A Review on Pharmacological Properties of *Vitis Vinifera*

Submitted By

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A thesis submitted to the Department of Pharmacy in partial fulfillment of the requirements for the degree of
Bachelor of Pharmacy (Hons.)

Department of Pharmacy
Brac University

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Declaration

It is hereby declared that

1. The thesis submitted is my/our original work while completing a degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through complete and accurate referencing.
3. The thesis does not contain material accepted or submitted for any other degree or diploma at a university or other institution.
4. I have acknowledged all primary sources of help.

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Approval

The thesis/project titled "A Review on Pharmacological Properties of *Vitis Vinifera and* its Phytochemical Constituents" submitted by Mahbub Alam Tushar (ID-16346012) of Summer 2016 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy (Hons.) on March 27, 2022.

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Ethics Statement

This study does not involve any kind of animal or human trial.

Abstract

Among different fruit plants, the grape plant is widely regarded as one of the essential sources of phenolic compounds, including resveratrol, phenolic acids, kaempferol, quercetin, catechins, proanthocyanins, etc. Several studies have demonstrated that those polyphenols or nutraceuticals obtained from the plant grapes have health benefits, including lowering the incidence of cardiovascular disease or cancer, improving cognition and neuronal function with aging and neurodegenerative diseases, and exhibiting antiallergic, antitumor, anti-inflammatory, antidiabetic, and antimicrobic properties. These polyphenols can also help us live longer lives by improving our health conditions, delaying the aging process, preventing chronic diseases, increasing our life expectancy, or supporting the structure and function of our bodies. The wine, grape seeds, and grape skins contain a significant amount of those phenolic compounds. Wine is regarded as a particularly excellent source of grape phenolic compounds. Research on polyphenols and pharmacological properties of *Vitis vinifera* have been summarized in this article.

Keywords: *Vitis vinifera*; Resveratrol; Phenolic; Flavonoids; Catechin; Antioxidant;

Dedication

I would want to dedicate this project to my family and my supervisor, Dr. Farhana Alam Ripa (Assistant Professor, School of Pharmacy, Brac University), with whom I have had the pleasure of working on this project.

Acknowledgment

Firstly, I am very grateful to my Almighty Allah for rewarding me with patience, self-confidence, and strength, which have been instrumental in completing this job successfully.

My heartfelt thanks to Dr. Farhana Alam Ripa (Assistant Professor, School of Pharmacy, Brac University), my project supervisor, for her kind assistance, direction, enthusiasm, excellent guidance, and supervision during this project work. She mentored me with her vast expertise and knowledge, and she did so while managing to find enough time for me despite her very hectic schedule. Her invaluable recommendations and criticism of my work throughout this assignment helped me inadequately complete this job.

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Finally, I would like to express my heartfelt thanks to my family and friends for their efforts on my behalf, which serve as constant sources of inspiration and motivation to strive for more incredible things. I would also like to express my gratitude to all of the faculty members at the School of Pharmacy, who have given me much encouragement to complete this project successfully.

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List of Acronyms

GP	Grape Pomace
GSEs	Grape Seed Extracts
GC	Gallocatechin
EC	Epicatechin
ECG	Epicatechin Gallate
EGC	Epigallocatechin
EGCg	Epigallocatechin Gallate
PB1	Procyanidin B1
PB2	Procyanidin B2
PD	Polymerization Degree
RSV	Resveratrol
CHS	Chalcone Synthase
STS	Stilbene Synthase
Trp	Tryptophan
MAO	Monoamine Oxidase
GSPE	Grape Seed Pomace Extracts
GSSE	Grape Seed Skin Extracts

Chapter 1

Introduction

1.1 Grapevine/ *V. vinifera*

If somebody were to inquire, what are the plants, and who are they? The answer will be that plants are mostly photosynthetic eukaryotes belonging to the Plantae kingdom. As recorded in antiquity, the Kingdom of Plantae contained all living creatures, except for animals. Chlorophyta, mosses, ferns, tendrils, grasses, shrubs, herbs, blooming plants, and trees are considered plants. Algae and fungi are also featured in the list. Although all plants or trees usually produce their food in the photosynthetic process, some species cannot do this. Those species are called parasitic plants (Fernando, 2012).

From the beginning of creation, the importance and contribution of plants in human life have been proving to be immense. There has been an essential function for plants in the food supply chain for a long time. People have been dependent exclusively on trees for their nourishment from prehistoric times. Nonetheless, it was reasonable that trees might be utilized for food purposes exclusively by the inhabitants of that era. However, over time, that thinking is likely to change. Over the ages, the animal world, especially the human species, realizes that the demand for plants is not only for food but also for their own needs in several sectors of their life. Plants may be found in natural habitats, such as rainforests and agricultural and urban environments. They provide food, clean air, and crucial ecological activities, and they are a significant part of our everyday life. They have absolute dominance in all biodiversity areas, balancing the food chain or protecting the ecosystem (Fernando, 2012). They are contributing in different ways. Though they are contributing a lot, it is also possible to raise the production of bioactive metabolites and chemically standardize extracts from plants using several innovative procedures (Tocci et al., 2011), (Tocci et al., 2012). Now we have to talk about the fruit plant *V. vinifera* according to the topic of our thesis paper. Now, what is usually meant by fruit plants? From a botanical sense, a fruit is a ripened ovary of a blooming plant that contains seeds and is juicy or dry. There are several multiple kinds of fruits, and each one has its specific attributes. Acorns, almonds, and other nuts and seeds (when still in their shells) are officially fruits, acorn and almond pods, maize kernels, tomatoes, and cucumbers. Grapes are essential to fruit species in the globes, and it is farmed most extensively in the Mediterranean Area. They are scientifically known as *V. vinifera* (family Vitaceae), and they are one of the world's most significant fruits, with gastronomic, medical, and industrial uses. Grapes are a rich source of polyphenols, compounds that bring several health benefits, cooperate to prevent severe degenerative diseases, and have antioxidant properties (Figure 2). Because of its ability to regenerate, the grapevine (*V. vinifera*) has long been considered a symbol of life, and it is often alluded to as the "tree of life" owing to its historical associations (Vivier & Pretorius, 2019). According to a report, over 60 million tons of grapes are harvested globally, making them a significant extended agro-economic activity (Teixeira et al., 2014). According to FAOSTAT, the Food and Agriculture Organization of the United Nations, 67 million grapes were produced in 2012, with around 23 million tons originating in European nations. Reasons behind the vast production of this fruit plant are its benefits, juice consumption, raisins, and other pharmacological properties because of various phytochemicals in it. Not to mention one more and maybe the most crucial aspect of their significance in viniculture or winemaking. From these perspectives, the vine can be described as a significant and urgent medicinal plant (Teixeira et al., 2014).

Ryan (2014), in his article, mentioned that since ancient times, alcoholic (ethanol-containing) drinks, such as beers, wines, and spirits, have supplied people with nutrition and refreshment. When alcoholic drinks are drunk with food, the experience becomes much more pleasurable (Ryan, 2014). Because wine is one of the most consumed alcoholic drinks globally, a significant amount of grape production is dedicated to vinification processes, significant traditional activity in numerous countries in Southwestern Europe (i.e., France, Greece, Italy, Portugal, and Spain) (Poudel et al., 2008). In vitro and in vivo studies have shown that bioactive chemicals from winery byproducts have intriguing health-boosting properties (Teixeira et al., 2014). Grape pomace (GP) results from the vinification or winemaking process, referred to as a "winery byproduct." They signify and represent a significant ecological and economic problem of waste management. Likewise, they are mainly used for animal food, embodied composts, ethanol manufacture, or are disposed of as waste. Some countries also use them as antimicrobial ingredients in pharmaceutical agents, including foods, cosmetics, and other additives. Around 70% after the winemaking extraction process, high polyphenolic contents show substantial antioxidant effects and prevent oxidative stress. As a response to the "French paradox," scientists have increased their focus on characterizing the chemical makeup of polyphenolics found in grapes and red wines and their health-promoting effects (Xia et al., 2013).

Figure 1: Picture of the Plant of V. vinifera

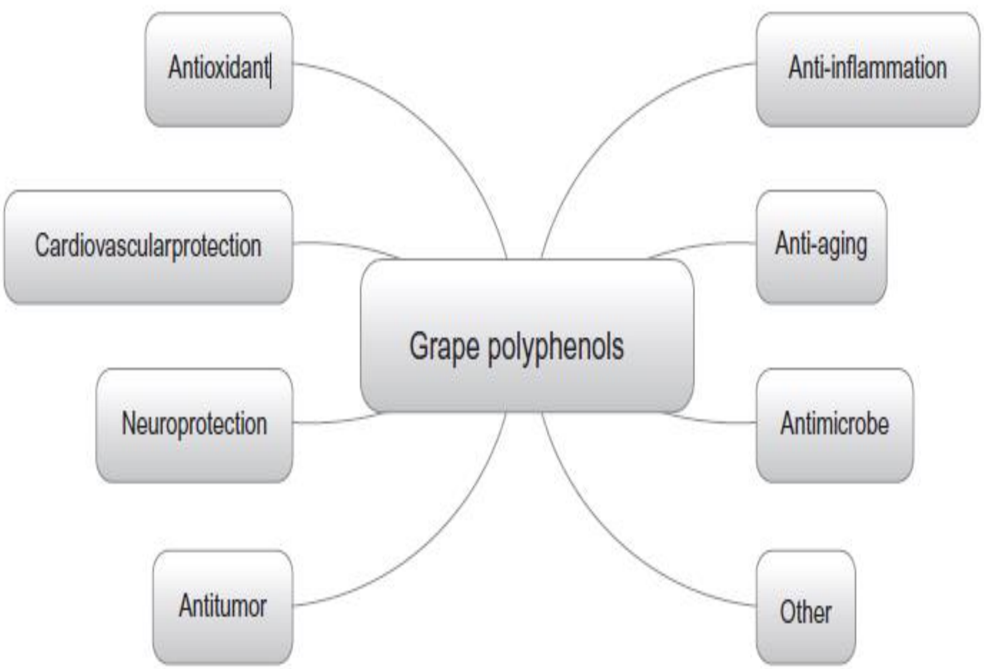


Figure 2: Biological Activities of Polyphenols from Grapes

1.2 Botanical Description & Classification

V. vinifera belongs to the Vitaceae family. Their inhabitants or native zones are the Mediterranean region, Central Europe, Southwestern Asia, etc. Generally, the grapes tree may be 3 to 6 feet long commonly. Nevertheless, it can spread mainly to 9 feet or 40-60 feet long if left unpruned. Their blooming time is between May to June. Deep, loamy, humus-rich soils with medium moisture and a sound drainage system are ideal for growing this plant in full sun. Give the best performance in gravelly loams. Though they can grow and give the best performance in deep, loamy soil, they can also grow well in all soils on average.

