IJPSR (2023), Volume 14, Issue 6 (Review Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 08 September 2022; received in revised form, 15 November 2022; accepted 18 November 2022; published 01 June 2023

PHARMACOLOGICAL EFFECTS OF *VITIS VINIFERA* SUBSP. VINIFERA: A REVIEW

Ashok Kumar [*1], Amit Sharma [1], Pragi [2] and Varun Kumar [2]

Department of Pharmacy [1], Faculty of Medical/Para Medical & Allied Health Sciences, Jagannath University, Jaipur - 303901, Rajasthan, India.
Department of Pharmacy [2], Jagannath University NCR Haryana, Bahadurgarh - 124507, Haryana, India.

Keywords:

Vitis vinifera, Resveratrol, Proanthocyanidins, Flavonoids, Polyphenols, Catechins, Syringic acid

Correspondence to Author:
Ashok Kumar

Research Scholar,
Department of Pharmacy,
Faculty of Medical/Para Medical & Allied Health Sciences, Jagannath University, Jaipur - 303901, Rajasthan, India.

E-mail: ckashok90@gmail.com

ABSTRACT: Grapes are one of the most widely grown fruits and have been used for winemaking since the ancient Greek and Roman civilizations. Grapes are rich in proanthocyanidins which have been shown to possess potent free radical scavenging activity. Grape seeds are a complex matrix containing 40% fiber, 16% oil, 11% proteins, and 7% complex phenols such as tannins, in addition to abundant quantities of gallic acid, *p*-coumaric, caffeic and ferulic acids etc. also present. Roots contain resveratrol, vitisins A & B and other stilbenoid compounds. Leaves of grapes include gallocatechin, catechins, procyanidins, epicatechins, hydroxybenzoic acid, syringic acid and coumarin. Grapes are rich sources of flavonoids and contain monomers, dimers, trimers, oligomers and polymers. The monomeric compounds includes (+)-catechins, (-)-epicatechin, and epicatechin-3-O-gallate. Grapes have pharmacological activities, like anti-inflammatory, antidiabetic, antioxidant, anti-aging, anti-cataract, antibacterial, antifungal, antiacne, antiobesity, antispasmodic, spasmolytic, anti-virus, wound-healing, antihypertension and antiplatelet and antihyperpigmentation. Studies have reported that grapefruit exhibit a broad spectrum of pharmacological properties against Alzheimer, tumor, leishmanial, Low-Density Lipoprotein, viral, oxidative stress, and had hepatoprotective activity. Their potential health benefits include protection against oxidative damage and anti-diabetic, anti-cholesterol, and anti-platelet functions. Recognition of such health benefits of proanthocyanidins and resveratrol has led consumers to use grapes as a dietary supplement. This paper summarizes the studies of grape fruit's phytochemical compounds and pharmacological properties.

INTRODUCTION: There are significant economic benefits from the development of native medicines and use of medicinal plants to treat various diseases [1]. The use of natural remedies to treat liver diseases has a long history. Plants which exhibits hepatoprotective activity contain number of chemical constituents such as phenols, coumarins, lignins, essential oils, monoterpenes, carotenoids, glycosides, flavonoids, organic acids, lipids, alkaloids and xanthenes [2].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.14(6).2670-77

This article can be accessed online on www.ijpsr.com

DOI link: http://doi.org/10.13040/IJPSR.0975-8232.14(6).2670-77

Recent studies has shown that herbal preparations are relatively non-toxic, safe and no series complications [3-4]. Oxidative stress affects the progression of liver diseases [5]. Grapes (*Vitis vinifera* Subsp. Vitaceae) are used as a drug therapy for many ailments grown globally [6]. It produces more than 67 million tons of fruit annually, making it the greatest fruit production in the world [7].

In recent years, several significant reviews have concluded the phytochemical and pharmacological effects of grapes and their active components in various portions of the fruit, including the skin, seeds, pomace, and stems [8-13]. Grapes are traditionally used as medicine in Pakistan, Italy, and Turkey for the treatment of bronchitis,

allergies, colds & flu, anemia, wound care, and laxatives [14-18]. They classify into edible seeds, seedless, grape wine, table grapes and raisin. North American and European Grapes varieties knowledge as *Vitis labrusca, Vitis rotundifolia* and *Vitis vinifera* respectively [19].

In India, the Grape is evaluated as one of the most important commercially prominent fruit crops, mainly in Maharashtra, Andhra Pradesh, Karnataka, Tamil Nadu, Punjab, Haryana, and Uttar Pradesh, due to its higher yields. In India, grape cultivation is about 40,000 hectare in Maharashtra shares about 20,000 hectare with production >5 lakhtones / year and an approximate turnover above 500 crores. Cultivation in Haryana increases progressively. The main grape-growing districts are Sirsa, Hisar, Bhivani, Jind and Gurgaon. They are cultivated as a temperate crop in Kinnaur (Himachal Pradesh) [20].

