Vitamin and Antioxidant Composition in Grape Seeds and Pomace of Wine Grape Varieties Cultivated in Georgia after Fermentation and Distillation

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Statement

Being the author of the submitted dissertation thesis, I declare that the thesis is original, prepared by me and does not contain materials published, accepted for publication or defended so far by other authors that are not mentioned or cited in accordance with the relevant rules.

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Abstract

To establish the possibility of application in cosmetology, the industry of biologically active additives (BAA) or for other reasons content of tocopherol, total phenols, anthocyanins, proline, total proteins, soluble carbohydrates and also total antioxidant activity was studied both in unfermented and fermented seeds of two species of grapevine – *Vitis vinifera* L. (Georgian varieties Rkatsiteli, and Saperavi) and *V. labrusca* var. *izabella*, and in fermented and unfermented berry skin of Rkatsiteli and Saperavi using spectrophotometric methods. It was revealed that a considerable amount of the studied substances remained in residues of the wine-making industry (both in seeds and berry skin). Thus, there is a possibility of their further processing and application. The wine industry in Georgia produces vast amounts of grape pomace that is currently mostly wasted, while only a minor amount is used for distilling alcohol. Distilling alcohol also produces a waste on which we found still considerable tocopherols, although antioxidant activity has been reduced. These results suggest that grape pomace can be an economically attractive resource for the pharmaceutical and food industries. The utilization of grape pomace for producing pharmaceutical and cosmetic goods with tocopherol and antioxidants can solve two problems: it can recycle waste and develop new profitable businesses in the area of biotechnology.

Keywords: Fermented grape seed extract, Rkatsiteli, Saperavi, antioxidants.

აბსტრაქტი

სპექტროფოტომეტრული მეთოდების გამოყენებით შესწავლილ იქნა ტოკოფეროლის, საერთო ფენოლების, ანთოციანების, პროლინის, საერთო ცილების, ხსნადი ნახშირწყლების შემცველობა და აგრეთვე საერთო ანტიოქსიდანტური მოქმედება ყურძნის ვაზის ორი სახეობის - კულტურული ვაზის *(Vitis vinifera L.)* ქართული ჯიშების, რქაწითელისა და საფერავის და ველური ვაზის *(V. labrusca var.)* იზაბელას ფერმენტირებულ და არაფერმენტირებულ წიპწაში და ასევე რქაწითელის და საფერავის ფერმენტირებულ და არაფერმენტირებულ მარცვლის კანში, შემდგომში მათი კოსმეტოლოგიაში, ბიოლოგიურად აქტიური დანამატების (ბად-ი) ინდუსტრიაში და სხვ. გამოყენების შესაძლებლობის შეფასების მიზნით. დადგინდა, რომ შესწავლილი ნაერთების გარკვეული რაოდენობა რჩება ღვინის წარმოების ნარჩენებში (როგორც წიპწაში, ასევე მარცვლის კანში). საქართველოში ღვინის წარმოება ტოვებს უზარმაზარი რაოდენობით ყურძნის გამონაწურ ჩენჩოს, რომელიც ამჟამად ძირითადად იყრება და რომლის მხოლოდ მცირე რაოდენობა გამოიყენება ალკოჰოლის გამოხდისთვის. კვლევამ აჩვენა, რომ ტოკოფეროლების მნიშვნელოვანი რაოდენობა რჩება ალკოჰოლის გამოხდის შედეგად წარმოქმნილ ნარჩენებშიც, თუმცა ამ შემთხვევაში მათი ანტიოქსიდანტური მოქმედება მცირდება. აღნიშნული შედეგები ცხადყოფს, რომ ყურძნის ჩენჩო ეკონომიკური თვალსაზრისით მიმზიდველი რესურსი შეიძლება იყოს ფარმაცევტული და კვების მრეწველობისთვის. ყურძნის ჩენჩოს გამოყენებამ ტოკოფეროლისა და ანტიოქსიდანტებით გამდიდრებული ფარმაცევტული და კოსმეტიკური საქონლის წარმოებაში შესაძლებელია გადაჭრას ორი პრობლემა: ნარჩენების გადამუშავება და ახალი, მომგებიანი ბიზნესის განვითარება ბიოტექნოლოგიის სფეროში.

ძირითადი საძიებო სიტყვები: ფერმენტირებული ყურძნის წიპწის ექსტრაქტი, რქაწითელი, საფერავი, ანტიოქსიდანტები.

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Content

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List of Abbreviations

IP	Isabella seeds before fermentation
IPF	Isabella seeds after fermentation
IS	Isabella skin before fermentation
ISF	Isabella skin after fermentation
MW	Mixed waste after distillation of alcohol
RP	Rkatsiteli skin before fermentation
RPF	Rkatsiteli seeds after fermentation
RS	Rkatsiteli seeds before fermentation
RSF	Rkatsiteli skin after fermentation
SP	Saperavi seeds before fermentation
SPF	Saperavi seeds after fermentation
SS	Saperavi skin before fermentation
SSF	Saperavi skin after fermentation

Introduction

Viticulture and winemaking in Georgia present mainstreaming and highly profitable sectors that contribute to the country's economic sustainability and progress. Despite world experience, the approach to the use of grape seed in Georgia is irrational, and it is not fully realized. However, it should be noted that this refers to "Kakhetian" style wine waste. About 80% of grape pomace (25-27% of which are seeds) can in the best-case scenario be used as food for livestock or discarded without any use. Annually, the amount of grape pomace left after the production of wine in Georgia is so great that the introduction of effective ways of its application is very urgent.

Thus, the main attention was paid to fermented grape seeds (the so-called "Chacha"), which remain after making wine by the "Kakhetian" method and can become a very effective raw material for biologically active additives (BAA). The creation of new products, which could be used as bioadditives in animal breeding or medicine from such grape waste, is very promising. The discovery of new sources of natural waste in order to create dietary supplements is very important for healthcare.

The grape seeds, left over after making the wine in the European way, are the valuable raw material for the pharmaceutical industry (Jockers 2013), but attempts to use grape seeds obtained after making wine in the "Kakhetian" way have not yet been made.

This research aimed to study the content of some antioxidants in the residues of fermented grape waste after making wine in the "Kakhetian" way and determine the possibility of their further use in cosmetology, in the production of biologically active additives or for any other purpose.

Grapevine is one of the most widely cultivated plants and a valuable product for the pharmaceutical, cosmetic and food industries worldwide (Gómez-Brandón et al. 2019). Grapes are grown for wine production, and after production, millions of tons of by-products and waste are left behind (Devesa-Rey et al. 2011; Domínguez, Sanchez-Hernandez, and

Lores 2017). Such a large amount of waste, mainly grape berry (hull), piles up over the years and turns into a growing problem from the environmental protection point of view (Simoes et al. 2019). At the same time, grape berry skin is a source of fibre, which has antioxidant activity and is a worthwhile by-product of wine production (Costa et al. 2019). It can be used as animal feed (Domínguez, Sanchez-Hernandez, and Lores 2017) and also for the production of food supplements with antioxidant effects (Pasini Deolindo et al. 2019).