However, a sound drainage system is always required. To maximize fruit production, good air circulation is almost essential. Besides the excellent air supply, it needs a support system, training, frequent spraying, and regular trimming to produce high-quality fruit. In the United States, cultivars are primarily cultivated in California. Because of the climate in the Eastern and Midwestern sections of the United States, plants typically do not fare well (winters are too cold in northern areas and summers too hot and humid in southern areas). Though grapes of this species are abundantly grown in Europe and America for wine production, their demand for fresh fruit is not insignificant. Not only that, but they are also used as currants, raisins, and sultanas (dried). Vines are very seldom planted for decorative reasons, and when they are, they are rarely used. This species has two types of wine: red wine and white wine. It is important to note that the primary difference between red wine and white wine is that the red grape skins are incorporated during the fermentation of red wine, giving it its dark red color. It is necessary to prune fruit-bearing grapes regularly and monitor them for pests and diseases.

Table 1: Taxonomic Ranks of V. vinifera

Taxonomic Ranks	**Example (V. vinifera)**
Kingdom	Plantae
Division	Tracheophyta
Class	Magnoliopsida
Order	Vitales
Family	Vitaceae – Grapes
Genus	Vitis L. – Grape
Species	V. vinifera – Wine grape

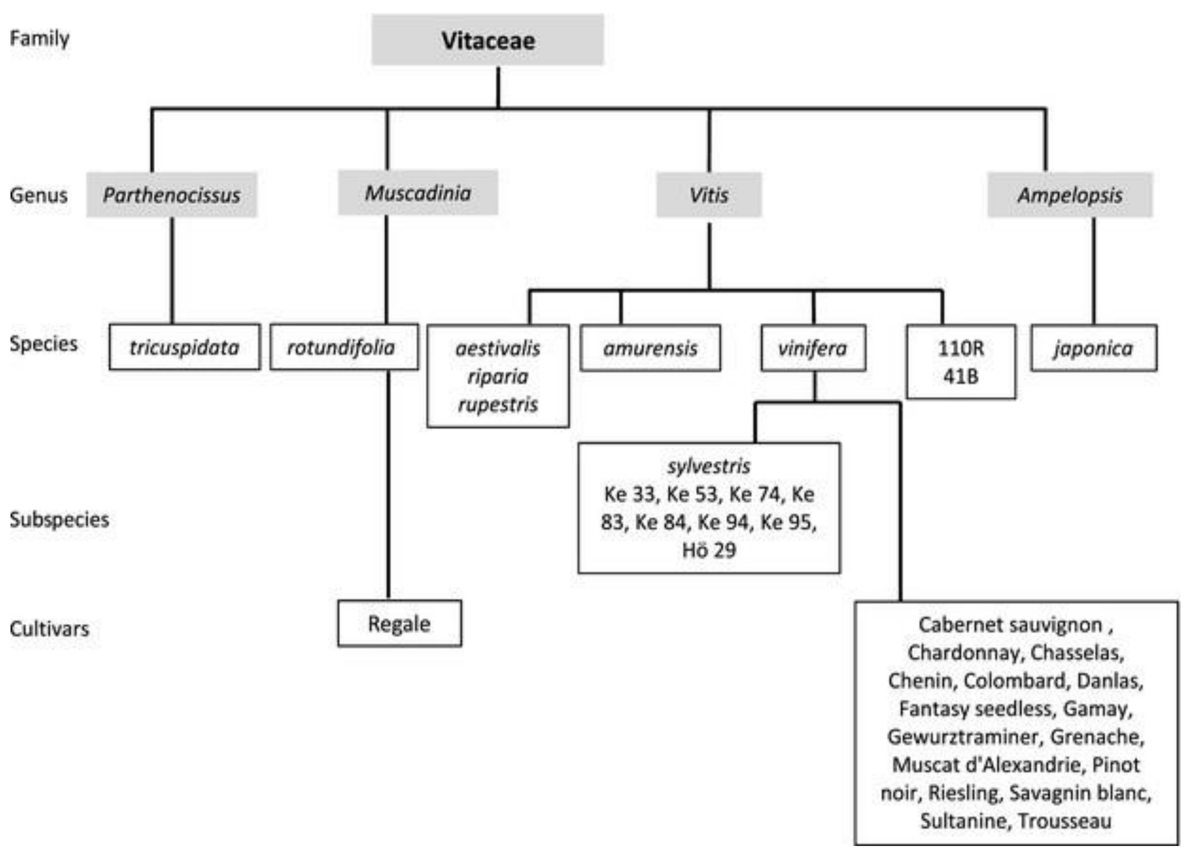


Figure 3: Condensed classification scheme of Vitaceae Family

1.3 History and Origin

V. vinifera is a member of the Vitaceae family. This family includes around 60 inter-fertile wild Vitis species in Asia, Europe, and North America under the Mediterranean, subtropical, and temperate climatic conditions. Among all other species of Vitis (genus), *v. vinifera* has made tremendous progress in the economic sector. However, *V. vinifera* and North American *V. rupestris*, *V. riparia*, *V. berlandieri*, etc., are also used as breeding rootstocks. They are ideal for utilization because of their resistance to grapevine infections such as Mildews, Phylloxera, Oidium, etc. Most cultivars are grown for fruit, juice, and wine (Rossetto, 2002). In the alluvial and colluvial deciduous and semi-deciduous woodland, the wild grapevine grows as a heliophilous liana (Levadoux, 1956). Except for the most southern areas of the Mediterranean Basin and the infra-Mediterranean zone, it is widely dispersed over Europe, Asia, and the Trans-Caucasus region (Arnold et al., 1998). In Europe, the 'Phylloxera crisis' significantly affected both cultivated and wild grape types. Modern wild grapevines are thus critically endangered and even extinct. Biodiversity protection is dependent on the future of *V. sylvestris* subsp. Vinifera (Arnold et al., 2005). The grapevine was domesticated between the 7th and 4th millennia B.C., between the Black Sea and Iran. Humans would have disseminated cultivated forms over Central Europe, the Middle East, and the Near East if they had originated in this region. Because of this, it is possible that these places served as secondary domestication centers (Terral et al., 2010).

History has shown that grapes have an epic contribution to Western Civilization. Grape cultivation and winemaking have made great strides in Western Civilization. By the ancient people, wine artificially produced from grapes was considered a beverage. There was a strange and magical idea about wine among the ancient Egyptians. Among them, wine was considered a gift from the gods. The Egyptians, Greeks, and Romans credited wine to Osiris, Dionysus, and Bacchus. The Old

Testament mentions several connections with wine. In Genesis, Noah started to work as a peasant after the Flood, planting a vineyard and drinking the wine produced by the vineyard (Figure 4). The grapevine is unique among cultivated plants due to viticulture traditions and wine's mythology. The discovery of wine was mainly an accident. The grapevine's fruit provides a perfect substrate for fermentation, and the surface of the grape berry is particularly favorable for yeast growth. With the expansion of worldwide wine commerce, it is possible that the storage glove resulted in the unexpected discovery of wine as a consequence of this international trade (Mullins et al., 1992).

Figure 4: Noah and the grapevine

Surprisingly, alcohol was banned in Islam around 600 AD. The ban has led to a sharp rise in the production of table grapes in North Africa, including in the Middle East. The cultivation of table grapes also started in Spain, and at the same time, table grapes became known all over the continent of Europe and later in the whole world. Due to the mention of table grape, we need to know first what is meant by table grape. Table grapes mean fresh grapes, which are usually eaten as fruit. Table grapes are lower in acid and sugar than wine grapes. There are two different things here: viticulture and viniculture, respectively. Winemaking and grape growing are two distinct processes. However, the term viniculture is often used to describe the process of making wine. During Ottoman rule (15th-19th centuries), table grapes were also brought to the Balkans, but unlike the Arabs, the Turks allowed their Christian people to plant wine grapes (Mullins et al., 1992).

As early as 1525, Cortez authorized the cultivation of grapevines across Mexico, and by 1550, the cultivation of grapes had extended to Peru, Chile, and Argentina. In 1556, Don Pedro del Castillo created Mendoza and started the Argentinian wine business using grapevines taken from Chile, which he imported. Legislation enacted to safeguard Spain's wine exports kept the colonial viticulture under control. Three centuries before the Protestant Reformation, only Catholic missions were allowed to cultivate grapes and produce wine, supposedly religiously. Father Juan Ugarte, a Jesuit missionary from what is now Lower California, planted the first grapevine on the west coast of North America in 1697. Missions were established in California from 1769 to 1810, and grapes were planted north of Los Angeles and San Francisco. In 1616, Dutch migrants in the Cape of Good Hope planted the first grapevines in South Africa. Vineyards prospered when the Huguenots from France settled in the area and brought their winemaking expertise. During the Napoleonic Wars, the decadent dessert wines of the Cape discovered a warm reception in England. During the French colonization of Algeria in 1830, wine-growing was revived in North America, which had been stunted for centuries by Islam. In Algeria, numerous vignerons who had been driven out in France by the fungal disease later established a substantial grape-growing sector focused mainly on the exporting of bulk wines. In 1788, the Botany Bay prison colony became Australia's first viticultural outpost. Viticulture was developed in New South Wales' Hunter Valley by 1820 after failed attempts to produce grapes near Sydney. German Lutherans created the Barossa Valley in South Australia Barossa Valley in the 1850s. South Australia and Victoria constructed irrigation communities along the Murray River, where grapes for drying became a significant business at the end of the 19th century. Beginning of the 19th century, French immigrants and religious groups cultivated grapes on New Zealand's North Island (Mullins et al., 1992).