Grapes are known in India since the 11th century BC. But much of its information was unknown until the Muslim infiltration. Muslim introduced grape fruits from Iran and Afghanistan by the end of 12th century, and later, these grapes were shifted to South India by them[20]. The formerly earlier varieties they introduced are Abi (Bhokri), Fakhri and Sahebi. Several reports show to have the cultivation of grapes during the times of Susrata and Charaka (1356 B.C.). The Grape cultivation in India has been restrained to one of kind states along with Andhra Pradesh, Haryana, Karnataka, Maharashtra, Punjab and Tamil Nadu. It is also suggested to be grown on a restricted scale in the western part of Uttar Pradesh, Rajasthan, and Himachal Pradesh [20]. Grapes had pharmacological activities like anti-inflammatory, antidiabetic, antioxidant, anti-aging, anti-cataract, antibacterial, antifungal, anti-acne, anti-obesity, antispasmodic, spasmolytic, anti-virus, wound-healing [21-22], antihypertension, antiplatelet and anti-hyper pigmentation [23-24].

Fresh fruits, dried fruits, and juice are the next most common uses for grapes, which account for 50-75% of their total consumption and significantly use in wine production [25].

DESCRIPTION: The grapevine (*Vitis vinifera*) is endemic to southern Europe and Western Asia and nowadays cultivated in all temperature areas of the world [23], which comprises approximately 60 inter-fertile wild *Vitis* species dispersed in Asia, North America, and Europe below subtropical, Mediterranean and continental temperate climatic conditions [1].

North American *V. rupestris*, *V. riparia* or *V. berlandieri* are used as breeding rootstock because of their resistance to grapevine pathogens, including *Phylloxera*, *Oidium* , and mildews. Indeed, a high volume of cultivars is widely cultivated for fruit, juice, and specifically for wine [26]. *V. vinifera* and American bunch grapes have hanging, flaky bark on older wood and have massive (up to 8-10" in width) cordate to orbicular leaves, which can be lobed. Grapes are extensively used in digestive issues such as constipation, jaundice, and thirst. The berries act as cardiac tonic. They improve the heart muscles and enhance blood's nutrient components (haemoglobin). Grapes assist in strengthening the lungs; grapes are used as primary ingredients in ayurvedic preparations, which can be administered for breathing complications like tuberculosis, cough, bronchitis, etc. Grapes help to improve fertility in men and women, and decrease inflammation.

In India, grapes are grown underneath semi-irrigated regions in north India. The temperature ranging from 35°C to 40°C, and 80-110 cm rainfall is required. These conditions favor growing colored grapes because hot days and cold nights support the developing coloured pigment viz. anthocyanin [27-28]. *V. vinifera* comes in seedless as well as non-seedless varieties, and they contain red, black, and white colour fruits [24]. Unripen fruits performa vital role to treat sore throat, dried fruit (raisins) constipation and thirst. The ripe, sweet grapes were used to treat more than a range of ailments involving cancer, cholera, smallpox, nausea, eye infections, and skin, kidney, and liver diseases. Furthermore, grapes are useful in bilious dyspepsia, dysuria, haemorrhage, chronic bronchitis, gout, and heart disorders [29].

Red grapes are basically less in calories and lack of fats and cholesterol. One serving (approx. 150 grams) of red grapes carries104 calories, 27 gm carbs, 1 gm protein, 0 gm fat, 23.4 gm sugar and 1.4 gm fiber. Grapes are high in vitamin K, a fat-soluble vitamin reserved in body tissues and the liver. The human body requires adequate vitamin K to construct strong bones and synthesize several proteins required for blood coagulation. If someone diets less in ingredients rich in vitamin K, a deficiency might lead to osteoporosis [30-31]. The current review provides an update on the pharmacological effects on which recent work was done and includes more recently published research.

Phyto-constituents: Several scientific studies regarding grape processing by-products have been revealed so far, it mainly specializes in grapes' seeds, stems, and skin, but a few research have been reported on leaves and tendrils of *V. vinifera*. The uncommon information regarding grape leaves shows the presence of organic acids, phenolic acids, flavonols, tannins, procyanidins, anthocyanins, enzymes, vitamins, and carotenoids, consequently high in nutritional and biological potential [32]. One of the few research-emphasized tendrils' composition reports flavonoids, polyphenols, and anthocyanins as important constituents with promising *in-vitro* anti-inflammatory consequences [33]. The principle constituents of grapes are phenolic compounds [9]. In 2009, A mico *et al.* suggested that the main ingredients of the grape stem ethanolic extract are: triterpenoid acids, oleanolic and betulinic acids; astilbenoid, daucosterol; *E*-resveratrol and its dimer *E*-viniferin; gallic acid as a simple phenol; catech in and gallo-catechin (flavanols); four 6′-*O*-acyldaucosterols and five 1, 2-di-*O*-acyl-3-*O*-*β*-D-galactopyranosylglycerols [34]. Stilbene derivatives: Trans-Resveratrol (trans-3, 5, 40-trihy-droxystilbene) has also been stated in grapes [23]. Anthocyanins and proanthocyanidins have an important role in the stability, taste, and colour of red grape varieties [35].*V. vinifera* seeds were found to contain a bund antquantities of gallic acid in addition to small eramounts of *p*-coumaric, caffeic and ferulic acids [36]. They contained higher amounts of bothgallic and *p*-coumaric acids than the seeds of other fruit species [37].

Five anthocyanidin-3-O-glucosides, including malvidin-3-O-glucoside, peonidin-3-O-glucoside, and cyanidin-3-O-glucoside, were identified and quantified in Corinthian currants (*V. vinifera* L., var. Apyrena) [38]. The (+)-catechin and (-)-epicatechin flavanols were the probable flavanols in red grape pomace extract (*V. vinifera* L. cv. Malbec), with malvidin-3-glucoside being the most potent anthocyanin. Additionally, piceatannol, a stilbene counterpart to resveratrol, were identified and measured for the first time in grape pomace [39]. It was suggested that the grape variety has a strong phenolic composition [40] similar to that of *V. vinifera* L. fruits [41].