Scientific Literature Review: Selection of Materials for Experimental Research

Viticulture and winemaking are the oldest and most important branches of agriculture in Georgia. The history of vine cultivation is closely related to the history of the Georgian nation. According to the latest studies Georgia is considered to be one of the origins of the cultivated grapevine - *Vitis vinifera L.* (Ekhvaia and Akhalkatsi 2006; Imazio et al. 2013).

Probably, the selective breeding of grape vines in Georgia started from 6000-4000 BC. The cultivated vine has spread to the Mediterranean Basin, the Middle East, and finally to America from here. Grape seeds are found in Iran, Turkey, Syria, Lebanon and Jordan. However, the age of the Georgian patterns and the excellence of the species confirm that the cultivation of grape vines and the production of wine in Georgia began 7000 years BC or even earlier.

According to archaeological evidence, Georgian tillers could already create wine in rather small amounts by this time, although vine domestication was still in the paradomestication stage. From ancient times the farmers used to look after and harvest the vine grapes growing in nature. 3000 years ago, Georgia already had full-scale winemaking and viticulture, with private land ownership, vineyards, Georgian traditional pitchers (kvevri) and cellars (Kikvidze 2020a; 2020b).

Archaeological remains of seeds confirm the long-term cultivation of vines in Georgia. In 1965, a joint expedition of the Simon Janashia State Museum of History and Tbilisi State University discovered the ancient settlement and its ruins in the Shulaveri field, where among the found materials one of the noticeable patterns was a grape seed. After analysis based on morphological and ampelometric data, Georgian and foreign scientists determined that it is a domesticated grape variety. Carbohydrate analysis revealed that the seed dates back 5000-7000 years B.C. and is the oldest not only in Georgia but all over the world. According to the studies on the late stone age, neolithic period, the culture of wine consumption was brought from Georgia to the cultural and economic life of mankind. The oldest domesticated grape seeds found in Shulaveri verify that at that time there had already been a well-developed winemaking culture in the Mtkvari gorge in southern and central Georgia. Intensive wine production marked the commencement of trade development (Javakhishvili 1934). According to the latest data, Georgia is fairly considered to be one of the first centres of origin of the cultivated grapevine (Ekhvaia and Akhalkatsi 2010; Ekhvaia et al. 2014).

According to legend, while enlightener St. Nino entered Georgia and started preaching the Christian religion, she carried a cross made of vine branches, which she had tied with her hair. In the distant past, churches were illustrated with carvings, depicting vines, and the entrance gates of the church were made of vines (Kikvidze 2020a; 2020b). Georgians had viewed vine-felling, which was frequently done by the conquerors of Georgia, to be one of the major sources of economic collapse. Taking care of the vine, patronage and transferring into inheritance to younger family members was a great tradition.

Prince (feudal lord) Alexander Chavchavadze, the owner of the Teliani Estate, made a great contribution to the development of Georgian winemaking. It was there that the production of local wine varieties began (Rkatsiteli, Mtsvane, Saperavi). Tsinandali Estate is a place where classical Georgian wine making was born. It was here that wine was bottled for the first time. The oldest item dates back to 1814. The Chavchavadze family promoted the introduction of European culture in Georgia. Alexander's bottled Georgian wine delighted

European guests. Saperavi of 1839 and other historical wines of the 19th century are kept in Tsinandali Enoteca, along with Tsinandali, Saperavi, Chateau Lafite, Chateau d'Yquem and many more. The collection includes more than 16,500 samples. (Tsinandali Museum Complex 2021)

The connections of the Colchian-Georgian civilization with the ancient world are particularly fascinating. The poem "Argonautica" about the journey of the Greeks tells a legend that the Greeks were "astonished by the guard wall of the king's palace, wide gates and columns that were erected in a row around the walls. There was a stone tower on top of the palace, on copper merlons. Jason and his retinue freely crossed the threshold of the palace gates, over which were rising blooming green-leaved vines. Four inexhaustible fountains stood under the vines. Hephaestion spurted these streams out of the earth's core. One was a fountain of milk, the other of wine, fragrant oil flowed from the third, while from the fourth, there was running water out from the grooved rock. That water used to become warm when the Pleiades set and ice cold and pure when they arose." (Apollonius of Rhodes 1948)

Vine and wine have an immense place in the life and culture of Georgia. Vine is met everywhere, in Georgian art, culture, poetry or prose on the frescoes of the temples. As stated, "there is no other country in the world that has one symbol for the vine and faith" (Chilashvili 2004).

In ancient myths, the grapevine in Georgia was considered a divine plant, "Tree of Life". Rejecting the mythical belief, the vine became the symbol of the new faith. The veneration of the vine begins with the spread of Christianity. According to the Bible, the Savior took the grapevine and said “I am the vine; you are the branches” (John 15, 5). The Bible provides the rules for receiving the Eucharist, which considers taking the wine and bread as communion with the blood and flesh of Christ.

There were studied medieval towers in the village of Zvare, where vine pruning tools were found (Ebralidze 2009). Zvare is located in the Keda district. A vineyard has always been cultivated there. According to Sulkhan-Saba Orbeliani's "The Georgian Dictionary", the term "Zuari" means vineyard of the owner, "Mezuare" means collector of vineyard, while

"Mezuere" means vineyard guardian. In 2012, there was found a wine cellar dated back to the Middle Ages, in the village Chaisubani, Chakvistskali gorge. Thus, it may be concluded that viticulture was the leading field of activities of the population. (Kakhidze and Surmanidze 2013, 222–65)

Georgia is often referred to as the "Cradle of Wine". The way of storing wine in traditional Georgian pitchers, so-called "Kvevri", is a cultural heritage. Georgia is considered to be a country where wine was produced back in the Neolithic era. Several decades ago, there were discovered *Vitis Vinifera Sativa* seeds while the archaeological excavations in Kvemo Kartli. Since then, Georgia has developed a winemaking culture that has maintained the ancient traditions to this day. As mentioned by Ilia Chavchavadze (1887), "breeding the vineyard is not just yesterday's activity for us and we have centuries-old experience for choosing the best options. Even those who are little familiar with our vineyard owners, confirm that there are almost no such peasant vineyard owners in our country who would not be able to give you a sensible exhortation and advice on this subject."

For centuries, countless invaders, conquering our country, set their main goal to destroy this area of agriculture, because they understood perfectly well that this would cause great economic, political and spiritual damage to the country. Despite the Georgian economy's recurrent declines, the recovery and development of its devastating fields were extensive. This was facilitated by the thorough knowledge of natural factors by the followers of this activity and, as we often say today, the correct translocation of vines together with other cultures, taking into account their agrarian specifics in the historical and geographical regions of Georgia. As a result of folk selection methods, the Georgian gene pool (525 varieties) of grapevines was created, including wine, table-wine, coloured and white grape vine varieties. From the very beginning, the Georgian peasants raised viticulture and especially winemaking to the level of art; and for this, there were used deliberate labour over many centuries and even millennia. That is why today every family makes their wine, and all wine makers are masters and skilled specialists in this field. The original rules for making wine in the pitchers, created by our ancestors, are passed on from generation to generation, just like the methods of producing such world-renowned wines with the place and varietal denominations as: "Khvanchkara", "Kindzmarauli", "Akhasheni", "Mukuzani", "Napareuli", “Manavi, "Tvishi", "Usakhelouri", "Ojaleshi", "Chkhaveri", "Rkatsiteli", etc.