1.4 Aim & Objectives of this Study

This review aims to gain a detailed overview and current knowledge of phytochemical constituents and pharmacological properties of *V. vinifera.*

The objectives of this study include the following:

1. To gather knowledge on the plant's and fruit's characteristics, botany, history, and traditional applications.
2. Enlisting major minerals and pharmacological activities of *V. vinifera.*
3. Identifying other research areas of *V. vinifera*.

1.5 Rationale of the Study

The study has been conducted to review and discuss *V. vinifera* and its constituents and pharmacological properties. It is essential to know about their metabolites and pharmacological actions. Many other valuable resources, websites, or essential articles have been used to write the review paper. It is desired that the study would contribute to the understanding of *V. vinifera* with more clarity and contextualize those aspects.

Chapter 2

Phytochemicals of *V. Vinifera.*

In addition to the many phytochemicals found in fruits and vegetables that have been shown to have beneficial effects on the human body, they may also guard against chronic illnesses such as cardiovascular disease and cancer via several methods. Among all those fruits and vegetables, the most popular is the grape plant *V. vinifera*. This plant contains many phytochemicals and may be used for food, medical and industrial purposes like the other fruits but the most significant one. The total amount of phenolic compounds in the plant is different in different parts of the plant. Condensed tannins, monomeric flavonols, phenolic acids, and resveratrol are most abundant in the skin. Besides grape skin, the grape seed contains many polyphenols too (5 to 8% phenolic compounds by weight) compared with the other parts of the plant, such as skin, pulp, leaf, stem, etc. They are mainly constituted of monomeric catechins or epicatechins known as procyanidins or proanthocyanidins, found in large quantities in the seeds. The rich presence of several components is responsible for the bitterness of grape seeds. These include catechins, procyanidin oligomers, etc. (Xia et al., 2013). Also, in the 'Journal of Antimicrobial Chemotherapy,' Masatomo Hirasawa and Kazuko Takada mentioned the complex constituents of grape seed extracts (GSEs). GSEs are a complicated combination of monomeric, oligomeric, and polymeric flavan-3-ols. (+)-catechin, (-)-epicatechin, (-)-epicatechin gallate (ECG), (-)-epigallocatechin (EGC), and (-)-epigallocatechin gallate (EGCg) is the main monomers found in grape seed extracts. EGCg, the primary component in green tea extracts, is toxic to many fungi, including *Candida albicans* (Hirasawa & Takada, 2004). In the United States, GSE3, a commercial preparation of grapeseed polyphenols, is sold as a dietary supplement because of its health advantages. Yamakoshi and his colleagues have shown by their study that procyanidins and their antioxidant metabolites found in the grape seed can slow the process of cataract formation (Bartolomé et al., 1996; M. H. Jang et al., 2008; Singleton, 1992; Sowmya et al., 2015).

Grapes are not only limited to cures, just like the long-term ailments skin problems, cancer, or heart problems but also a source of numerous nutrients. They can also prevent some less common but no fewer incapacitating conditions such as Alzheimer's and urinary bladder dysfunction (Choi et al., 2012). As a free-radical-hunting antioxidant, the extract of *V. vinifera* is ideal for protecting biological components from oxidation. Phytochemicals and antioxidants from the fruit extract were shown to have high in vitro antioxidant activity (Raja & Dubey, 2020). The grape (*V. vinifera*) ranks with apple, watermelon, and banana as the world's most popular fruit. Europe produced 41%, followed by Asia at 29% and the Americas at 20% for 75 million tons in 2014. Polyphenolic antibacterial substances found in black grape peel may be utilized to limit the development of harmful germs in food (Raja & Dubey, 2020). Melatonin was recently revealed to be present in the grape's chemical. Regular intake of grape products may have health advantages because of the synergistic impact of Melatonin and the many polyphenols found within (Iriti & Faoro, 2009). We all know, to some extent, that secondary metabolites in grapevine exist in wood, leaves, stems (rachis and pedicels), and berries. Although berries and stems are used as a fruit and for winemaking, leaves are typically not ingested by humans, with a few exceptions, such as the traditional Greek meal dolmadakia, which consists of grape leaves filled with rice (Iriti & Faoro, 2006; Pezzuto, 2008). Primary roles in plant/grapevine ecology include phytoalexins and resistance to infections and phytophagic and tolerance to abiotic stressors, such as severe climate conditions, UV, photooxidation, drought, and anthropogenic contaminants in the environment (Jeandet et al., 2002).

2.1 Phenolics

Flavonoids and nonflavonoids are the two main types of phenolics found in the fruit and other plant parts. Anthocyanins, flavan-3-ols, and flavonols are among the most important flavonoids. Anthocyanins, a kind of flavonoid found primarily on the skins of plants, are a source of flavan-3-ols found equally in skins and seeds. Stilbenes and phenolic acids are examples of non-flavonoids (Yang & Xiao, 2013).

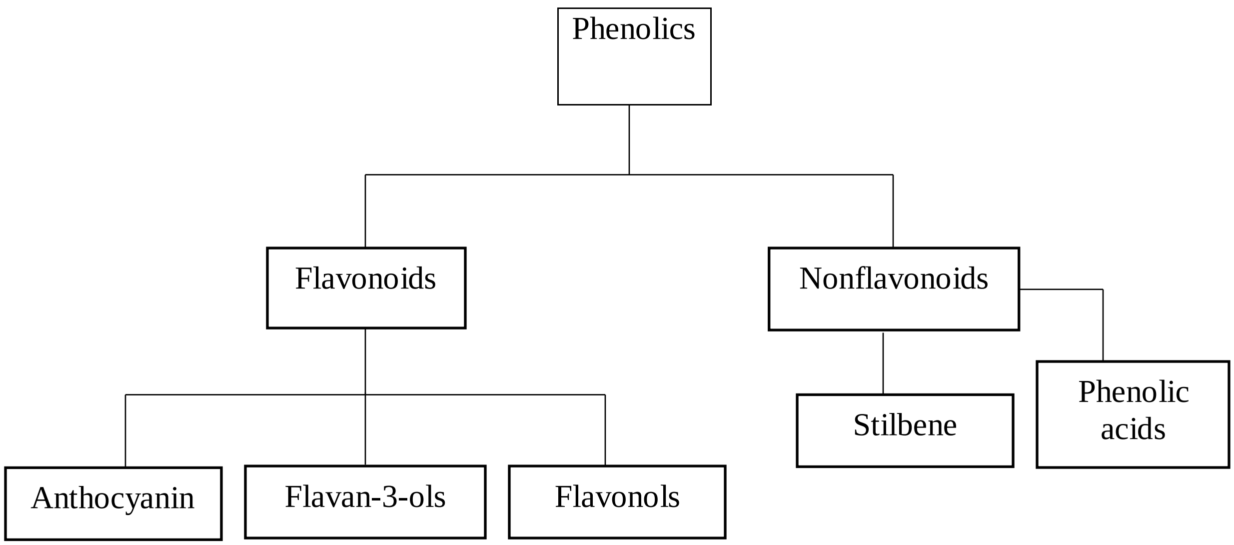


Figure 5: Classification of Phenolic Contents

Phenolics are the third most prevalent ingredient in *v. vinifera*, behind carbs and acids in abundance. In the case of red and white grapes, red grapes can manufacture anthocyanins, but white grapes cannot do so; the total phenolic content of red grape skins is greater than the total phenolic content of white grape skins. Consequently, red winemaking grapes have a substantially greater phenolic content than grapes used for table wine production. According to recent research findings, genetic variables and environmental circumstances significantly control the heterogeneity of phenolic content and profile and the stage of development of the plant organ. Total phenols, flavonoids, catechins, flavanols, and specific phenolics, such as (+)-catechin, (-)-

epicatechin, ECG, astringin, procyanidin B1, and B2, quercetin glucoside, piceid, and resveratrol monomers were found to vary with variety (Yang & Xiao, 2013).

2.1.1 Flavonoids

The generic structure of flavonoids is very much exciting and straightforward. Three carbons (an oxygenated heterocyclic ring) connect two aromatic or benzene rings. This oxygenated heterocyclic ring is called a C ring. In figure 6, a generic structure of flavonoids has been shown.

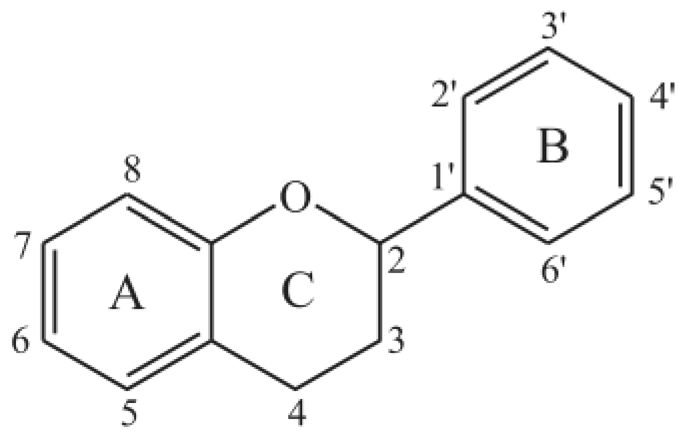


Figure 6: General Structure of Flavonoids

However, flavonoids are categorized or subdivided based on this heterocyclic ring. Compounds of flavonoids are-

1. Flavonols (quercetin, kaempferol, and myricetin),
2. Flavones (luteolin and apigenin),
3. Flavanols/Flavan-3-ols (catechins, epicatechin, epigallocatechin, and epicatechin gallate),
4. Flavanones (naringenin),
5. Anthocyanidins, or isoflavonoids (genistein, daidzein, dihydrodaidzein, and equol).