According to Esatbeyoglu *et al*., [42] grape root extract is made up of stilbenoid compounds such resveratrol, vitisins A and B, picaetannol and miyabenol [42]. Trans-piecid, cis-piecid, vitisinol B, viniferether A, and viniferether B are additional stilbenoid chemicals in the grape root, as are ampelopsin C, ampelopsin E, hopeaphenol and isohopeaphenol [43]. The flavan-3-ol compounds in grape leave include gallocatechin, catechins, procyanidins, procyanidin B1, procyanidin A1 and epicatechins. Grape leaves also contain hydroxybenzoic acid (quinic acid, gallic acid, vanilic acid, and syringic acid), hydroxycinnamic acid (caftaric acid, caffeic acid, and fertaric acid), coumarin, dihydrochalcon [44]. The flavonol substances were myricetin, kaempferol, quercetin and quercetin-3-O-glucoside.

Anthocyanins, coumarin (aesculin, fraxin, aesculutin and umbelliferone), flavone (apigenin-7-O-glucoside and luteolin-7-O-glucoside) and flavanone (taxifolin, naringenin and hesperetin) [43] condensed tannin, also be found in leaves [45]. Grape seeds are rich in phenolic compounds and have likely beneficial effects on human health as peptic ulcer protective [46-47] and expressed to exhibit scavenged superoxide radicals [48]. Grape seed extract is composed of the following: procyanidin, gallic acid, epicatechin, catechin, and Quercetin [49]. Other ingredients like protein, fiber, minerals, and water are 11%, 35%, 3% & 7%, respectively. Additionally, 7 to 20% of lipid content also present [50].

Flavonol glycosides were found in the white grape seed extract after being examined by ultra-high-performance liquid chromatography-tandem mass spectrometry [45]. In the context of the black grape, the seed was exposed to resveratrol, anthocyanidins, and flavonol glycosides [51-52]. Sochorova *et al.,* added caffeic acid, coumaric acid, coutaric acid, ferulic acid, and fertaric acid, also claimed that grape seed extract also had other phenolic components, including quercetin-3-D-glucoside, quercitrin, myricetin, catechin, and epicatechin [53]. Using gas chromatography-mass spectrometry (GC-MS), Felhi discovered that grape seed extract contain higher amount of linoleic acid, primaric acid, caffeic acid, p-hydroxy-phenylacetic acid, and gallic acid compared to the seeds of other fruit species [37].

Grape skin contained flavonols, anthocyanins [54], flavan-3-ols, stilbenes, and phenolic acid [55]. While quercetin, vanillic acid, kaempferol, syringic acid, and gallic acid were identified in the grape pomace extract of *V. vinifera* L. var. Chilean [56]. By using liquid chromatography-high-resolution mass spectrometry (LC-HRMS), researchers were able to identify the flavonols quercetin, rutin, kaempferol, caftaric acid, caftaric acid, ferulic acid, (-) epicatechin, (+) catechin, resveratrol and procyanidin in the grape juice from *V. vinifera* L. var. Sangiovese [57]. Gallic acid, syringic acid, caffeic acid, chioric acid, gallocatechin, ferulic acid, procyanidin B1, procyanidin A1, procyanidin C1, epicatechin, catechin, catechingallate, anthocyanin, flavanone, flavone, and flavonol were all present in the grape stem (quercetin, quercetin-3-O-glucoside, and kaempferol). Additionally, stilbenic substances such as transastringin, trans-resveratrol side, ampelopsin A, D and F, vitisin A, B, and C and miyabenol C are present in stem sections [43]. The different chemical groups of polyphenols identified in different fruit parts are carbohydrates, alkaloids, flavonoids, glycosides, saponins, tannins and sterols [58].

In order of significance, the phytochemicals found in *V. vinifera* L. are as follows:

(a) Resveratrol; (b) Pterostilbene; (c) Gallic acid; (d) Ferulic acid; (e) Caffeic acid; (f) Caftaric acid; (g) Syringic acid; (h) Quercetin; (i) Kaempferol; (j) (+) Catechin; (k) Epicatechin; (l) Anthocyanin; (m) Proanthocyanidin; (n) Ampelopsin A; (o) Vitisin A; (p) Vitisin B.

The proanthocyanidins with a DP higher than eight that are present in ripe fruits showed more potent inhibition of α-amylase and α -glucosidase than the less-polymerized proanthocyanidins present in unripe fruits [59].

Pharmacological Effects: When the total antioxidant activity of the extracted tendril was tested on NCTC 2544 cells and increased concentration to 25, 50, 62.5 and 100 mg/mL of *V. vinifera* tendril aqueous extract in DMEM for 24 h at 37°C. To increase the GSH levels and increase the reduced glutathione level at 25 mg/mL. Membrane integrity was assessed by the lactate dehydrogenase release in the medium [44].

Polyphenols are effective in periodontal disease mainly due to their effects on inflammation signals, antioxidant and antibacterial activity [60]. Polyphenols, such as epigallocatechin, quercetin, and caffeic acid, have already been confirmed by their *in-vitro* cytoprotective action on the cells exposed to nicotine or lip polysaccharides [61]. Grape seed extract contains oligomeric proanthocyanidins (PACs), which show strong antioxidant activity. PACs have been able to control high levels of malondialdehyde (MDA) and carboxymethyllysine, reduce superoxide dismutase, and reduce glutathione (GSH) activity in mice with induced diabetes mellitus [62].