The 30s of the XX century were marked by the new stage of viticulture and winemaking development in Georgia. New vineyards were planted. Winemaking has acquired a solid industrial scale. Extensive scientific and practical activities have been carried out, which laid the foundation for further revival and development of the industry.

In the 80s, the area of vineyards exceeded 150 thousand hectares; wineries produced 500-700 thousand tons of grapes per year. The resulting wine products were mainly sold in the former USSR, and some were exported to foreign markets.

The tough political and socio-economic situation created in the country since the 90s, as well as the wars in Abkhazia and Samachablo, caused severe damage to viticulture and winemaking, considerably reducing the production and commercial potential of the industry.

Chapter 1. Research Tasks

The following tasks were performed to achieve the goals of the research:

1. Selection of those grape varieties which are most widespread in Georgia and are used in large quantities for wine production;
2. Search for such grape seeds, selected for the research, that have not been processed to compare the composition with the fermented seeds;
3. Study of the vitamin activity of fermented and unfermented seeds; Effect of those vitamins that are characterized by strong antioxidant activity;
4. Determination of the amount of proteins, fats and carbohydrates in fermented seeds;
5. Assessment of the antioxidant activity percentage of fermented grape seed based on the definition of polyphenolic compounds.

Chapter 2. Modern Viticulture-winemaking

In the last period, there has been a legal framework for the promotion of the field in the country, which contributed to the attraction of Georgian and foreign investments. The cultivation of vineyards has renewed; the wine industry has been equipped with the logistical base corresponding to the world standards; the production of unique Georgian wines has been restored. However, still much remains to be done to create a favourable environment for the development of this direction in the country.

Among the main wine producers in Georgia, the following companies should be noted today: Teliani Valley, Georgian Wine and Spirits Company - GWS, Telavi Wine Cellar - TWC, Sameba, Tbilvino, Vaziani, etc (it is impossible to list all of them due to lack of space). These companies possess logistic bases corresponding to world standards, which determines the high quality of their products. The ancient Georgian wine making traditions are combined with modern technological advances in them. These companies primarily sell their products in Russia, but they are also successfully marketed in Ukraine, the Baltics, Japan, the United States, the Netherlands, and other countries.

Chapter 3. Georgian Grape Varieties

There were several independent centres of the development of viticulture: Central Asia, China, Western Asia, etc. Currently, more than 6000 varieties of grapes are spread worldwide. Georgia used to be and remains one of the most important centres in terms of the origin of cultivated grapes and the development of winemaking. More than 500 varieties, representing 8.3% of the entire world assortment, have developed here. There are 2.5 times more vine varieties in Georgia than in Azerbaijan (200 varieties); 5.5 times more than in Armenia (90 varieties); 2.5 times more than in Central Asia (200 varieties) and 3.5 times more than in Dagestan (150 varieties). There were up to 1180 varieties known in the former Soviet Union. More than 500 of them were Georgian sorts, hence exceeding 42% of total varieties. (Ketskhoveli, Ramishvili, and Tabidze 1960) The standard assortment range includes 62 varieties, including 29 wine grapes and 9 table grape sorts. Ivane Javakhishvili mentions 413 vine varieties in the book "Economic History of Georgia" (Javakhishvili 1934).

The primary classification of Georgian vine varieties was made by Kolenati (1846), who had divided cultivated grapevines into setoseness, *V. vinifera Aneboylla* and setose *V. vinifera Trichopylla*. According to the modern classification, Georgian grape varieties are united into an ecological-geographical group of the Black Sea basin (Proles pontica Negr.) and have a high taxonomic rank. Varieties included in the hearth of Colchis forms development are united into the *convar. pontica subconvar. georgica Negr.* group, while the varieties in the hearth of Alazani forms development are united into the *convar. orientalis subconvar. caspica Negr.* group. The abovementioned classification, according to the leaf setoseness, has been specified and detailed by N. Tsertsvadze (1989), who divided all Georgian varieties into three groups: 1. Convar. *pontica* subconvar. *georgica* Negr. provar. *tomentosae* Tserts. (Varieties with felt-like setose leaves, separated from wild vines – *V. vinifera* subsp. *silvestris* Gmel. and improved through selection by local inhabitants); 2. Convar. *pontica* subconvar. *georgica* Negr. provar. *araneosae* Tserts. (Varieties with web-like setose leaves, separated from wild grapevines — *V. vinifera* subsp. *silvestris* Gmel. and cultivated vine varieties — Convar. *pontica* subconvar. *georgica* Negr. provar. *tomentosae* Tserts.); 3. Convar. *orientalis* subconvar. *caspica*. Negr. (Varieties with setoseless leaves, separated from wild vine subspecies — *V. vinifera* subsp. *silvestris* Gmel. *abberans* Negr., as well as cultivated species — Convar. *pontica* subconvar. *georgica* Negr. provar. *tomentosae* Tserts. and Convar. *pontica* subconvar. *georgica* Negr. provar. *araneosae* Tserts.).

Rkatsiteli is a standard, widespread grape variety in Georgia. The largest area of its distribution is in Kakheti. High quality European and Kakhetian table white wine is made from it, as well as high-quality dessert wine material and good local table grapes (Ketskhoveli, Ramishvili, and Tabidze 1960). Rkatsiteli is a local Kakhetian vine variety. It originated during the formation of cultivated vine varieties in the Alazani hearth, located in the valley of the river Alazani. In the distant past, Rkatsiteli was called Kukura (Javakhishvili 1934).

One of the other standard, widespread vine varieties of Georgia is also Saperavi. It is one of the best representatives of the global range of red vine varieties. Especially high-quality table red wine from Saperavi is produced in Kakheti. As for the high concentration Saperavi wine, it is made in Crimea and Uzbekistan (Ketskhoveli, Ramishvili, and Tabidze 1960). Saperavi is a Georgian vine variety. It originates from the local hearth of the vine variety. Direct indications of the time and place of Saperavi origin are not known, since the text on the agricultural history of Georgia has not been preserved before the 13th century (Javakhishvili 1934).

The main advantage of Saperavi is in the unity of its technological properties, which are expressed in its relatively high crop capacity, good resistance to fungal diseases, frost resistance, good adaptation to environmental conditions, and high-quality wine (almost all wine sorts are made from it: table, high concentration and dessert wines), and it's very solid agricultural properties (Beridze 2012).

Chapter 4. Chemical Composition of Grape Seed

The vine is a source of a number of such biologically active substances as fatty acids, vitamins, phenyl substances, etc. (Glampedaki and Dutschk 2014). Products that are made from it are used in the food industry, perfumery and medicine (Zhu et al. 2015). Grape seeds are also very popular. Their extract is characterized by the ability to bind free radicals (Badavi, Ali Abedi, Dianat, et al. 2013). The extract is also widely used as a toxin binding agent (Okman et al. 2014).

Before drying, seeds contain 30-40% moisture, 6-10% - fatty substances, 3-7% - tanning matter and 1-2% minerals. As for the dried seeds, they contain up to 22% fatty substances and such fat-soluble bioactive agents as tocopherols, carotenoids, sterols. Bulgarian specialists have developed a technology for the complex processing of seeds, valuable natural raw material, which provided the use grape-seed oil, enotannin, ethanolignin, tannin-lignin compound, food extracts for commercial liqueurs, to accelerate the wine aging, food additives, cosmetics-perfumery production (Gorgodze 2013).