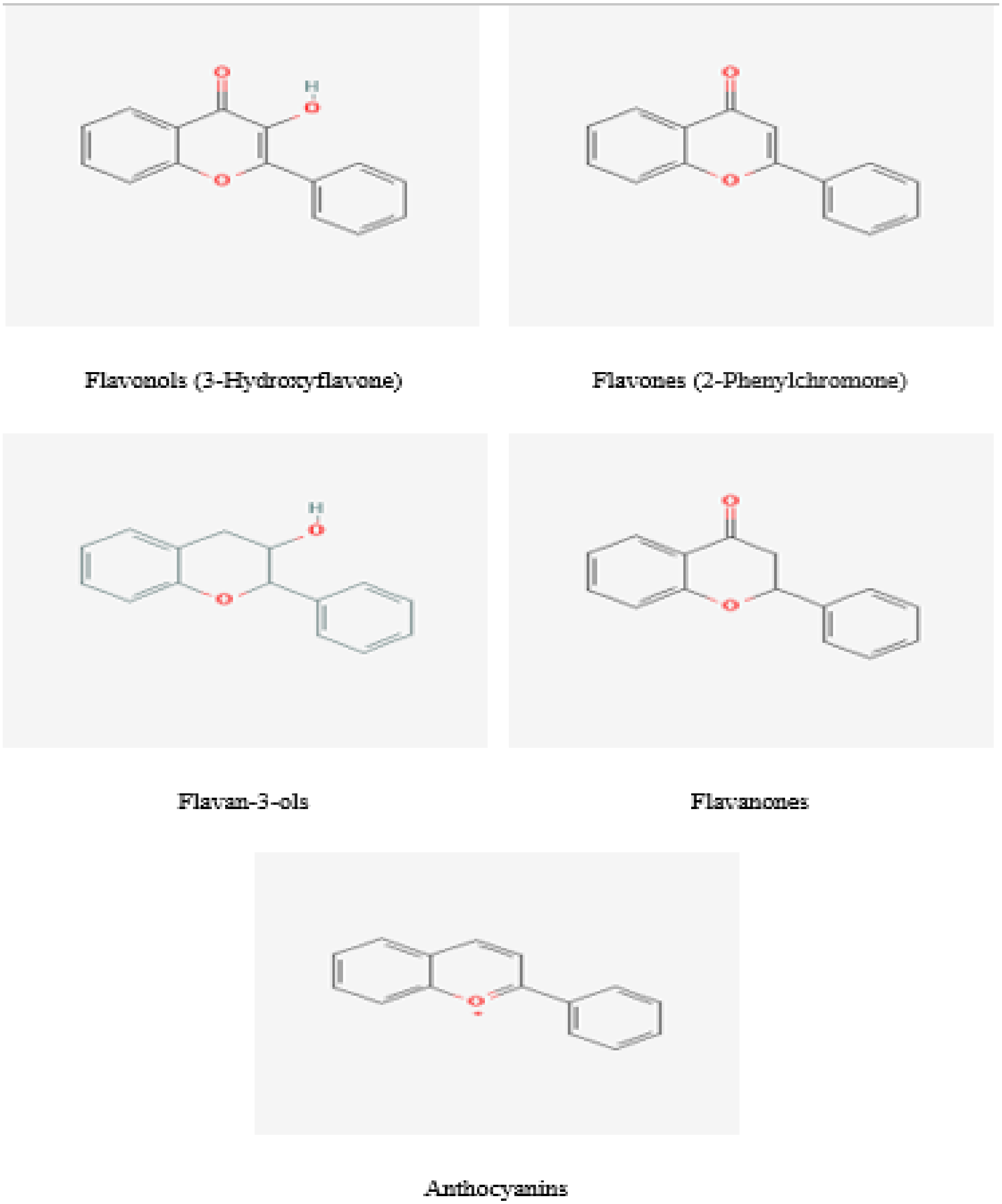


Figure 7: All the Main Classes of Flavonoids

Anthocyanins/ Anthocyanidins

Anthocyanins, also known as flavonoid pigments, are prevalent in the plant kingdom, whereas anthocyanidins are sugar-free analogs of anthocyanins (Figure 8). Sugars are added to distinct side groups of the flavylium ion to produce anthocyanins. Anthocyanins are naturally non-toxic and water-soluble. They carry red and blue colors because of their pigments in red, black, and blue grapes (Shi et al., 2003). A report says that around 10,000 tons of anthocyanins from black grapes are used every year. Vivo mainly identifies flavonoid pigments called anthocyanins on the flavylium nucleus. In terms of structure, anthocyanins are split into two groups: sugar-free anthocyanidin aglycons and sugar-containing anthocyanin glycosides. Grapes contain anthocyanidin compounds that are usually seen in six different forms. The case of an anthocyanin molecule has three major parts: one is the aglycone base part upon than flavylium center (nucleus), an acidic group of acyl acids, and a group of sugars, etc. In *V. vinifera*, there might be as many as 17 different pigments. This group includes the 3-monoglucosides of cyanidin, delphinidin, malvidin, peonidin, and petunidin, as well as compounds that have been acylated with acetic, caffeic, or coumaric acids. Anthocyanins in grape skins are primarily composed of the 3-O-glucosides of delphinidin, peonidin, and petunidin, with minor amounts of malvidin and cyanidin. In addition to playing a critical part in the color excellence of red wines, grape anthocyanins are increasingly being employed in colorants and nutraceuticals (Shi et al., 2003; Yang and Xiao 2013).

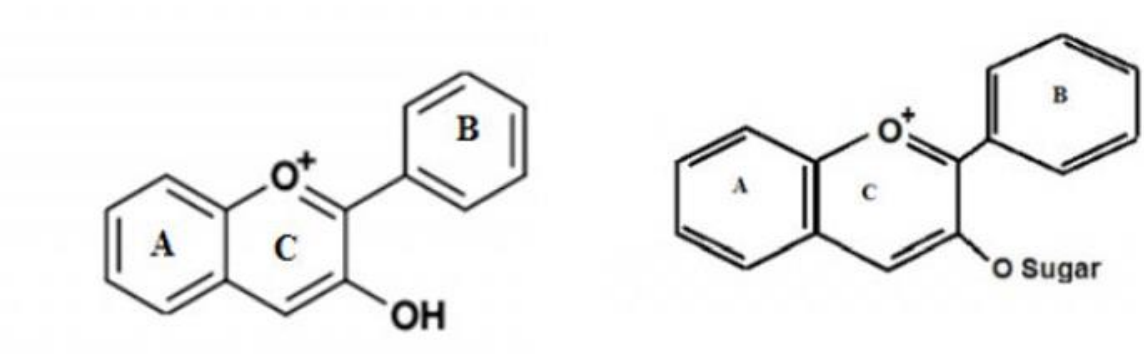
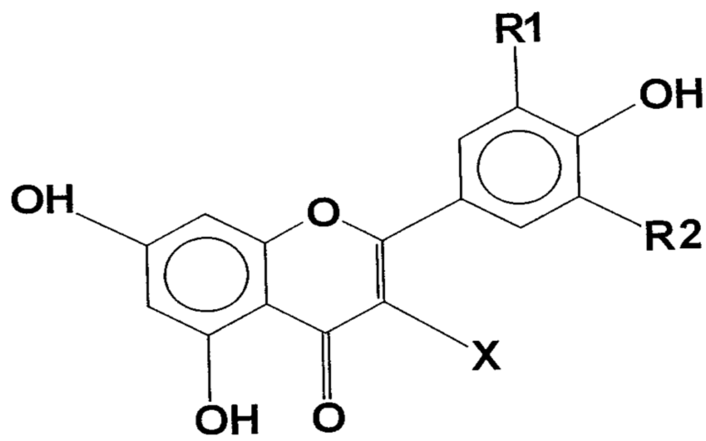


Figure 8: Structures of Anthocyanidins and Anthocyanins, respectively

Flavonols

In every part of the plants' flavonols are found. For example- seeds, pomace, skin, stem, or even converted forms of the grape-like juice, raisins, can also find this flavonol constituent (Nassiri-Asl & Hosseinzadeh, 2016). In this species (*V. vinifera*), there are generally four variants of flavonols, i.e., Kaempferol, Quercetin, Myricetin, Isorhamnetin, and those flavonol aglycones are generally found in the red varieties of this species. Nevertheless, the highest concentrations of quercetin and kaempferol derivatives of flavonol glycosides were detected in the skins of white grapes, while isorhamnetin was also found at lesser levels. Quercetin is usually present in the grape skin in the glycoside form. Quercetin is a powerful antioxidant. On the other side, kaempferol and myricetin are the two simple flavonoid aglycones in grapes (Yang & Xiao, 2013).

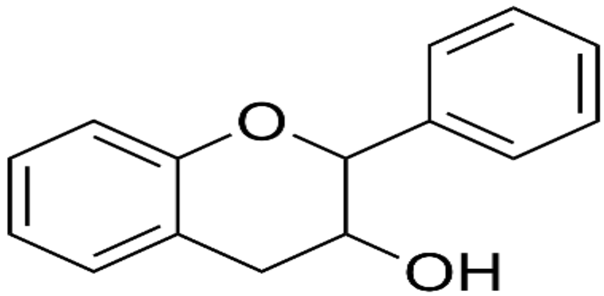


X=OH;

*Figure 9: Structure of Flavonols (*Janssen et al. 1998; Koponen et al. 2008)

Flavanols (Flavan-3-ols)

Flavanols are the most abundant of the group of Flavonoids found in the seeds and skin of this grape variety. Another of their synonyms is Flavan-3-ols, and this name is used to determine the location of the hydroxy group in the C ring. The primary five monomers of flavanols are- (+)-catechin (C), (−)-epicatechin (EC), (−)- gallocatechin (GC), (−)- epigallocatechin (EGC), and (−)-epicatechin 3-gallate (ECG) (Figure 10). However, some common dimers are also found on the skin of grapes, i.e., Procyanidin B1 (PB1) and Procyanidin B2 (PB2). Catechin (C) and epicatechin (EC) monomers are generally colorless flavanols, and also, they are monomeric units of proanthocyanidins. The polymerization degree (PD) of proanthocyanidins, called condensed tannins, typically ranges from three to eleven but may reach as high as 17 in some instances. They are also abundant phenolics in grapes.