Anti-Alzheimer Activity: The causes of Alzheimer's disease (AD) are oxidative stress and

inflammation as triggers, leading to increased levels of Reactive Oxygen Species (ROS) and minimizing the energy to the brain [63]. AD progression reflects the gene expression of Amyloid Precursor Protein (APP) & Tau. *Vitis vinifera* fruit contains antioxidants play a vital role in AD therapy to minimize /slow down the disease progression by the formation of amyloid plaques, Tau tangles, and reduced oxidative stress [64].

Anti-tumour Activity: In several human clinical studies *Vitis vinifera* seed extracts have been shown effective in human colorectal carcinoma [65], head and neck squamous cell carcinoma [66] and prostate cancer cells [67]. So, daily supplementation of extract might be effective as an anti-tumour agent.

Anti-leishmanial Activity: The ethanolic extract of *V. vinifera* L. leaves showed a prominent activity against *L. infantum* promastigotes [68].

Antidiabetic Activity: When *Vitisvinifera* seeds extract given at dose of 100 mg/kg through oral route, for 20 days to diabetics rats, show antioxidant effects against produced Reactive Oxygen Species and protect liver cells [69].

Muscat Variety seeds Ethanolic Extract at a dose of 250, 500 mg/kg, ingested orally for 28 days to diabetic rats at a concentration of 55 mg/kg. Which resulting in decreased Alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) and Thiobarbituric acid reactive substances (TBARS) and prevent histopathological changes in liver prevented the decrease in malate dehydrogenase (MDH), succinic dehydrogenase (SDH) while increased LDH [70].

Grape Skin Aqueous extract at a dose of 200 mg/kg/d to diabetics 'mice, increased glucose transporter (GLUT-4)/ glucose did not change secretion of insulin [71]. Investigation on the anti-inflammatory, anti apoptotic and pro-proliferative effects of *Vitis vinifera* L. seed extract on the livers of rats with induced type 2 diabetes mellitus [72]. Consumption of vine seeds has been found to improve the overall liver condition inrats with diabetes mellitus [73].

Cardiovascular Effects: Grapes Skin (*V. vinifera* L.) have polygalloyl polyflavan-3-ols are very effective to stop the human platelet aggregation and low-density lipoprotein oxidation *in-vitro* [74-75].

Antimicrobial and Antiviral Effects: Antimicrobial activity has been reported in several components of grapes, including gallic acid, hydroxycinnamic acids, flavanols, trans-resveratrol, and tannins. Moreover, antilisterial activity has been reported for grape seed extract (1%). The seed and skin of Ribier grapes extracts decreased L. monocytogenes numbers from 106.107 CFU/ml to node tectable colonies within 10 minutes [76]. Polyphenols can form complexes with metal ions and macromolecules such as polysaccharides and proteins [77]. They are an attractive option for developing Nutraceuticals and functional food ingredients [78]. In particular, proanthocyanidins have been shown to inhibit the key enzymes (α-amylase and α-glucosidase) related to Type 2 Diabetes Mellitus (T2DM), being a natural alternative to the synthetic drug Acarbose [79-81]. Acarbose has been validated to exert an anti-postprandial hyperglycaemia effect. However, it causes undesirable side effects such as flatulence and diarrhoea, with corresponding abdominal pain and a loss of nutrient absorption [82].

Hepatoprotective Activity: Hepatotherapeutic potency of the isolated polyphenols from seedless (pulp and skin) black *Vitisvinifera* against CCl_4-induced hepatotoxicity *in-vitro* and *in-vivo*. Further, the test sample had highest content of phenolics showing *in-vitro* synergistic antioxidant and anti-hepatotoxic activities resveratrol-enriched and phenolics-enriched and silymarin. Though, it exhibited multiple *in-vivo* regulatory functions via reducing oxidative stress and inflammation, which in turn decreased necroptosis and pro-fibrotic mediators (mixed lineage kinase domain-like protein (MLKL), collagen type I alpha 1 chain and transforming growth factor (TGF)-β1) [83].

Clinical Studies: In this study, supercritical fluid extraction (SFE) technique was used and is designed for temperature, CO, pressure and ethanol concentration using orthogonal array design as well as the yield system, whole phenols and antioxidants from grape seeds (*Vitis labrusca* B.). The effects of output temperatures and pressures were found to be significant in all of these response changes in the SFE process. They found that the antiradical assay showed that SFE extracts of grape seeds could consume more than 85% of 1, 1-diphenyl-2-picrylhydrazyl (DPPH) radicals. Grape seed

extracts were also analyzed for hydroxybenzoic acid containing gallic acid (1.21 ~ 3.84 µg/ml), protocatechuic acid (3.57 ~ 11.78 µg/ml) and p-hydroxybenzoic acid (206.72 ~ 688.18 µg/ml) [84].

CONCLUSION: The data presented here indicate that the marked antioxidant activity of grapes extracts that contain large amounts of flavonoids and phenolic compounds may act similarly as reductones by donating the electrons and reacting with free radicals to convert them into more stable products and terminate free radical chain reaction. Grape leaves. Skin and roots have many phytoconstituents which produce potential pharmacological effects against- Alzheimer, carcinoma L. leishmanial, diabetes, cardiovascular disorder, hepatoprotective, antimicrobial and antiviral activity antioxidant activities as well. Due to its wide range of chemical constituents, furthermore, studies could be performed in the future to get good results.

