

Wound-healing activity: Wound healing activity of Grape oil containing hydroxyproline is demonstrated by 84.6% reduction in wound area on the 13th day [65]. Grape skin also exhibited wound-healing activity, where the wound area was closed on the 13th day [66].

Antispasmodic activity: *V. vinifera* leaves extract had a spasmolytic effect [67]. Antispasmodic activity of 1-(3', 4'-dihydroxyphenyl)-3-(2", 4", 6"-trihydroxyphenyl)-propan-2-ol isolated from grape seeds extract was confirmed by decreasing the response of histamine-induced contraction [68].

Actions useful in Covid Era: Herpes simplex virus type 1 (HSV-1) and severe acute respiratory syndrome coronavirus 2 were used to investigate the antiviral activity of *V. vinifera* leaf extract (SARS-CoV-2). Leaf extract suppressed both HSV-1 and SARS-CoV-2 reproduction in the early stages of infection by directly inhibiting the proteins present on the viral surface at a relatively low concentration of 10 g/mL [69].

Marketed Formulations of *Vitis Vinifera* [70]

Table 1

Sr. no	Marketed drug	Class	Manufacturer	Type of formulation	Dose of *V. vinifera*	
1	Aactaril	Skin antiseptic	Himalaya		Soap	3.3 mg
2	Alpitone	Appetite Enhancer	Emami [Zandu]		Syrup	50 mg
3	Amyron Tab	Antianaemia	Aimil		Tablet	20 mg
4	Diakof	Cough and cold preparation	Himalaya		Syrup	35 mg
5	Forzyme	Digestives	Health care		Syrup	60 mg
6	Koflet	Cough and cold preparation	Himalaya		Lozenges	35 mg
7	Miko-L	Nutritional Products	Genesis		Softgel Capsule	25 mg
8	Ojus Syr	Anorectal preparation	Charak		Syrup	200 mg
9	Oxitard	Supplements	Himalaya		Capsule	71 mg
10	Tulsidryl	Cough and cold preparation	Arlak Ayurveda		Syrup	60 mg

Patents Filed On *Vitis Vinifera* [71]

Table 2

Sr. No	Application Date	Application No	Applicant Name	Field of invention	Title of Invention
1	13/05/2019	201941018984	Makka Sai Kumar	Biotechnology	Evaluation of anti-leukemic activity of Allium sativum and *Vitis vinifera* for synergistic action on ……
2	11/02/2016	201641004921	Itc Limited	Biotechnology	Composition comprising and *Rographis paniculata* extract, and Vitis vinifera l. Extract and uses thereof
3	15/03/2012	747/DEL/2012	Amity University	Biotechnology	"Biofabrication of thermally stable selenium nano balls using dried Vitis

					vinifera (raisin) extract"
4	01/02/2012	283/DEL/2012	N. V. Satheesh Madhav	Pharmaceuticals	A novel bio- mucoadhesive alprazolam nanoparticulate dispersion for nose to brain delivery using Vitis vinifera as a bio-retardant.
5	03/03/2010	414/MUMNP/2010	1. Catholic University Industry-Academic Cooperation Foundation 2. H.L. Genomics	Pharmaceuticals	Process for preparing *Vitis vinifera* pip extract and pharmaceutical composition for preventing or treating rheumatoid arthritis comprising the same.

Conclusion

Several pharmacological benefits of Vitis Vinifera extracts and their active ingredients have been summarised in this review paper, including anti-inflammatory, antioxidant, anti-asthmatic, cardioprotective, anti-microbial, and anti-aging. As indicated by the numerous pharmacological actions discovered, every component of Vitis Vinifera was rich in pharmacological compounds that had value for humans. The pharmacological activity of grapevine extracts varies depending on the part of the grapevine and the type of extract employed. As a result, *Vitis vinifera* can be useful to people in both conventional and research applications.

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