Flavanols

Figure 10: Structure of Flavanols

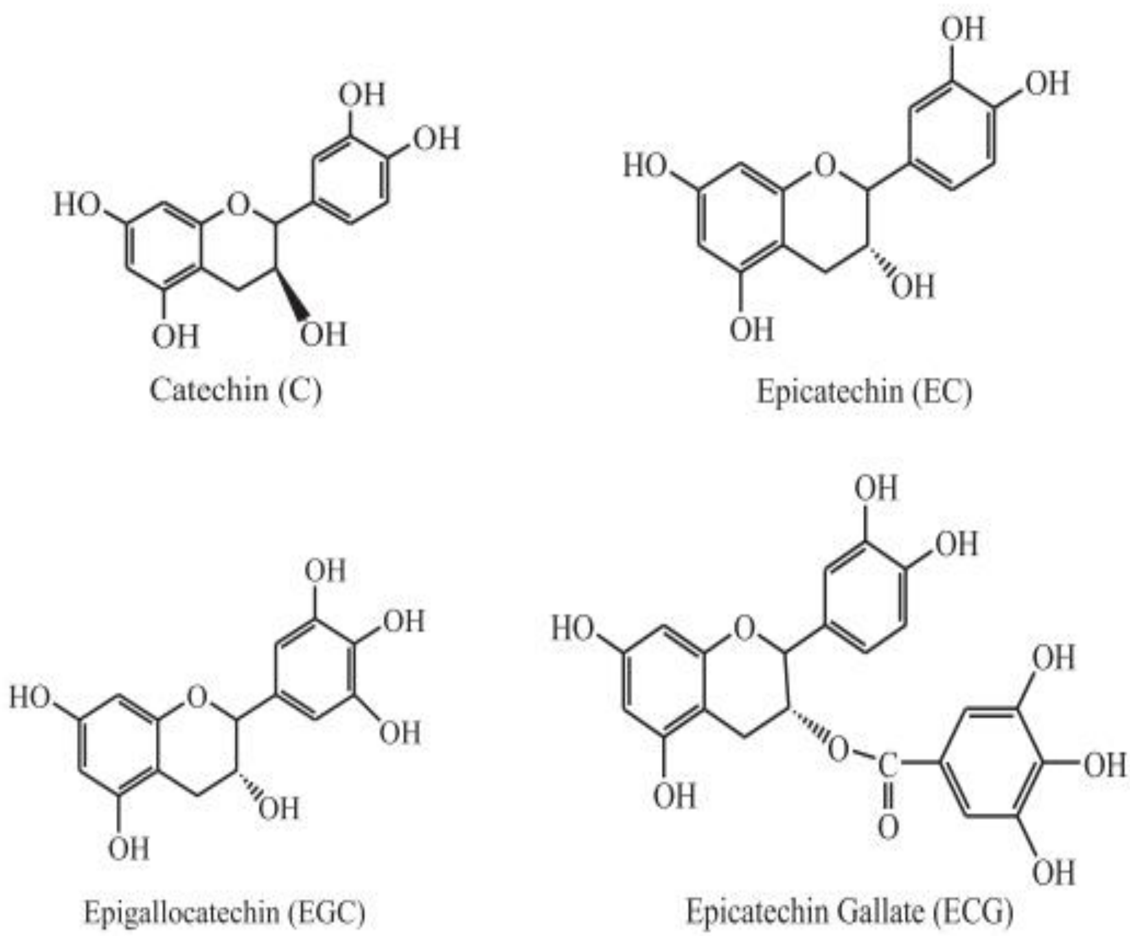


Figure 11: Structure of the Derivatives

2.1.2 Non-Flavonoids

The differences between flavonoids and non-flavonoids are many. The structural difference between flavonoids and non-flavonoids is that flavonoids compounds are mainly composed of two phenol rings (ring A and B), whereas these non-flavonoids contain only one phenol ring (Figure 12). Non-flavonoid phenolics contain various subclasses that are important in the production of wine, including benzoic acids, hydroxycinnamates, and stilbenes, among others. In the case of hydroxycinnamates, the phenolic acid ring is conjugated to the carboxylate group, where a double bond is formed between the carboxylate group and the phenolic ring. Anthocyanins and tannins are flavonoids that add to the wine's color and texture. Stilbenoids like resveratrol and phenolic acids like benzoic, caffeic, and cinnamic acids are examples of non-flavonoids.

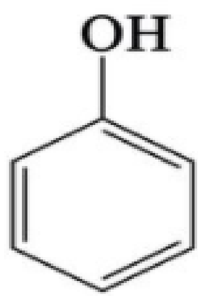


Figure 12: Basic Structure of Non-flavonoids

Non-flavonoids are furthermore classified. Those compounds are-

1. Phenolic acids
2. Stilbene

Phenolic Acids

Viral phenolic acids in the genus Vitis are benzoic acid derivatives and cinnamic acid derivatives. Benzoic acid derivatives contain seven carbon atoms (C6-C1), and cinnamic acid derivatives contain nine carbon atoms (C6-C3). In Figures 13 & 14, the benzoic acid structure and cinnamic acid structure have been shown. Naturally, phenolic acids found in grapes move as free radicals or in conjugated forms. They generally emerged as esters or amides. Fertaric acid, coutaric acid, and caffeic acid are three prevalent hydroxycinnamic acid derivatives found in grapes and wine Syringetin and laricitrin derivatives have also been found in red grapes (Mattivi et al., 2006; Yang & Xiao, 2013).

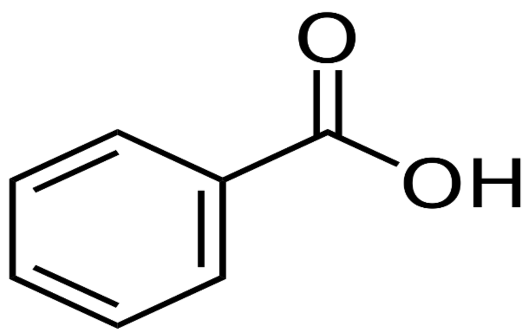


Figure 13: Structure of Benzoic Acid

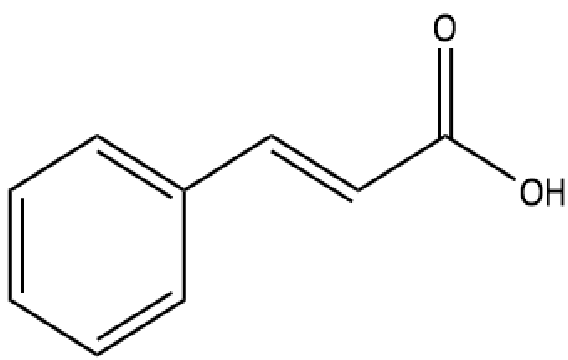


Figure 14: Structure of Cinnamic Acid

Stilbene

Stilbene, a phenolic compound, has two aromatic rings linked by an ethane bridge (Figure 15). Although the grape is more common in grape skin, a lesser amount of stilbene may be found in stems, seeds, and grape skin. Thirty stilbenes and their compounds have been found in plants. Piceid, pterostilbene, resveratrol, and viniferins are some of the phytochemicals found in red wine (resveratrol oligomers). Stilbene control the brilliant blue fluorescence noticed on the surfaces of grape leaves or grape berries when exposed to long-wavelength ultraviolet light (Yang & Xiao, 2013). Many studies have shown that these phenolic compounds called stilbene have antifungal and antioxidant effects. The efficacy of resveratrol (RSV) in stilbene is much more effective and supreme than grape's other components. E.g., antitumor, antioxidant, anti-inflammatory, antiplatelet, and cardioprotective effects are exhibited by RSV (Balea et al., 2020). Even resveratrol might protect against ischemia, epilepsy, and neurodegenerative illness (Teixeira et al., 2014). Resveratrol is a stilbene, a molecule with a straightforward structural design. Most normal & mutant kir6.2 animals are strongly inhibited by pterostilbene, an active ingredient of *V. vinifera* (Nassiri-Asl & Hosseinzadeh, 2016).

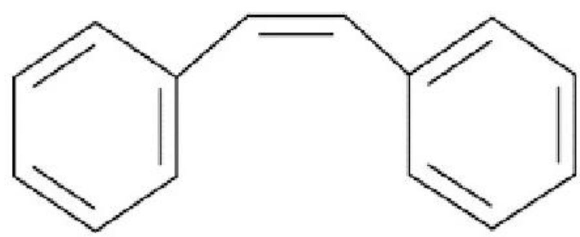


Figure 15: Basic Structure of Stilbene

Resveratrol (Figure 16) is a polyphenol generated from plants that have been shown to have protective effects against various diseases related to aging. Grape skin, almonds, and pomegranate are the most common places to find them. According to specific theories, the antioxidant resveratrol may benefit by interacting with particular polyphenol binding sites in the plasma membrane. This is how the chemical structure of resveratrol (RSV) works: It has two isomers, cis- and trans-resveratrol (Figure 17). Metabolites of resveratrol are used for chemotherapeutic treatment. The majority of the biological actions of resveratrol are mediated via its metabolites. Resveratrol, for example, has been shown to suppress oxidized reduced lipoprotein and cyclooxygenase, constrain the authorization, but also neurotoxicity of beta-amyloid (Aß), modulate apoptotic signaling pathways, and stimulate sirtuin as well as AMP-activated protein kinase, all of which have been implicated as in caloric restriction-longevity impact.

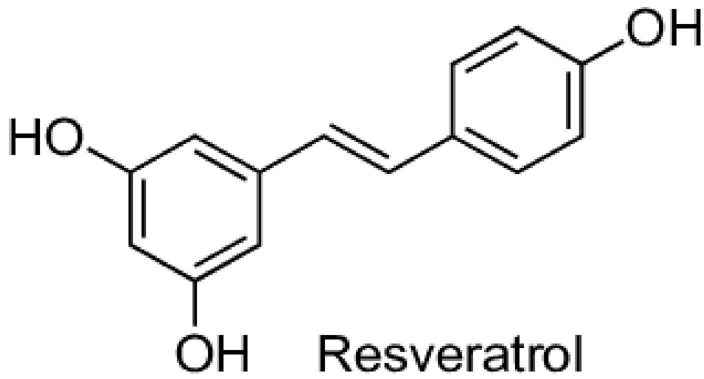


Figure 16: Chemical Structure of Resveratrol (trans-3,4′,5-trihydroxystilbene)

We previously reported that resveratrol, like other polyphenols (such as quercetin and catechins), could protect neuronal hippocampal cells from the toxicity of nitric oxide (NO) as well as Aß peptides, raising the possibility that polyphenols could help prevent age-related neurodegenerative disorders. Lipid binding and autoradiographic investigations in the rat brain show polyphenol-specific cellular membrane binding sites, which might explain polyphenols' neuroprotective effects.