ACKNOWLEDGEMENT: The authors thank Jagannath University NCR Bahadurgarh for providing the necessary facilities and support.

CONFLICTS OF INTEREST: The authors declare no conflict of interest.

REFERENCES:

1. Azaizeh H, Fulder S, Khalil K and Said O: Ethnomedicinal knowledge of local Arab practitioners in the Middle East Region. Fitoterapia 2003; 74: 98-108.
2. Sharma SK, Ali M and Gupta J: Plants having Hepatotprotective activity. Phytochemistry and Pharmacology 2002; 2: 253-270.
3. Momin A: Role of Indigenous Medicine in Primary Health Care, 1st International Seminar on Unani Medicine, New Delhi, India 1987
4. Antoine Bigard, Charles Romieu, Yannick Sire and Laurent Torregrosa: *Vitis vinifera* L. Diversity for Cations and Acidity is Suitable for Breeding Fruits Coping with Climate Warming. Front Plant Sci 2020; 11: 01175.
5. Ajith TA, Hema U and Aswathy MS: *Zingiber officinale* Roscoe prevents acetaminophen induced acute toxicity by enhancing hepatic antioxidant status. Food Chem Toxicol 2007; 45: 2267-2272.
6. Afzalzadeh MR, Ahangarpour A and Amirzargar A: The effect of *Vitis vinifera* L. juice on serum levels of inhibin B, sperm count in adult male rats. World J Mens Health 2015; 33: 109–116.
7. Fontana AR, Antoniolli A and Bottini R: Grape pomace as a sustainable source of bioactive compounds: extraction, characterization, and biotechnological applications of phenolics. J Agric Food Chem 2013; 61: 8987–9003.
8. Flamini R, Rosso MD, Marchi FD and Vedova AD: An innovative approach to grape metabolomics: stilbene profiling by suspect screening analysis 2013; 9(6): 1243–1253.
9. Tang YL and Chan SW: A review of the pharmacological effects of piceatannol on cardiovascular diseases. Phytother Res 2014; 28: 1581–1588.
10. Yang J and Xiao YY: Grape phytochemicals and associated health benefits. Critical Reviews in Food Science and Nutrition 2013; 53(11): 1202–1225.
11. Xia EQ, Deng GF, Guo YJ and Li HB: Biological activities of polyphenols from grapes. Int J Mol Sci 2010; 11: 622-646.
12. Bordiga M, Travaglia F and Locatelli M: Valorisation of grape pomace: An approach that is increasingly reaching its maturity – a review. Int J Food Sci Technol 2019; 54(4): 933–942.
13. Dias C, Raul DP, Alfredo A, Teixeira A, Rosa E, Barros A and Saavedra MJ: Phytochemistry and activity against digestive pathogens of grape (*Vitis vinifera* L.) stem's (poly)phenolic extracts. LWT Food Science and Technology 2015; 61: 25-32.
14. Tetik F, Civelek S and Cakilcioglu U: Traditional uses of some medicinal plants in Malatya (Turkey). J Ethnopharmacol 2013; 146: 331-346,
15. Hayta S, Polat R and Selvi S: Traditional uses of medicinal plants in Elazığ (Turkey). J. Ethnopharmacol 2014; 154: 613-623.
16. Ishtiaq M, Mahmood A and Maqbool M: Indigenous knowledge of medicinal plants from Sudhanoti district (AJK), Pakistan. J Ethnopharmacol 2015; 168: 201-207.
17. Sargin SA, Selvi S and Lopez V: Ethnomedicinal plants of Sarigol district (Manisa), Turkey. J Ethnopharmacol 2015; 171: 64-84.
18. Egea T, Signorini MA, Bruschi P, Rivera D, Obon C, Alcaraz F and Palazon JA: Spirits and liqueurs in European traditional medicine: Their history and ethnobotany in Tuscany and Bologna (Italy). J Ethnopharmacol 2015; 175: 241-255.
19. Girard B and Mazza G: Functional grape and citrus products. In Functional Foods Biochemical and Processing Aspects; Mazza G. Ed. Technomic Publishing Co. Inc.: Lancaster, PA, USA 1998; 1: 139–191.
20. Shanmugavelu KG: Grape cultivation and processing. Third Edition 2003; 97-106.
21. Zahid M, Lodhi M, Rehan ZA, Tayyab H, Javed T, Shabbir R, Mukhtar A, Sabagh, A, Adamski R and Sakran MI: Sustainable development of chitosan / Calotropisprocera-based hydrogels to stimulate formation of granulation tissue and angiogenesis in wound healing applications. Molecules 2021; 26: 3284.
22. Zahid M, Lodhi M, Afzal A, Rehan ZA, Mehmood M, Javed T, Shabbir R, Siuta D, Althobaiti F and Dessok ES: Development of hydrogels with the incorporation of *Raphanus sativus* L. seed extract in sodium alginate for wound-healing application. Gels 2021; 7: 107.
23. Marjan NA and Hossein H: Review of the Pharmacological Effects of *Vitis vinifera* (Grape) and its Bioactive Compounds. Phytother Res 2009; 23: 1197-104.
24. Insanu M, Karimah H, Pramastya H and Fidrianny I: Phytochemical Compounds and Pharmacological Activities of *Vitis vinifera* L.: An Updated Review. Biointerface Research in Applied Chemistry 2021; 11(5): 13829-13849.
25. Venkitasamy C, Zhao L, Zhang R and Pan Z: Grapes. In Integrated Processing Technologies for Food and Agricultural By-Products, S. Eds. Academic Press 2019; 133–163.