Numerous articles are devoted to the studies of the structure of phenolic compounds, the development and improvement of their research methods, their distribution in plants, biosynthesis and other related issues by scientists from different countries. Following scientists contributed to the study of phenolic compounds in grapes and wine: R. Willstätter, and E.H. Zollinger (1917), P. Karrer and R. Widmer (1927), P. Ribéreau-Gayon et al. (2006), S. Durmishidze and N. Nutsubidze (1954), N. Gelashvili and K. Jmukhadze (1970), Sturua et al. (1973), R. Begunova (1953), V.L. Singleton and J.A. Rossi (1965), C. Valuiko (1973) et al. Phenolic carbonic acids, flavonoids (catechins, anthocyanins, leucoanthocyanin, flavonols) and flavonoid polymerization products are considered to be the main phenolic compounds in wine and are deeply studied.

There are two benzene nuclei linked to each other by an oxygen-containing heterocycle in flavonoids. This group includes complex compounds formed by polymerization, for example, condensed tannins formed by polymerization of catechin molecules. They are one of the most important components of red and Kakhetian wines. The same group also includes flavonoids, anthocyanins, resveratrol, myricetin, quercetin, kaempferol, isorhamnetin, Catechin (Kvlividze and Bezhuashvili 2005; Ebelashvili 2006).

Cis- and trans-resveratrol, myricetin and quercetin have especially high antioxidant properties among phenolic compounds. These compounds are mainly transferred from grape seeds or grape stalks to wine. Anthocyanins (dye substances) predominate in the skin of grapes, while catechin in seeds and grape stalks; as for resveratrol, it is phytoalexin and is synthesized by the plant in the skin of the grape berry. The main stalk of bunch and seeds are rich in phenolic compounds from the steep parts of grapes. However, their number in the skin is small. Seeds are distinguished by the total index of phenols (Oniani 2013). Phenolic compounds, especially flavonoids, have anti-inflammatory, choleretic, diuretic, antiulcer, antispasmodic, anti-radiation and antitumor properties. They promote the regeneration of tissues, including the liver tissues; influence the functioning of the gastrointestinal tract and muscles. Because of these properties, they are also called bioflavonoids (Baravoi 1984; Kudrin, Bihunov, and Tsimberg 1991; Weber et al. 2007).

According to recent studies, quercetin, kaempferol, resveratrol suppress the development of malignant tumours; Proanthocyanins inhibit the development of cardiovascular disease; Malvidin and p-Coumaric acid have bactericidal properties, while tannin has antiviral effects. The grape phenolic complex is characterized by universal biological activity and has a therapeutic effect against up to 20 different diseases. The first information about the content of phenolic acids in vines and wine can be found in the scientific literature from the last years of the XIX century (Ormotsadze 2006).

Bettinger extracted protocatechuic acid from the leaves of the vine. This fact was followed by extracting salicylic acid. Salicylic acid was found and quantified in Concord grapes. There was an opinion about its presence in the wine, which was later confirmed. Later, salicylic acid was isolated and identified from such *V. vinifera* varieties as white Shasla, white Muscat, Rkatsiteli, Mtsvane (Vakarchuk 1990).

S. Durmishidze (1955) was the first who isolated and identified connected gallic acid from the leaves of the Saperavi vine and the seeds of the Saperavi and Rkatsiteli varieties. The content of oxicinnamic acids in vines has also been studied. The first studies on the content of oxicinnamic acid in grapes and wine were carried out in the early 50s. Separated caffeic acid and ferric acid. Later, P-Coumaric, caffeine and furfuric acids, as well as sinapinic acid were also found in various organs and parts of the vine. Protocatechuic acid has been found in the skin and seeds of Rkatsiteli grapes. Gallic acid and its dimer ellagic acid are constituents of hydrolyzed tannins. According to some authors, oxybenzone acids are included in lignin (Pekur 1981).

Using gas-liquid chromatography, M. Giashvili found cinnamic, protocatechuic, gentisin and sinapinic acids in stalks of bunches of Rkatsiteli variety and cinnamic in the skin (Giashvili 1979).

There are currently well-studied catechins and phenolic compounds derived from their polymerizations. N. Gelashvili and K. Jmukhadze studied the quantitative content of catechins in different parts of the grape and found that the number of catechins is significantly higher in grape seed and stalks (1970). According to Singleton and Esau (1969), the content of catechins in grape seed is higher than in stalk and skin (N. Gelashvili 1961).

Anthocyanins. The study of vine and wine anthocyanins began in the late nineteenth century (Kudrin, Bihunov, and Tsimberg 1991). The structural composition of vine anthocyanins was first established by Willstätter, Karrer and Widmer. Dyes in grapes are presented in free form, as in the case of anthocyanidins (the same aglycone), and in the form of glycosides, as of anthocyanins, which are mainly connected to sugar molecules. Depending on the amount of glucose moiety, there are distinguished monoglycosides and diglucosides of anthocyanins.

Grape berry skins contain pink, red, blue and purple variations of anthocyanin pigments. Consequently, they give the grapes various colours from pink to dark purple. The colour of anthocyanins is significantly influenced by pH. Anthocyanins become red while turning sour; However, the anthocyanin staining is enhanced in the acidic region by the coexistence of various organic and inorganic compounds (Valuiko 1973). Some researchers believe that acidylated anthocyanins have a great influence on the final colour of grapes and they have biogenetic properties and taxonomic value (Somaatmadja, Powers, and Wheeler 1965).

Anthocyanins are water-soluble vacuolar pigments that, depending on their pH, may appear red, purple, blue, or black. In 1835, the German pharmacist Ludwig Clamor Marquart gave the name Anthocyan to a chemical compound that gives flowers a blue colour for the first time. The blueberry, strawberry, black rice, and soybean are rich in anthocyanins. Some of the colours of autumn leaves are derived from anthocyanins. (Davies 2004; Archetti et al. 2009). Anthocyanins are flavonoids. It contains plant leaves, roots, flowers and fruits. Anthocyanins are obtained from anthocyanidins and they have no odour. It is not approved as a food additive or as a food colouring (European Food Safety Authority 2013).

Amino acids. Free amino acids are found in all parts of the bunch of grapes, and their amount changes significantly during the growth and ripening of the berries. At the same time, the separate parts of the bunch of grapes differ according to the amino acid content.

Up to 20 amino acids are found in free form by the chromatographic method in different grape juices. The following amino acids are found in various types of white and red wines: alanine, valine, glycine, isoleucine, leucine, serine, threonine, aminobutyric acid, asparagine, glutamine, methionine, cystine, cysteine, arginine, histidine, lysine, proline, tryptophan, tyrosine, phenylalanine (Shatirishvili and Maglakelidze 1998).

Chapter 5. Antioxidant Activity of Grape Seed

Researches have shown that the French are less prone to heart disease than other peoples. For obvious reasons, this effect was attributed to the higher consumption of red wine by the French. Polyphenolic compound resveratrol, which is characterized by strong antioxidant qualities, were identified in red wine. "French paradox" was related to resveratrol.