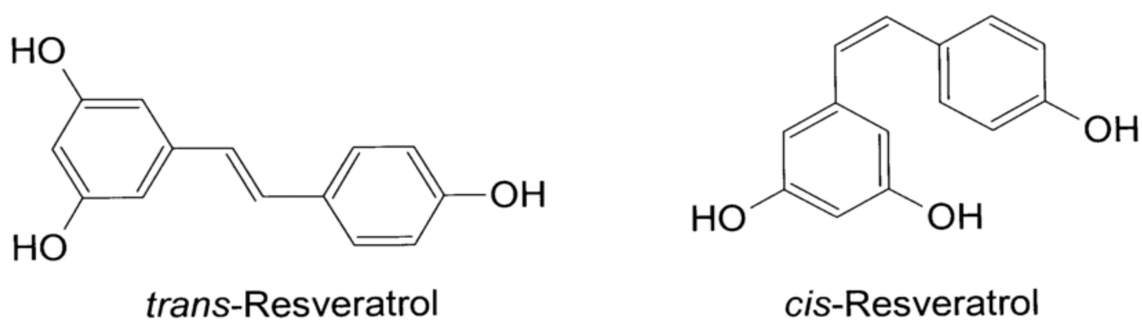


Figure 17: Chemical Structures of Cis-Resveratrol and Trans-Resveratrol

2.2 Carotenoids

Carotenoids are a kind of phytonutrient that is found in high concentrations in fruits and vegetables. They aid in the absorption of light energy by plants, which is then used in photosynthesis. Carotenoids work as antioxidants for the skin, shielding it from the sun's ultraviolet rays and increasing the skin's tone, brightness, photo-protection, and firmness. Beta-carotene and lutein are the most prevalent carotenoids found in red grape types. In wines, significant amounts of luteoxanthin, neoxanthin, and violaxanthin, have been discovered. Isoprenoid tetraterpens (C40) are carotenoids discovered in ripe grapes and are characteristic of the isoprenoid family. Carotenoids undergo oxidation, resulting in volatile and odoriferous chemicals such as ionone, damascenone, and ionol (Yang & Xiao, 2013).

2.3 Melatonin

Melatonin (N-acetyl-5-methoxytryptamine) was recently identified in grape skin and is thought to have a calming effect. Melatonin adds a further layer of complexity to the already complex chemistry of grapes. Melatonin and its probable synergistic effect with the wide range of polyphenols found in grape products add to a better understanding of the reported health advantages associated with frequent intake of grape products. In addition to being a more potent antioxidant than resveratrol, Melatonin has the potential to repair the prooxidant DNA damage caused by low quantities of resveratrol when used in conjunction with other antioxidants (Iriti & Faoro, 2006, 2009).

Chapter 3

Traditional Uses & Pharmacological Effects of *V. Vinifera*

3.1 Traditional Uses

The demand for the grape plant as an ethnomedicinal plant is high in Turkey. This plant (*V. vinifera*) is used as an ethnomedicinal plant in some popular cities in different regions of Turkey, such as Elazığ, Malatya, and Manisa. If we go back in time, we can observe that grapes helped form blood in the Malatya region, whereas grapes were good in treating anemia in the Elazığ region. There are many components in a grape plant, including seeds, branches, fruit, dried fruit, leaves, and latex, which may treat allergies, anemia, bronchitis, cold, carminatives, flu, and wound care Manisa residents. They are frequently utilized as a traditional medicine in Pakistan due to their high nutritional value. It is believed that grapes have carminative properties in Pakistan's Northwestern area. In Pakistan's Sudhanoti area, the leaves and whole grapes may be used as a blood cleanser, anti-phlegm, and thirst quencher, among other things. Tuscany and Bologna are two Italian regions where wine and alcoholic drinks derived from the vine *V. vinifera* are used to cure problems in the digestive system. In the Republic of Cyprus, wine, vinegar, and spirit derived from the vine (*V. vinifera*) are used as tincture, emollient, and mouthwash. *V. vinifera* is often used to treat bleeding, dysentery, and varicose veins. They also act as an antibacterial, a demulcent, a diuretic, an inflammatory, a laxative, and a stomachic agent (Insanu et al., 2021). According to research by Beni et al. (2013), grapes may be turned into edible goods, such as grape syrup, from their raw state (Beni et al., 2013).

3.2 Pharmacological Effects

The pharmacological properties of *v. vinifera* are extensive due to their polyphenolic content, including antiallergic, antibacterial, anticancer, antidiabetic, antifungal, anti-inflammatory, antimutagenic, antioxidant, antiplatelet, antiproliferative, antiulcer, antiviral activities/properties, skin protection, and cardioprotective, neuroprotective, hepatoprotective, and vasoprotective effects as well (Bomser et al., 2000; Raja & Dubey, 2020). GP is a polyphenol content, which has a strong antioxidant effect, suggests that it may help prevent disease-related oxidative stress. Fetească neagră and Pinot noir grape pomace extracts contain a high concentration of polyphenols and exhibit significant antioxidant activity in vitro. Fermented samples contain higher levels of polyphenols, but fresh samples contain higher levels of antioxidant activity (Balea et al., 2020). Nutraceuticals and dietary constituents derived from *V. vinifera* (grapevine) products are abundant in grapevine products. Likewise, they have been utilized as medications for treating a wide range of conditions (Topalović et al., 2020). According to some definitions, Nutraceuticals have health advantages or safeguards against chronic diseases. Nutraceuticals may help you live longer by improving your health, delaying the aging process, preventing chronic diseases, increasing your life expectancy, or supporting the structure and function of your body. In addition, to these antioxidants activities, another activity is currently being spoken of as very strong, and that one is antifungal activity. One of the most common human pathogens that causes both mucosal and deep tissue infections is Candida. GSEs with a high polymeric flavan-3-ol content may help treat mucosal infections, such as vaginal candidiasis (Simonetti et al., 2014).

3.2.1 Antiallergic Effects

According to a study published in the journal Asthma, the grape variety *V. vinifera* (Red) contains a combination of polyphenols and antioxidants that help reduce airway inflammation, alleviating allergy symptoms such as swollen sinuses and congestion. There has recently been an increase in the number of people suffering from type-1 allergy, including food allergy, pollen allergy, and skin conditions such as atopic dermatitis. Therefore, it is necessary to develop effective and safe food products to manage and cure such allergies due to the severe threat to patients and their loved ones. Many steps must be completed before allergic symptoms appear. Basophils and mast cells play a critical part in developing allergic inflammatory reactions. These reactions are triggered by the release of different biochemical mediators, such as histamine and serotonin, from these cells due to degranulation responses (Andersson & Lidholm, 2003; Metzger, 1992; Rona et al., 2007).

Numerous studies have demonstrated that phenolic compounds found in various vegetables and fruits have antiallergic properties. Grape is one of these fruits. Grapes contain a high concentration of polyphenols such as catechin, epicatechin, gallic acid, and polymeric proanthocyanidins, which are concentrated primarily in the seeds and skin of the fruit. Many experimental results indicate that *V. vinifera* might be a promising therapeutic agent in managing allergic Asthma. This may be due to the anti-stress, mast cell stabilizing, and anti-inflammatory properties of *V. vinifera*, among other things.

3.2.2 Antibacterial Effects

A molecule's antibacterial and antiviral activity is linked to compounds that selectively kill bacteria and viruses or slow their growth without causing extensive tissue damage. In the fight against infectious diseases, antibacterial agents are crucial. As antibacterial agents, the role of *v. vinifera* is extensive. Seeds are undoubtedly the most crucial ingredient. Grape seed extract (GSE) has been shown to have antimicrobial effects on many microbes. When it comes to fighting Gram-positive bacteria and Gram-negative bacteria, the GSE is superior. Numerous significant clinical viruses and fungi are inhibited by it. Consequently, following some other findings, the antibacterial activity may be attributed to the diversity of phytoconstituents present in GSEs as well as the fact that distinct antibacterial substances are present in plant extracts, each of which may act differently and synergistically to impact the antimicrobial properties of the extract (Felhi et al., 2016).

Grape seeds contain 60-70 percent of the grape polyphenols found in whole grapes. Grape seeds contain a variety of polyphenols, including proanthocyanidins and procyanidins, which are beneficial to the body. The antioxidant properties of these grape polyphenols are severe and at their maximum (Choi et al., 2012; Shi et al., 2003). According to research, grape catechins have also been antibacterial inhibitory activity against pathogenic bacteria. The actions of EGC, EGCg, and GC are also bacteriostatic. The antibacterial effect of catechins against pathogens and bacteria has been studied, and the results are similar to those obtained against *C. albicans*. According to one report, catechins' bactericidal effects on *Staphylococcus aureus* and *Escherichia coli* were caused primarily by the catechins' ability to act on and damage the bacterial membranes of these bacteria. Catechins' antibacterial properties are primarily attributed to the gallic acid functional group and a member of the hydroxyl group, present in high concentrations. Catechin action is characterized by the induction of rapid leaking of small molecules trapped within the liposome's intraliposomal space and the agglomeration of the liposomes (Fukai et al., 1991; Hirasawa & Takada, 2004; Ikigai et al., 1993).

3.2.3 Anticancer Effects

Research teams and food manufacturers have become highly involved in polyphenolic compounds from grapes in recent years, owing to the antioxidant properties and the fact that they are abundant in the diet. Grape plants have been shown to have vigorous antioxidant activity in both vitro and in vivo studies, inhibiting cancer cell proliferation and platelet aggregation and lowering cholesterol levels (Yang & Xiao, 2013). They are thought to prevent various ailments associated with oxidative stress and cancer (Raja & Dubey, 2020).