26. Terral JF, Tabard E, Bouby L, Ivorra S, Pastor T, Figueiral I, Picq S, Chevance JB, Jung C, Fabre L, Tardy C, Compan M, Bacilieri R, Lacombe T and This P: Evolution and history of grapevine (*Vitis vinifera*) under domestication: new morphometric perspectives to understand seed domestication syndrome and reveal origins of ancient European cultivars. Ann Bot 2010; 105(3): 443–455.
27. Romeyer FM, Macheix JJ and Sapis JC: Changes and importance of oligomeric procyanidins during maturation of grape seeds. Phytochemistry 1986; 25: 219-221.
28. Jackson DI and Lombard PB: Environmental and management practices affecting grape composition and wine quality a review. Am J Enol Vitic 1993; 44: 409-430.
29. Arora P, Ansari SH, Najmi AK, Anjum V and Ahmad S: Investigation of anti-asthmatic potential of dried fruits of *Vitis vinifera* L. in animal model of bronchial asthma. Allergy, Asthma & Clinical Immunology 2016; 12: 42.
30. Hawary S, Fouly K, Gohary HM, Meselhy KM, Slem A and Talaat Z: Phytochemical and biological investigation of *Vitis vinifera* L. (*Flame cultivar*), Family Vitaceae cultivated in Egypt. Nat Sci 2012; 10(10): 48-59.
31. https://www.livestrong.com/article/509099-nutrition-benefits-of-red-grapes/
32. Mateo JJ and Maicas S: Valorization of winery and oil mill wastes by microbial technologies. Food Res Int 2015; 73: 13-25.
33. Fraternale D, Rudov A, Prattichizzo F, Olivieri F, Ricci D, Giacomini E, Carloni S, Azzolini C, Gordillo B and Palacios MJ: Chemical composition and "in vitro" anti-inflammatory activity of *Vitis vinifera* L.(var. Sangiovese) tendrils extract. J Funct Foods 2016; 20: 291-302.
34. Amico V, Barresi V and Chillemi R: Bioassay-guided isolation of antiproliferative compounds from grape (*Vitis vinifera*) stems. Nat Prod Commun 2009; 4: 27–34.
35. Zheng FM and Zhang H: Phytochemical Constituents, Health Benefits and Industrial Applications of Grape Seeds: AMini-Review. Antioxidants 2017; 6 (71): 1-14.
36. Jabeen A, Baig MT, Shaikh S, Nausheen S, Kashif SS, Shahid U, Soomro H, Mirza AS: Review on Pharmacological Effects of Grape Seed Oil. RADS Journal of Biological Research and Applied Science 2021; 12(2).
37. Weidner S, Rybarczyk A and Karamac M: Differences in the phenolic composition and antioxidant properties between Vitiscoignetiae and *Vitis vinifera* seeds extracts. Molecules 2013; 18: 3410–3426.
38. Chiou A, Panagopoulou EA, Gatzali F, Marchi SD and Karathanos VT: Anthocyanins content and antioxidant capacity of Corinthian currants (*Vitis vinifera* L., var. Apyrena). Food Chemistry 2014; 146: 157–165.
39. Antoniolli A, Fontana AR and Piccoli P: Characterization of polyphenols and evaluation of antioxidant capacity in grape pomace of the cv. Malbec Food Chem 2015; 178: 172–178.
40. Konuskan DB, Kamiloglu O and Demirkeser OK: Fatty acid composition, total phenolic content and antioxidant activity of grape seed oils obtained by cold-pressed and solvent extraction. Indian J Pharm Educ 2019; 53: 144–150.
41. Carrasco CDA, Lopez SR and Kalasic NH: Phenolic composition and antioxidant capacity of pomaces from four grape varieties (*Vitis vinifera* L.) J Sci Food Agric 2015; 95: 1521–1527.
42. Esatbeyoglu T, Ewald P, Yasui Y, Yokokawa H, Wagner AE, Matsugo S, Winterhalter P and Rimbach G: Chemical Characterization, Free Radical Scavenging, and Cellular Antioxidant and Anti-Inflammatory Properties of a Stilbenoid-Rich Root Extract of *Vitis vinifera*. Oxid Med Cell Longev 2016.