As mentioned above, wine also contains many other antioxidant compounds that, together with resveratrol, contribute to the healing effect of wine, resveratrol itself is 10-20 times more powerful antioxidants than such natural antioxidants like vitamins C and E. Thus, over 100 studies since 1979 have shown that wine reduces the risk of cardiovascular diseases in women and men. Drinking a moderate amount of wine reduces the risk of developing cardiovascular diseases, reduces the formation of blood clots, restores the function of dilation and narrowing of blood vessels in response to pressure changes (Berashvili et al. 2006).

Grape seeds contain a high amount of resveratrol, which inhibits with a strong antioxidant effect the oxidation of low-density lipoproteins and prevents the formation of atherosclerotic plaques. Therefore, increasing the concentration of resveratrol in the blood prevents lipid peroxidation of low-density lipoproteins (Renaud et al. 1998).

There is evidence that resveratrol has a certain effect on the growth and development stages of tumours of various origins. Resveratrol acts as an inhibitor of free radicals and an antimutagen in the event of tumour initiation. Resveratrol has been shown to inhibit tumour cell proliferation. It has been reported to suppress tumour growth by inhibiting cyclooxygenase-1. The latter is an enzyme that converts arachidonic acid into a compound that stimulates the growth of tumour cells. It appeared that resveratrol had a proapoptotic effect on tumour cells. All of this points to the curative function of resveratrol (Roy and Lundy 2005; Ribéreau-Gayon et al. 2006).

Resveratrol regulates the concentration of cholesterol and glucose in the blood; has a pronounced antiseptic and anti-inflammatory effect; reduces the release of histamine and has an anti-allergic effect; strengthens the nutrition of the walls of blood vessels and improves blood circulation; promotes the restoration of healthy cells and the healing of wounds (ulcers); protects the body from pathochemical reactions caused by stress; prevents premature aging of the skin; improves memory and vision; characterized by strong anticancer effects and inhibits tumour cell proliferation and metastasis (G. Yang et al. 2014; Kaur et al. 2006).

Usage of resveratrol has been studied for the prevention and treatment of cognitive disorders several times over the past decade. Animal studies have shown its effectiveness in improving cognition (Khorshidi et al. 2021).

Chapter 6. Medical Use of Grape Seed

Enough material is accumulated concerning free radicals, causing many diseases, such as cancer, cardiovascular diseases, diabetes, autoimmune disorders, neurodegenerative disease. Free radicals represent a group of atoms or molecules that interact with electrons. Antioxidants bind free radicals and protect various substances like lipids, proteins, enzymes, carbohydrates against damage. It should be noted that grape seed extract, in combination with vitamins, creates a powerful antioxidant protective system that controls blood glucose levels and improves fat metabolism. It can eliminate early-stage diabetic disorders (Shakta Mani Satyam and Bairy 2013).

One of the leading causes of death in people with diabetes is coronary heart disease. It has been found that diabetic patients have a higher risk of myocardial infarction than non-diabetic individuals. The mentioned is caused by oxidative stress. It was found that grape extract has a much stronger antioxidant activity than vitamins C and E. It has a positive effect on the myocardium. There is a hypothesis that grape seed extract has the free radicals bounding effect (Suwannaphet et al. 2010; Montagut et al. 2010; Badavi, Ali Abedi, Dianat, et al. 2013). Studies show that grape seeds protect diabetic animals from heart diseases (Badavi, Ali Abedi, Dianat, et al. 2013; Badavi, Ali Abedi, Reza Sarkaki, et al. 2013; Mansouri, Khorsandi, and Abdollahzade Fard 2015), biliary dysfunction (Chen et al. 2015), brain disorders (Yonguc et al. 2015), different types of neuropathies (Pinna, Morazzoni, and Sala 2017) pulmonary insufficiency.

Since 1990, the use of polyphenols for the prevention of various diseases has increased significantly. Grape seeds are used to treat such diseases as amyloidosis. Gallic acid in grape seeds is a key component that protects cells from protein aggregation during amyloidosis (Y. Liu et al. 2013).

It is hypothesized that a healthy, low-fat diet rich in vegetables and fruits is essential for cancer prevention because they contain catechins, bioflavonoids, proanthocyanidins, and phytoestrogens. There was found an anticarcinogenic effect of grape seed extract against various types of tumours. It has cytostatic and apoptotic properties due to epigallocatechin and procyanidin (Dinicola et al. 2012).

Studies reveal that grape seed extract reduces the risks of developing prostate cancer (Raina et al. 2007), bowel cancer cells (Singletary and Meline 2001; Kaur et al. 2006), lung cancer (Xue et al. 2018; Mao et al. 2016), breast and liver cancer (Kim et al. 2004; Hamza et al. 2018). It also reduces the risk of developing leukaemia (Walter et al. 2011; Brasky et al. 2011).

The substances contained in grape seeds regulate the concentration of glucose and cholesterol in the blood, inhibit the synthesis of histamine and, as a result, have an anti-allergic effect. They also have a positive effect on blood circulation, promote tissue regeneration and protect the body from oxidative damage (S. Mani Satyam et al. 2014); slow down skin aging (Dumoulin, Gaudout, and Lemaire 2016; Yamakoshi et al. 2004), effect positively on memory and vision, have antiviral (B. H. Ali 2002) and anti-inflammatory action (Joshi, Su, and D'Souza 2015); they are also characterized by anti-tumour properties and suppress the proliferation of tumour cells (Ali Asghar Hemmati et al. 2015).

It was revealed that diseases such as cancer, diabetes, cardiovascular diseases, autoimmune disorders, neurodegenerative diseases and some others, are caused by the effects of free radicals (D. A. Ali, Badr El-Din, and Abou-El-magd 2015). Antioxidants bind free radicals and protect such vital substances as lipids, proteins, enzymes and carbohydrates (Poljsak, Šuput, and Milisav 2013). They are effective in the case of antibiotic-induced nephrotoxicity (López-Alarcón and Denicola 2013). The antioxidant effect of grape seeds is fifty times higher than that of vitamins C and E (Debasis Bagchi, Bagchi, and Stohs 2002).

Polyphenol content in such unused bioresources of grape cultivars as a stalk of bunch, seeds and pomace has an anticancer effect (Salehi et al. 2019). Grape seed extract enhances anti-inflammatory potential (Harbeoui et al. 2019), prevents stroke risk (Kadri et al. 2019). Grape seed can be used as a treatment for alopecia by inhibiting the enzyme 5 alpha-reductase and reducing hair loss (Dhariwala and Ravikumar 2019). The proanthocyanidin content in grape seed extract, as well as isolated procyanidin, stimulate hair follicles and promote hair growth (Takahashi, Kamiya, and Yokoo 1998; Takahashi et al. 1999; Ayako Kamimura and Takashashi 2002; A. Kamimura et al. 2006).

The strong antioxidant effect has a positive influence on bone healing (Gurger et al. 2019). Grape seed improves symptoms in case of autoimmune bone destruction and reduces autoimmune response (Cho et al. 2009; M. K. Park et al. 2011; J. S. Park et al. 2012; Jhun et al. 2013; Ahmad et al. 2013).

Melasma is chronic hyperpigmentation of the skin and requires special dermatological care. Its treatment is a huge challenge for dermatologists. Numerous studies have revealed that antioxidant therapy of grape seed extract is effective in the treatment of hyperpigmentation. These therapeutic antioxidants are one of the alternative and effective varieties for patients and medical professionals seeking diverse treatments (Babbush, Babbush, and Khachemoune 2021).