Cancer is the second major cause of death in the US and many other countries. The outlook for patients with metastatic breast, colon, lung, or prostate cancer (four of the most prevalent and lethal cancers, accounting for more than half of all cancer deaths in the USA) is bleak. Most cancers have not been controlled by conventional therapy or surgery. Thus, developing mechanism-based cancer management strategies is urgently required. Non-toxic chemoprevention may be one option. Many natural agents have shown chemopreventive potential in various bioassay processes and animal models. It is understood that an excellent chemopreventive agent should have definite properties. One is resveratrol because it has the required properties to act as a therapeutic drug. As a perfect non-toxic agent to give antiproliferative effects against deathly cancer, resveratrol has those mentioned properties:-

1. little or no toxicity in natural and healthy cells;
2. high efficiency against multiple sites;
3. oral consumption;
4. low cost; and
5. human acceptability;

V. vinifera is an excellent rich source of antioxidants resveratrol, which can help protect against cancer. According to research, resveratrol may potentially prevent cancer from developing in the liver, breast, stomach, and lymphatic system, among other places. Resveratrol exerts its effects by stimulating or unplugging molecular pathways (Pathways involved in cancer progression and tumor initiation) in the body. Resveratrol also has many other anti-properties to improve the human immune system discussed in the phytochemicals section (Figure 18). Among women, breast carcinoma is the most prevalent form of non-skin cancer. There is evidence that resveratrol directly affects breast cancer cell proliferation. According to some studies, resveratrol has altered autocrine expansion modulator paths in breast cancer cells (Aziz et al., 2003; Gehm et al., 1997).

Secondly, non-melanoma skin carcinoma is the most prevalent cancer in the USA, accounting for almost half of all cancers. Over a million individuals with skin cancer are diagnosed in the USA every year. Skin cancer is classified as either melanocytic or epithelial in humans, depending on the cellular origin. Resveratrol has been shown to prevent skin cancer. According to some studies, resveratrol effectively prevents chemically-induced skin carcinogenesis: Trans-resveratrol, a polyphenol in red wine, maybe the most potent anticancer polyphenol (M. Jang et al., 1997; Soleas et al., 2002). Few studies have examined whether resveratrol can help prevent liver cancer by acting as a chemopreventive. According to the findings of many studies conducted in cell culture systems, resveratrol has antiproliferative and cancer chemopreventive effects against colorectal cancers, particularly colon cancer. The antioxidant resveratrol has chemopreventive impacts on colonic melanoma cells by inhibiting the cell cycle in these cells (Wolter et al., 2002, 2018).

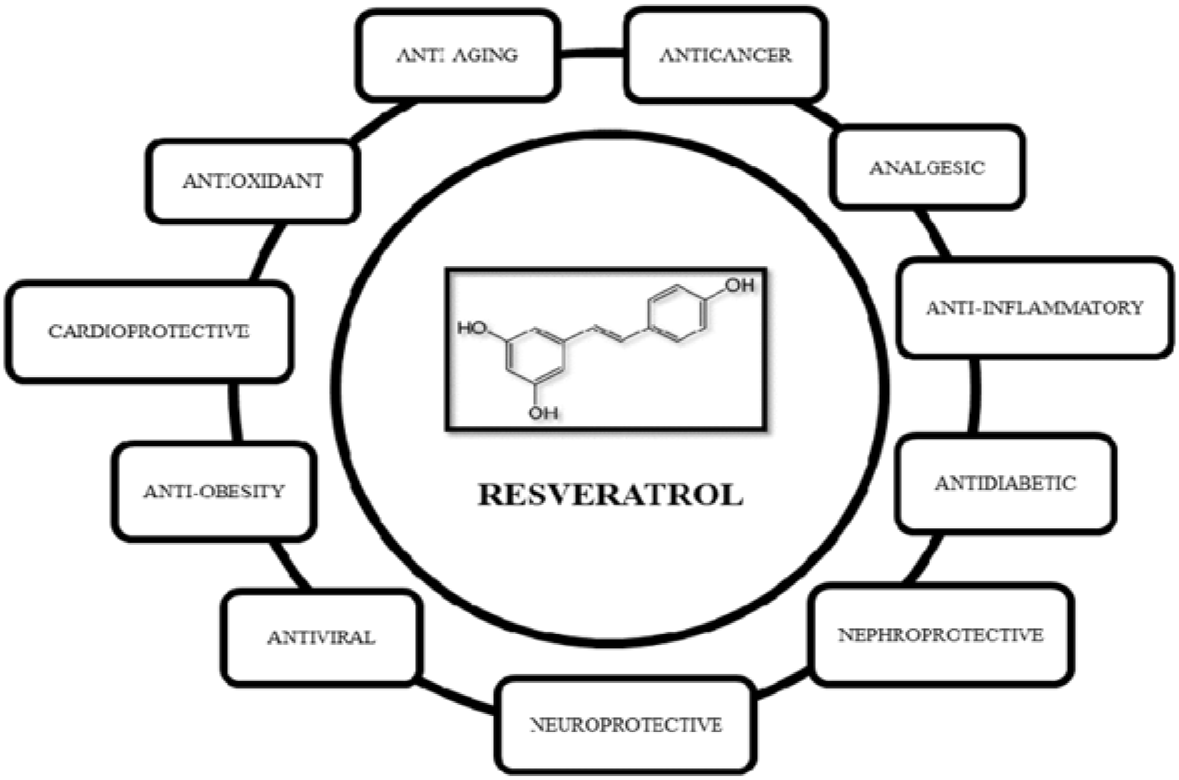


Figure 18: Some significant physiological effects of resveratrol (Aziz et al., 2003)

Several studies have demonstrated that proanthocyanidins can also inhibit the growth of cancer cells. Grape seed extract contains proanthocyanidins, which are antioxidants. Additionally, they have antioxidant properties. Following the results of a modest randomized study of grape seed extract, it was discovered that antioxidants other than proanthocyanidins might have the ability to inhibit the advancement of certain types of cancer. Grape skin extracts containing polyphenolic compounds and grape seed extracts have been shown to have inhibitory activity in colorectal carcinoma cell lines (Topalović et al., 2020).

3.2.4 Antidiabetic Effects

Diabetes is a long-term illness that affects how our bodies convert food into energy. Most of the the food we eat is converted to sugar (also known as glucose) and absorbed into our bloodstream. Glucose is usually allowed to enter the body's cells from the bloodstream to provide energy to the body. Insulin secretion from the pancreas is responsible for transferring this glucose from the bloodstream to the cells as energy. However, the main problem occurs here. In patients with diabetes, blood glucose levels rise (Hyperglycemia) when insulin-producing beta cells are destroyed or somehow the hormone (insulin) is ineffective. Consequently, diabetic patients are more likely to develop other life-threatening, deadly diseases such as cancer.

In developed countries, people with diabetes and metabolic disorders have increased. The primary reason for this is different advanced lifestyles, which are too lethargic and devoid of exercise, dietary disparities, and irregular eating hours, among other things. Poor nutrition is powerfully associated with diabetes, one of the ten leading causes of death in the US (Broumand, 2006).

Different fruits and vegetables have a significant contribution to the prevention and cure of diabetes, and scientists have been conducting various experiments on these at different times. One of the most widely used tests on grape plants to prevent or cure diabetes is to test on rats. Diabetic rats are symbolized here as models. According to an article, although GSPE (Grape Seed Proanthocyanidin Extract) effectively treats diabetic nephropathy, very little is known about the workable protein changes. Nine kidney proteins have been identified to return to normal levels after GSPE therapy in diabetic rats. These proteins are engaged in amino acid metabolism, glycosylation damage, and oxidative stress. GSPE also protected diabetic rats' hearts from glycation-related damage (M. H. Jang et al., 2008; Li et al., 2008). Red grapes also have a very influential role against diabetes, especially their skin extracts. It is beneficial because RGSE (Red Grape Skin Extracts) protects proteins from oxidative damage, affecting protein carbonyl and thiol oxidation. RGSE achieves its beneficial outcome through its antioxidative and anti-glycation properties, which help prevent diabetic complications caused by advanced age-related glycosylation (Topalović et al., 2020).

3.2.5 Antifungal Effects

Grapeseed skin, stem, berries, and other unknown or even known compounds of *v. vinifera* are also very effective against fungal diseases and fungal infections. Member of the Vitaceae family, *V. vinifera* is rich in phytoalexins. Pterostilbenes and stilbenes are biologically active compounds with antifungal properties against various pathogens. Pterostilbene, which is found in grape pomace and leaves, on the other hand, has potent antifungal properties. Stilbenes have a significant antifungal activity, which recommends that these compounds may be able to respond to grapevines' resistance to fungal diseases and that they may be used as factors of disease resistance in the future (Jeandet et al., 2002). Other notable compounds of *v. vinifera* follow this, e.g., catechin, epicatechin, gallocatechin, etc. Grape seed extracts contain a high concentration of catechin. Some experiments have found that catechin, found in grapes, has very effective antifungal effects against *C. Albicans*. It was also discovered that the addition of EGCg (epigallocatechin gallate) to amphotericin B increased the antifungal activity of amphotericin B. Some recent studies have also revealed that the synergistic antifungal activity of the conjunction of antimycotics and EGCg against *C. albicans* is exceptionally effective in some cases. The compounds 3,4'-dimethoxy-resveratrol and 3,5-dimethoxy-resveratrol are found in grape (*V. vinifera*) canes. Antifungal activity has also been demonstrated for both compounds at a low minimum inhibitory concentration. Resveratrol of grapes also has antifungal properties (Insanu et al., 2021; Iriti & Faoro, 2009; Jeandet et al., 2002).