43. Goufo P, Singh RK and Cortez I: A Reference List of Phenolic Compounds (Including Stilbenes) in Grapevine (*Vitis vinifera* L.) Roots, Woods, Canes, Stems, and Leaves. Antioxidants 2020; 9.
44. Fraternalea D, Bellisb RD, Calcabrini C, Potenzab L, Cucchiarinib L, Mancinib U, Dachac M and Riccia D: Aqueous Extract from *Vitis vinifera* Tendrils is Able to Enrich Keratinocyte Antioxidant Defences. Natural Product Communications 2011; 6(9): 3015-3019.
45. Aouey B, Samet AM, Fetoui H, Simmonds MSJ and Bouaziz M: Anti-oxidant, anti-inflammatory, analgesic and antipyretic activities of grapevine leaf extract (*Vitis vinifera*) in mice and identification of its active constituents by LC–MS/MS analyses. Biomedicine & Pharmacotherapy 2016; 84: 1088-1098.
46. Rodriguez MR, Romero PR, Vozmediano CJL, Gascuena MJ and Romero GE: Phenolic compounds in skins and seeds of ten grape *Vitis vinifera* varieties grown in a warm climate. J Food Comp Anal 2006; 19: 687–693.
47. Kim TH, Jeon EJ, Cheung DY, Kim CW, Kim SS, Park SH, Han SW, Kim MJ, Lee YS and Cho ML: Gastroprotective effects of grape seed proanthocyanidin extracts against non-steroid anti-inflammatory drug-induced gastric injury in rats. Gut Liver 2013; 7: 282–289.
48. Beshbishy HA, Mohamadin AM and Abdel-Naim AB: *In-vitro* evaluation of the antioxidant activities of grape seed (*Vitis vinifera*) extract, blackseed (*Nigella sativa*) extract and curcumin. J Taibah Univ Med Sci 2009; 4: 23–35.
49. Cadiz GMD, Borras LI, Lozano SJ, Joven J, Fernandez AS and Segura CA: Cocoa and Grape Seed Byproducts as a Source of Antioxidant and Anti-Inflammatory Proanthocyanidins. Int J Mol Sci 2017; 18.
50. Shinagawa FB, Santana FCD, Torres LRO and Mancini FJ: Grape seed oil: A potential functional food. Food Sci Technol 2015; 35: 399–406.
51. Navarro PJ, Cazals G, Enjalbal C, Izquierdo-Canas PM, Gomez-Alonso S and Saucier C: Flavanol Glycoside Content of Grape Seeds and Skins of *Vitis vinifera* Varieties Grown in Castilla-La Mancha, Spain. Molecules 2019; 24.
52. Niknami E, Sajjadi SE, Talebi A and Minaiyan M: Protective Effect of *Vitis vinifera* (Black Grape) Seed Extract and Oil on Acetic Acid-Induced Colitis in Rats. Int J Prev Med 2020; 11: 102.
53. Sochorova L, Prusova B, Jurikova T, Mlcek J, Adamkova A, Baron M and Sochor J: The Study of Antioxidant Components in Grape Seeds. Molecules 2020; 25.
54. Colombo F, Lorenzo DC, Regazzoni L, Fumagalli M, Sangiovanni E, Sousa PDL, Bavaresco L, Tomasi D, Bosso A, Aldini G, Restani P and Dell AM: Phenolic profiles and anti-inflammatory activities of sixteen table grape (*Vitis vinifera* L.) varieties. Food Funct 2019; 10: 1797-1807.
55. Tkacz K, Wojdylo A, Nowicka P, Turkiewicz I and Golis T: Characterization *in-vitro* potency of biological active fractions of seeds, skins and flesh from selected *Vitis vinifera* L. cultivars and interspecific hybrids. J Funct Foods 2019; 56: 353-363.
56. Cotoras M, Vivanco H, Melo R, Aguirre M, Silva E and Mendoza L: *In-vitro* and *in-vivo* Evaluation of the Antioxidant and Prooxidant Activity of Phenolic Compounds Obtained from Grape (*Vitis vinifera*) Pomace. Molecules 2014; 19.
57. Fia G, Gori C, Bucalossi G, Borghini F and Zanoni B: A Naturally Occurring Antioxidant Complex from Unripe