Breast cancer is the most common cancer with a high mortality rate. Research shows that grape seeds suppress MCF-7 cell proliferation and reduce cell apoptosis by inhibiting EGFR/VEGF/MMP9 (Kong et al. 2021). Grape seed extract increases testosterone levels and decreases the risk of breast cancer (Eng et al. 2003; Kijima et al. 2006).

Grape seed extract counteracts the loss of PS-induced hippocampal neurons and depressive-like behaviour by relieving oxidative stress. Grapeseed is an effective therapeutic agent for adolescents with depression (Sun et al. 2021). Taking grape seeds as a dietary supplement significantly increases the immune response and resistance to diseases, against a.hydrophila (Mehrinakhi et al. 2021).

Grape seed contains polysaturated fatty acids and these fatty acids have strong anti-radiation and anti-proliferative activity (Messina et al. 2021).

The Canon of Medicine is Avicenna's most important book, describing the effects of food on fertility. Avicenna recommends several foods, including grapes, which may be used as a dietary supplement in cases of male infertility (Sadogh, Gorji, and Moeini 2021).

Osteoarthritis is a complex pathological condition that affects thousands of people. Grape seeds suppress cell apoptosis and the aging process of chondrocytes. Studies have shown that inhibition of DPP4 (dipeptidase-4) protects cartilage by activating Sirt1, which is associated with many pathophysiological processes, especially in such age-related diseases as neurodegenerative disorders and osteoarthritis. According to the experiment, Procyanidin in grape seeds is a competitive method for treating osteoarthritis (K. Wang et al. 2020). Grape seed extract protects the body from osteoarthritis (Woo et al. 2011), reduces pain and cartilage degradation, strengthens bones and enhances their growth (Kojima et al. 2004; Kamitani et al. 2004; Yahara et al. 2005; Ishikawa et al. 2005). Oral administration of grape seed extract improves osteointegration (defined as the direct connection between bone and implant) of the implant caused by estrogen deficiency. It can assist with bone health issues such as bone loss, the healing process, and osteointegration (Tenkumo et al. 2020).

Certain chemotherapeutic agents, such as doxorubicin, are known to trigger cardiotoxicity as a result of oxidative stress. Antioxidant activity of grape polyphenols has been found to protect against doxorubicin-induced cardiotoxicity in studies (Sergazy et al. 2020).

Literature on medical usage of grape seeds are summarized in the Table 1 below.

TABLE 1 MEDICAL USAGE OF GRAPE SEED

	Phenolic compounds	Total antioxidant activity	Tocopherol (Vitamin E)	Source
Oncology	+	+	+	Kijima I, et al. 2006; Eng et al. 2003
Cardiology		+		Gal et al. 2021
Obesity		+		Caimari et al. 2013
Nervous system			+	Hemmati et al. 2015; Izadpanah et al. 2019; Hemmati et al. 2011

Dementia		+	+	Ono et al. 2008; Wang et al. 2008; Asha Devi et al. 2011; Abhijit et al. 2018
Inflammation		+		Terra et al. 2007
Covid 19	+	+		Gal et al. 2021
Reproductive system			+	Lédée-Bataille et al. 2002
Osteoarthritis	+	+		Wang et al. 2020.
Allergy	+			Bagchi et al. 2000; Ma et al. 2017; De la Iglesia 2010

Chapter 7. Using Grape Seeds in Agriculture and Food Industry

Polyphenols, sugars, alcohol, tannins, and other valuable substances are found in 10-30% of grape pomace (Muhlack, Potumarthi, and Jeffery 2018). These substances are distinguished by their high antioxidant effect (Xia et al. 2019) and also a high content of alpha-tocopherol, which can be used as a food oil preservative (Melo et al. 2016).

Aluminum phosphide is a well-known agricultural pesticide that protects the stored grain from insect damage. Accidental consumption of small amounts may cause irreversible damage to the human body. Studies show that grape seed, when combined with taurine, is a natural cardioprotective medication and reduces oxidative stress caused by aluminum phosphide (Anand, Binukumar, and Gill 2011).

The addition of grape seed proanthocyanidin extract, as shown in studies, improves the quality of meat products, muscle fibre properties, and antioxidant potential of ready-to-eat pork. They can effectively change water retention capacity, meat density and nutritional value (Xu et al. 2022).

The grape waste industry produces large amounts of protein-rich seeds that can be a sustainable source of non-animal protein. Its techno-functional properties can be used to improve the stabilization of wine colour and to regulate the acidity of red wines (Cejudo-Bastante et al. 2022).

Since grape seeds have antioxidant properties, adding them to raw and roasted peanuts enhances their storage life (Priyadarshi, Riahi, and Rhim 2022).

Porous materials obtained from the waste of the wine industry are used to make essential oils for insect control. The porous material of grape seed is developed after the extraction of grape seed oil. The product obtained as a result of this process gains additional value and becomes interesting in terms of the use of post-industrial waste products (Todasca et al. 2020). It has also been proven that the potential for tumour prevention and antioxidant effect in skin, seeds and pulp is determined by the time of harvest. The amount of anthocyanidins is the highest in green seeds (Fronza et al. 2022).

As a result of the processing of vine and grape waste, there are obtained LSP-1 and LSP-2, lignin-silicon complex preparations, which have a biostimulating nature and are used for rooting vines to obtain genetically identical seedlings. (Vashakidze 2006)

Chapter 8. Grape Seed Preparations

The production of preparations from grapes in the form of healthcare food supplements, as well as basic medicines, is widespread around the world. Many medicinal drugs are made from it. This remedy is characterized by all those positive properties, which have already been detailed in the Chapter on Medical Use of Grape Seeds. Despite the popularity and range of application of this drug, it is not recognized by the FDA as a monotherapy treatment for certain diseases. It should not be used as a substitute for prescribed drugs.

Grape seeds are mainly used in solid form, as a food supplementary additive. Food supplements usually do not require registration and do not require a set of documentation that is required in case of a full range of medications. Many food supplements on the market, however, include hazardous metals or other contaminants. As a result, identical products should only be purchased from trustworthy vendors.

Grape seed products, like other medicinal drugs, have contraindications such as allergic reactions: rash, swelling of the face, tongue, throat. Their side effects also involve diarrhoea, vomiting, nausea, dry mouth, headache, muscle aches.

Grapeseed is known for its incompatibility with various medications. Such medicinal drugs include the following categories: thinners - warfarin, naproxen, clopidogrel; antidepressants - Amitriptyline, Clomipramine, Fluvoxamine, Imipramine; some asthma medications: theophylline; Cardio and blood pressure medications: verapamil, propafenone, propranolol; medications for mental illness: Chlordiazepoxide, Clozapine, Diazepam, Haloperidol, Mirtazapine, Olanzapine. (Drug.com, n.d.)

Several medical preparations are made from grapes in Georgia. These medications include Procyanidin, Phenovin (Figure 1) and Phlebil. Procyanidin contains dry grape seed extract with 65% of total procyanidin content. Phenovin contains red grape dry skin extract, standardized with 9% resveratrol and 15% anthocyanin content. The grape seed extract is also part of the Phlebil. These drugs have antiaggregatory, antithrombotic, anti-inflammatory effects. They reduce the level of total cholesterol and low-density lipoproteins in the blood. They have a phytoestrogenic effect, are used in case of fibrocystic breast disease and lymphostasis, following breast surgery as well as for improving the functioning of the venous system in the lower extremities. (Aversi Rationale, n.d.)