3.2.6 Anti-inflammatory Effects

Anthocyanins, which are found in grapes, help to reduce inflammation. They may also reduce the risk of various diseases, including Alzheimer's, diabetes, eye problems, heart disease, and obesity. Resveratrol also has been shown in studies to protect the heart from inflammation. In one study of

60 people with heart disease, those who took two 50-mg resveratrol capsules daily for three months saw reduced inflammatory gene markers like interleukin 6 (IL-6). Adults who consumed grape extract daily had higher levels of adiponectin, according to a 2012 study. Decreased amounts of such a hormone are linked to obesity and higher cancer risk (Balea et al., 2020).

Promising human kidney cells can boost intraphagocytosis and minimize inflammation in the parenchyma in ischemia by consuming resveratrol supplements. Recurring colitis may be prevented by consuming grape polyphenols, which have been shown to lower inflammation and oxidative damage, stimulate affected tissue repair, minimize colonic peroxidation, and suppress the activation of iNOS (Inducible Nitric Oxide Synthase) in the colon. In an ear inflammation model, grape seed extract treatments dramatically decreased ear biopsy weight and ear edema. Polyphenols in grapes have been shown to decrease the generation of inflammatory cytokines, which is an important finding (Xia et al., 2013).

When taken in large concentrations, the leaf extract of *v. vinifera* has a significant anti-inflammatory effect. The antioxidants kaempferol, quercetin, resveratrol, and quinic acid are among the anti-inflammatory compounds—high amounts of *v. vinifera* var. leaf extract. Fetească Neagră has an anti-inflammatory effect, as shown by reducing inflammatory cytokines in cells generated by lipopolysaccharide. Portuguese and Turkish raisins of the genus *v. vinifera* also have anti-inflammatory properties (Insanu et al., 2021; Lorenzo et al., n.d.). Raisins (*V. vinifera*) are dehydrated grapes widely eaten as a source of vitamins, minerals, and polyphenols. Several studies have shown that raisins have anti-inflammatory and antioxidant effects, while hydro-alcoholic preparations, often used to make dietary supplements have anti-inflammatory action at the gastrointestinal level (Lorenzo et al., n.d.). An anti-inflammatory agent is also possible using GP extracts (Balea et al., 2020).

3.2.7 Antioxidant Effects

In the context of nutrition, antioxidant activity may be characterized as a restriction or suppression of food oxidation (particularly of lipids and proteins) by the inhibition of oxidative chain reactions, and antioxidants are molecules that defend our cells from free radicals, which are thought to have a role in the development of cancer, heart disease, and other illnesses. Free radicals are chemicals that are formed when our bodies break down food or when we are subjected to cigarette smoke or radiation, among other things. Numerous in vitro and in vivo investigations have shown that grapes possess significant antioxidant activity. This vineyard fruit includes a range of phytochemicals such as anthocyanins, proanthocyanins, phenolic acids, stilbene, etc. All these phytochemicals act as powerful antioxidants.

It has been found that grapes, particularly grape seeds, have a high level of antioxidant activity. Different grapes have shown that the antioxidant capacity of phenolics is linked to the density of phenolics present in the system. It was found that procyanidin dimers and trimers and catechin oligomers extracted from the seeds of a Petite Syrah wine had antioxidant inhibition activity LDL oxidation in vitro (Teissedre et al., 1996). High antioxidant activity is found in the procyanidin dimers B2 and B8, the trimer C1, and the monomers catechin, epicatechin, and myricetin (Teissedre et al., 1996; Yang & Xiao, 2013).

RSV, already known as a potent antioxidant, is one of the many grape phenolics. This is because there is a strong connection between the concentration of RSV and grapes' antioxidant properties. The high antioxidant properties of anthocyanin pigments also help the plant defend itself against free radicals generated by UV radiation and metabolic activities. Stilbenoids have also been shown to provide potential health advantages in the form of antioxidants (Yang & Xiao, 2013).

Several studies have indicated that raisins (*V. vinifera*) possess significant antioxidant qualities, and raisins are often utilized as dietary supplements in most situations, which is undoubtedly really advantageous. Procyanidin B5 and B5-3'-gallate have been shown to have the most extraordinary antioxidant property in an epidermis lipid peroxidation experiment. Procyanidin B5 and B5-3'-gallate have also been the highest effect in an epidermis lipid peroxidation experiment (Bijak et al., 2019).

Flavonoids work as antioxidants by giving electrons to radical chains and preventing them from forming. The finding of Melatonin in grapes, which occurred recently, offers new avenues of investigation in grape study. The study shows that Melatonin is also a potent antioxidant, complementing its neurohormonal effects. Melatonin has been shown to preserve neuronal cells, avoiding damage to nigral dopaminergic cells in animal models in vivo and in vitro studies (Iriti & Faoro, 2009).

3.2.8 Antiplatelet Effects

Grape is an ancient plant that has been used to treat heart and blood vessel illness, hypertension, hyperlipidemia, skincare, and a variety of other problems for thousands of years. Compared to other fruits and vegetables, grape seeds have much more powerful polyphenols, which have anticoagulant/antiplatelet and antithrombotic properties. Grape (*V. vinifera*) seed preparations have also been shown to have blood-thinning properties. When used with other blood-thinning medications, including aspirin, clopidogrel (Plavix), or warfarin (Coumadin), certain studies have shown that it may increase the risk of bleeding.

Grape skin extracts, including poliflavan-3-ol, have also been shown to work as an antiplatelet agent by preventing the aggregation of human platelets (Insanu et al., 2021). Researchers conducted an antiplatelet study utilizing the vasodilator-stimulated phosphoprotein (VASP) assay, which showed that grape seeds extract might prevent adenosine diphosphate (ADP)-induced agglomeration in white blood cells (Bijak et al., 2019). Fetească neagră and Pinot noir grape pomace extracts contain high quantities of resveratrol, a potent antiplatelet compound (Balea et al., 2020).

Chapter 4

Discussion

The plant of grapes provides numerous advantages that cannot be exaggerated in the entire topic. Even though I have gathered a great deal of valuable material from various sources for my review paper, discussing the enormous variety of grape plants is not enough. However, this is sufficient to collect my points for *V. vinifera*. It is a well-known grape species belonging to the family Vitaceae (Figure 3). Some findings in the paper tell that it is one of the most widely cultivated fruit plants around the globe. The most important findings have been concisely summarized. The phytochemicals found in the fruit are the first of these important discoveries. Grapes include phytochemicals or substances that are crucial in their growth and development and the development of humans. Those findings show that besides being a fruit plant, it may also serve as a medicinal plant, owing to the high concentration of phenolic compounds in its leaves, skins, seeds, roots, other plant extracts, etc. (Chapter 2). Various references have shown that resveratrol (RSV), a polyphenol is abundant in grape skins. From my findings, I have got that resveratrol works as an antioxidant that mainly protects the body from heart disease or even cancer. The presence of non-flavonoid molecules such as stilbenes or phenolic acids is also noteworthy. This resveratrol, which may be found in several noteworthy fruits, has many physiological effects (Figure 18). In addition, the principal five monomers, i.e., catechin, epicatechin, epicatechin gallate, epigallocatechin, and epigallocatechin gallate, show strong antibacterial and antifungal effects that can be called a groundbreaking revolution in the history of medical science. From many references, it also has been found that those five principal monomers show powerful anti properties against bacterial and fungal pathogens. Those common pathogens are *S. aureus, E. coli*, *C. albicans*, etc. Because of their unique nutritional content and ethnomedicinal applications, grapes have long been used in various traditional recipes. The pharmacological effects or activities of *V. vinifera* are innumerable. Grape extracts have numerous benefits, which have been highlighted in various research. *V. vinifera* has the potential to be an effective therapeutic agent in the treatment of allergic asthma or treating diabetic patients, or even cancer patients. Proanthocyanidins are found in their seed extracts, which are essential antioxidants. According to research, grapes have also been proven to be effective in preventing and treating heart disease, renal disease, liver disease, and blood vessel disease. While some disadvantages may be found in almost every research study, they will be addressed in future studies as they are identified now. Something new is uncovered once again, and something significant is revealed. Historically, grapes have been employed in laboratories and pastures for various scientific purposes. In conclusion, grapefruit is a delicious fruit tree, but as a medicinal plant, it contributes a lot, and that is why further research is needed to establish and support those claims for *V. vinifera* and more.

Chapter 5

Conclusion and Future Perspectives

The main topic of discussion in the full review paper is the various phytochemicals of *V. vinifera* (Grape) and its numerous pharmacological activities. Beginning with the first debate on grapes (*V. vinifera*), it has been abundantly apparent that this species of grapes (*V. vinifera*) and grapes themselves contain a substantial number of polyphenolic substances (phenols). Furthermore, phenolic compounds are unquestionably essential for the human body to prevent various ailments from developing. Grapes have historically been extensively utilized in many parts of the world for health advantages. Moreover, examining the grape's historical beginnings indicates that it has made no diminution in its contribution to globalization from its far-flung origins. Overall, it can be said clearly that grapes should be included in the fruit and vegetable enhanced diets advocated by health experts and universally regarded as suitable for human health and disease prevention. Experts are still working on different extracts of the fruit and its different qualities or effectiveness. A wide range of biological activities, including antioxidant activity, antiplatelet activity, antidiabetic activity, anti-inflammatory activity, cancer cell proliferation inhibition, induction of phase II enzymes, and reduction in lipid oxidation, have been linked to grape phytochemicals in both in vitro and in vivo studies. These findings could partly explain why grapes are thought to reduce the risk of chronic diseases.

Regarding future perspectives, it is essential to talk about different types of secondary metabolites and their production pathways that are still being researched because it is not entirely yet clear, and further research and investigations are required. As is the case with GSPE, GSSE or proanthocyanins, or mother anthocyanins, the inclusion of RSV compounds is also critical because of its urgency. Aside from the known chemical stability advantage, it has to be seen whether or if proanthocyanins are likewise more physiologically active than their parent anthocyanins in the future. Future research should also investigate the impact of GSSE on particular metal chelators. Seasonal variations in climatic conditions impact grape quality too. So also furthermore, researchers are required to resolve this issue too with more accuracy for the breeding of grapevine and so on.

Further development of appropriate gene technology solutions for the grape plant is also needed. Additional issues need to be identified and addressed in future investigations. As a starting point for discussion, this review will also consider whether genetic enhancement in grapevines is beneficial and what has been done so far.

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