Grapes: The Case of Sangiovese (*Vitis vinifera*). Antioxidants 2018; 7.
58. Zulfiqar AB, Nowshehri JA and Shah MY: Pharmacognostic Standardisation and Phytochemical Evaluation on the Seeds of two Vitis vinifera L. Varieties Grown in Kashmir Valley, India. Pharmacogn J 2016; 8(5): 465-470.
59. Zhang T, Santosa RW, Zhang M, Huo J and Huang D: Characterization and bioactivity of proanthocyanidins during Malay cherry (Lepisanthesalata) fruit ripening. Food Biosci 2020; 36: 100617.
60. Ruiz FA, Garcia FMS, Perez LMC, Martinez CE and Gandara JS: Influence of major polyphenols on antioxidant activity in Mencia and Brancellao red grapes. Food Chem 2008; 113: 53–60.
61. Li L, Sun W, Wu T, Lu R and Shi B: Caffeic acid phenethyl ester attenuates lipopolysaccharide-stimulated proinflammatory responses in human gingival fibroblasts via NF-_B and PI3K/Aktsignaling pathway. Eur J Pharmacol 2017; 794: 61–68.
62. Sochor J, Sochorova L, Prusova B, Baron M, Cebova M, Jurikova T, Mlcek J, Adamkova A and Nedomova S: Health Effects of Grape Seed and Skin Extracts and Their Influence on Biochemical Markers. Molecules 2020; 25: 5311.
63. Markesbery WR: Oxidative stress hypothesis in Alzheimer's disease. Free RadicBiol Med 1997; 23(1): 134-147.
64. Rapaka D, Raghavulu BV, Vishala T and Annapurna CA: *Vitis vinifera* acts as anti-Alzheimer's agent by modulating biochemical parameters implicated in cognition and memory. Journal of Ayurveda and Integrative Medicine 2017; 1-7.
65. Kaur M, Singh RP, Gu M, Agarwal R and Agarwal C: Grape seed extract inhibits *in-vitro* and *in-vivo* growth of human colorectal carcinoma cells. Clin Cancer Res 2006; 20: 6194–6202.
66. Sun Q, Prasad R, Rosenthal E and Kativar SK: Grape seed proanthocyanidins inhibit the invasive potential of head and neck cutaneous squamous cell carcinoma cells by targeting EGFR expression and epithelial-to-mesenchymal transition. BMC Complement. Altern Med 2011; 11: 134.
67. Park SY, Lee YH, Choi KC, Seong AR, Choi HK, Lee OH, Hwang HJ and Yoon HG: Grape seed extract regulates androgen receptor-mediated transcription in prostate cancer cells through potent anti-histone acetyltransferase activity. J Med Food 2011; 14: 9–16.
68. Mansoura R, Najoua H, Kahla NAB, Saoussen H, Zine M, Farouk M and Hamouda B: The Effect of Vitisvinifera L. Leaves Extract on *Leishmania infantum*. IJPR 2013; 12(3): 349-355.
69. Chis IC, Ungureanu MI and Marton A: Antioxidant effects of a grape seed extract in a rat model of diabetes mellitus. Diab Vasc Dis Res 2009; 6: 200–204.
70. Giribabu N, Kumar E and Rekha SS: Vitisvinifera (Muscat Variety) seed ethanolic extract preserves activity levels of enzymes and histology of the liver in adult male rats with diabetes. Evid Based Complement Alternat Med 2015; 542026.
71. Moura SR, Costa GF and Moreira AS: Vitisvinifera L. grape skin extract activates the insulin-signalling cascade and reduces hyperglycaemia in alloxan-induced diabetic mice. J Pharm Pharmacol 2012; 64: 268–276.
72. Felhi S, Baccouch N, Salah BH, Smaoui S, Allouche N, Gharsallah N and Kadri A: Nutritional constituents, phytochemical profiles, *in-vitro* antioxidant and antimicrobial properties, and gas chromatography–mass spectrometry analysis of various solvent extracts from grape seeds (*Vitis vinifera* L.). Food SciBiotechnol 2016; 25: 1537-1544.
73. Giribabu N, Karim K, Kilari EK, Kassim NM and Salleh N: Anti-Inflammatory, Antiapoptotic and Proproliferative Effects of *Vitis vinifera* Seed Ethanolic Extract in the Liver of Streptozotocin-Nicotinamide-Induced Type 2 Diabetes in Male Rats. Can J Diabetes 2018; 42: 138–149.
74. Kar P, Laight D, Shaw KM and Cummings MH: Flavonoid-rich grapeseed extracts: a new approach in high cardiovascular risk patients. Int J Clin Pract 2006; 60(11): 1484-1492.
75. Shanmuganayagam D, Beahm MR and Kuhns MA: Differential effects of grape (*Vitis vinifera*) skin polyphenolics on human platelet aggregation and low-density lipoprotein oxidation. J Agric Food Chem2012; 60: 5787–5794.
76. Kanagarla NSSAV, Kuppast IJ, Veerashekar T and Reddy CL: A review on benefits and uses of *Vitis vinifera (*Grape). Research and Review in Biosciences (RRBS) 2013; 7(5).
77. Scalbert A and Williamson G: Dietary Intake and Bioavailability of Polyphenols. J Med Food 2000; 3: 121–125.
78. Tungmunnithum D, Thongboonyou A, Pholboon A and Yangsabai A: Flavonoids and Other Phenolic Compounds from Medicinal Plants for Pharmaceutical and Medical Aspects: An Overview. Medicines 2018; 5: 93.
79. Kalita D, Holm DG, Labarbera DV, Petrash JM and Jayanty S: Aldose Reductase by Potato Polyphenolic Compounds. PLoS ONE 2018; 13: 191025.
80. Kumar S, Narwal S, Kumar V and Prakash O: α-glucosidase inhibitors from plants: A natural approach to treat diabetes. Pharm Rev 2011; 5: 19–29.
81. Musa MY, Griffith AM, Michels AJ, Schneider E and Frei B: Grape seed and tea extracts and catechin 3-gallates are potent inhibitors of α -amylase and α-glucosidase activity. J Agric Food Chem 2012; 60: 8924–8929.
82. Wang M, Chen J, Ye X and Liu D: *In-vitro* inhibitory effects of Chinese bayberry (MyricarubraSieb. EtZucc.) leaves proanthocyanidins on pancreatic α-amylase and their interaction. BioorgChem2020; 101: 104029.
83. Serie AMM and Habashy NH: *Vitis vinifera* polyphenols from seedless black fruit act synergistically to suppress hepatotoxicity by targeting necroptosis and pro-fbroticmediators. Scientific reports/nature 2020; 10:2452.
84. Ghafoor K, Fahad Y, JuhaimiAL and Choi YH: Supercritical Fluid Extraction of Phenolic Compounds and Antioxidants from Grape (*Vitisla brusca* B.) Seeds. Plant Foods Hum Nutr 2012; 67: 407–414.

How to cite this article:
Kumar A, Sharma A, Pragi and Kumar V: Pharmacological effects of *Vitis vinifera* Subsp. Vinifera: a review. Int J Pharm Sci & Res 2023; 14(6): 2670-77. doi: 10.13040/IJPSR.0975-8232.14(6).2670-77.