FIGURE 1 PHENOVIN (BY AVERSI RATIONALE, GEORGIA) PACKAGE

Grape seeds are used in 2% skin cream which, due to its antioxidant and significant antimicrobial activity, can restore endothelium, it also has an anaplerotic effect and prevents wound infection (Ali A. Hemmati et al. 2011).

Activated carbon, which is a strong adsorbent, is also produced from grape seeds. It is used as a toxin suppressor for the treatment of allergic dermatitis, flatulence and acute poisoning (Okman et al. 2014).

The American company "NSP", which produces biologically active substances as capsules, has developed the preparations "Grapine" (Figure 2), which is sold in the global pharmaceutical market. In addition to grape seed, it contains pine bark extract. The preparations are used as an antioxidant that protects the nervous system from oxidative stress.

FIGURE 2 GRAPINE (BY NSP, USA) PACKAGE

Chapter 9. Tocopherol and Fertility

Among males, treated at fertility centres in the United States and having adequate levels of plasma antioxidants, zinc, selenium, or vitamin E, no correlation was found between vitamins and sperm parameters or clinical outcomes in male infertile couples. Higher levels of antioxidants are not beneficial for sperm or male fertility in men with circulating antioxidants in the normal range vendors. (Knudtson et al. 2021)

The study confirms the presence of oxidative stress in the case of sperm dysfunction in Turkish men suffering from idiopathic infertility. (Aktan et al. 2013)

Antioxidants are widely used to treat male infertility. (Agarwal et al. 2021)

The role of quercetin and vitamin E in streptozotocin-induced (STZ) testicular abnormalities in diabetic rats and the possible mechanism of action they use to protect themselves were investigated. Treatment with quercetin and vitamin E resulted in a 34% decrease in apoptogenic cytochrome c secretion. This protected the testes from excessive apoptosis. Histology also showed that the treatment prevented testicular cell death. The results show that quercetin/vitamin E can scavenge free radicals that protect against testicular damage in diabetes. (Ojo and Olorunsogo 2021)

Reactive oxygen is required for spermatogenesis and sperm function, but excessive levels will lead to oxidative stress, impairment of sperm and sperm function due to membrane damage, and DNA fragmentation. The addition of antioxidants might theoretically act as a free radical protection system. Dietary supplements are often used because infertile males have greater amounts of reactive oxygen. Overdose of sperm can lead to a reduction in stress, which is also harmful to fertility and can lead to several diseases. Before using exogenous antioxidants, it's advisable to check the redox status first. (Kopa, Keszthelyi, and Sofikitis 2021)

Almost 15% of couples suffer from infertility. Infertility is a common health problem. It is known that about 50% of infertility cases are associated with a male partner. Oxidative stress is an imbalance in the levels of reactive oxygen species and antioxidants. In fact, oxidative stress is considered one of the most popular pathologies, observed in 50% of all infertile men. Consequently, an increased level of active oxygen can lead to infertility due to DNA damage or lipid peroxidation, as well as due to inactivation of enzymes and oxidation of proteins in sperm. Antioxidants such as vitamins E and C, glutathione, coenzyme Q10, carnitines, selenium, N-acetylcysteine, carotenoids, zinc and pentoxifylline reduce OS induced sperm damage. Research study oxidative biochemistry associated with sperm health and determine who will be most at risk of oxidative infertility. (Beygi et al. 2021)

According to the current definition, an exosome is a measure of the impact on all potential external genetic factors and their influence on health throughout a person's life. Although intentionally added chemicals (e.g., food additives) and food contact materials (e.g., packaging, pesticides) have been assessed as safe to some extent, it is not reported to what extent they can affect health and reproduction. The study aimed to determine the in vitro and in vivo effects of dietary supplements on the rat brain and sperm/testes, especially due to oxidative stress. Treatment with α-tocopherol significantly improved oxidative stress. Our research suggests that some dietary supplements may affect sperm function and cause oxidative stress in the testicles and brain, leading to infertility and short-term memory loss, and some antioxidants may improve these dysfunctions. (Minamiyama, Takemura, and Ichikawa 2021)

Oxidative stress, which is frequently linked to mitochondrial malfunction and ovarian cell apoptosis, can cause vicious cycles in which the underlying cause reverses other defects, resulting in an overall decline in ovarian activity and a reduction in the number and quality of ovicell. Correct diagnosis of the molecular mechanisms involved in ovarian aging may serve to develop a treatment strategy that will slow down the disintegration of the ovary and increase the number and quality of eggs that can be obtained in an attempt at in vitro fertilization. Antioxidants, melatonin, growth hormone, and mitochondrial therapy are some of the treatment options available. (Tesarik, Galán-Lázaro, and Mendoza-Tesarik 2021)

Induction of oxidative stress in men in the process of sperm preparation for assisted reproductive techniques may weaken sperm parameters. Vitamin E is considered to be an enhancer of male fertility. The aim of this experimental study (in vitro) was to evaluate the effect of vitamin E supplement on sperm quality and lipid peroxidation at various periods of taking the sperm samples. Research has confirmed that a vitamin E supplement (in vitro) can protect sperm from the harmful effects of oxidative stress. (Ghafarizadeh et al. 2021)

The evaluation of the effect of vitamin E and Se supplements on oxidative markers and sperm quality parameters showed, that the addition of vitamin E and Se leads to significant improvements in oxidative stress markers and sperm quality parameters. (Chand et al. 2021)

Fertility refers to the ability to conceive a child, which is one of the main reasons for having a family. Fertility is affected by a combination of factors. Micronutrients are essential for anabolic and catabolic activities in the body, so they can be effective factors in fertility. The review of the studies has shown that the consumption of micronutrients, including vitamins D, E, C, A, zinc, iodine, selenium, folate and omega-3 fatty acids, can play a role in improving male and female fertility parameters. Infertile men and women were found lacking in each of them. Because the body no longer meets the essential needs of basic physical activities as a result of the shift to ready meals and sedentary lives, it appears that recommending micronutrients to men and women can avoid many fertility issues and lower the cost of infertility treatment (Paknahad et al. 2021).

The tubules that form spermatozoa, in which spermatogenesis occurs, are covered and protected by Sertoli cells to promote the development of germ cells, which undergo meiosis to form haploid gametes. Supplements with α-tocopherol significantly lower cholesterol-mediated stress and restore seminiferous tubules apoptosis. α-tocopherol can reduce testicular damage by improving histopathological features and inhibiting seminiferous tubular apoptosis. (Sozen et al. 2021)

Chapter 10. Vitamin E and Cancer

Vitamin E, which is a mixture of eight isoforms (four tocopherols and four tocotrienols), is an effective antioxidant that protects polyunsaturated fatty acids from oxidation and can break the lipid peroxidation chain used to treat heart disease, atherosclerosis, muscle disorders or infertility in men. In-vitro studies show that one of the effects of tocopherol is reducing the activity of cancer stem cells. Studies on the involvement of vitamin E not only in terms of protection of reactive oxygen species from mutagenic effects, but also for antiangiogenic activity, ability to infiltrate tumour cells, and suppress metastases, are increasingly frequent in the scientific literature. The significance of vitamin E in the prevention of tumour processes and some malignant neoplasms in women is of particular interest. The findings of the study suggest that vitamin E may have anticancer properties in the fight against breast, cervical, endometrial, and ovarian cancers. (Markowska et al. 2021)

Cisplatin, an anticancer drug that is used to treat a variety of cancers, can cause reproductive toxicity during chemotherapy. In light of this, the present study was designed to investigate the possible protective effects of normal vitamins C and E and nanoparticles (embedded in chitosan) against cisplatin-induced reproductive toxicity. Vitamins C, E and their nanoparticles proved to be an effective therapy in this regard. Vitamins C and E and their nanoparticles maintained weight, testosterone levels, and testicular disorders associated with an improved histological view of testicular tissues. The development of vitamin C and E nanoparticle medications is beneficial in reducing cisplatin-induced reproductive toxicity in male cancer patients receiving chemotherapy. (Rauf et al. 2021)

Vitamin E derivatives have many essential functions in the medication supply containing biological components with hydrophobic, stable, water-soluble enhancing compounds, and anti-cancer effects. (Markowska et al. 2021)

Chapter 11. Cosmetics and Grapes

Given its anti-aging properties and ability to repair damaged skin, grape seed extract is a powerful ingredient that can be incorporated into a daily beauty routine. The history of its application in cosmetology dates back to ancient times and is still a unique means of making skincare products.

The study aimed to develop, describe, and compare grape seed extract (GSE) based formulations due to the significant benefits of GSE in decreasing oxidative stress. Development considered the extraction of GSE from the Vitis vinifera L. HPLC confirmed catechin, epicatechin, gallic acid, epicatechin gallate, and procyanidin dimers. Storing observable formulations, stability and rheological parameters, formulations significantly compensate for exogenous aging factors and affect free radicals and oxidative stress. It may be safe to incorporate bioactive botanical antioxidants into the management of dehydrated and aging facial skin to evaluate the cosmetic benefits for the dermis. (Rafique et al. 2021)

On the Georgian market today, there are many different types of cosmetics, which are considered to be the N1 anti-aging products, including shampoos, gels, oils, and creams. One of the examples of this in Georgia is anti-aging wine serums and creams-gels, which have been produced by the company "Botanik" since 2018 (Figure 3). These products include Saperavi wine, buckwheat oil, vitamins A and E, vegetable collagen, almond oil, carbopol, potassium sorbate and are used for dry and combined skin. Anthocyanins, flavonoids, vitamins, amino acids, micro and macro elements of Saperavi wine are biologically active substances essential for the skin. Anthocyanins and flavonoids stop the skin aging process. They are powerful regenerator and nourisher remedies, enhance the functioning of the collagen structure of the skin, give the skin elasticity and smoothness.

FIGURE 3 ANTI-AGING NIGHT SERUM (BY BOTANIK, GEORGIA) PACKAGE

Environmental factors attack the skin daily, causing the production of reactive oxygen species (ROS) and inflammation. One way to regulate oxidative stress in the skin involves protein phosphatase 2A (PP2A). That is a phosphatase, which was previously associated with Alzheimer’s disease and aging. Oxidative stress reduces PP2A methylation in normal human skin fibroblasts. Grape seed extract regulates PP2A methylation levels, oxidative stress signalling and skin aging (Huber et al. 2021).

Chapter 12. Fighting the Coronavirus

A new coronavirus broke out across the world at the end of 2019. Coronavirus (CoV) is a new coronavirus strain. The coronavirus-transmitted sickness was originally reported in the Chinese city of Wuhan, where it was given the official name "Coronavirus-2019" (CO stands for abbreviated "Corona", VI for abbreviated "virus" and D for abbreviated "disease"). Prior to its official naming, the disease was called "New Coronavirus 2019" or "2019-nCoV."

Virus COVID-19 is a new virus and is linked to the same group of viruses as severe respiratory distress syndrome (SARS) and some forms of colds.

The virus is spread by direct contact with the respiratory droplets of an infected person (which occurs when coughing or sneezing) and by contact with surfaces infected with the virus. The COVID-19 virus survives on surfaces for several hours but is killed by simple disinfection. Symptoms may include fever, cough, and breathing difficulties. In more severe cases the infection can lead to pneumonia or shortness of breath.

In relatively rare cases the disease can be fatal. Scientists around the world are working to find and develop COVID-19 treatments. Optimal care aids include oxygen for critically ill patients and those at risk of severe disease, while more powerful respiratory aids such as ventilation for severe and critical patients.

According to current studies, resveratrol, which contains grape seed extract, with the chemical name 3,5,4'-trihydroxy-trans-stilbene, also known as a stilbene, has protective properties against cardiovascular and cerebrovascular diseases, protects against inflammation, nervous system, body from oxidative stress, inhibits tumour formation, reduces inflammatory process, fights diabetes, obesity and fibrosis. Resveratrol-containing products are used against various diseases (Chen et al. 2015). Resveratrol is known as a preventative measure for cardiovascular diseases (Zou et al. 2019), and it has also been proven to protect heart cells from myocardial fibrosis. (Olson et al. 2005)

Acute respiratory disease (SARS-CoV-2) has infected 126 million people worldwide and killed 2 million. Coronavirus is characterized by chronic inflammation, neutrophilia, lymphocyte dysfunction, lymphopenia, decrease in T lymphocytes. It causes infiltration of lung macrophages. In many cases, patients develop lung damage as well as respiratory distress syndrome. Resveratrol reduces the inflammatory process and inhibits it. It affects signalling pathways including mitogen-activated protein kinase (MAPK) and nuclear factor kappa B (NF-κB), thereby subsequently inhibiting inflammation. Because of its anti-inflammatory and antioxidant effects, given the severity of the disease and the unsatisfactory outcome of the patient's treatment, considering the key role played by inflammation and cytokinetic storms, there is a conclusion that resveratrol may be useful in the treatment of COVID-19. Resveratrol 600 mg once per day may be used as a potential adjunctive therapy in the treatment of the covid virus. (Mahmoudian-Sani et al. 2022) The cardioprotective effect of resveratrol, its antiviral capabilities in the near future suggests that resveratrol can be used against coronavirus (Gal et al. 2021).

The severity of coronavirus and its lethal consequences are determined by factors such as age, sex, and other disorders. Multiple deficiencies related to interferon production by dendritic cells or macrophages in response to viral infections are associated with aging and are resulting in dysregulation of inflammatory immune responses and excessive oxidative stress. Age-related dysregulation of immune function may lead to a more pronounced pathophysiological response to SARS-CoV-2 infection in elderly patients and may accelerate the risk of biological , even after recovery. Suppression of viral replication and attenuation of inflammatory and oxidative reactions is essential for better treatment outcomes. Resveratrol is a powerful antioxidant with antiviral activity. The molecular mechanism of resveratrol reduces basal inflammation and oxidative stress and also has an antiviral effect on the body. (Liao et al. 2021)

Coronavirus represents a high risk also for diabetic and elderly patients due to a large number of lethal cases. 35% of patients who died from this disease were diagnosed with diabetes. This coronavirus reduces the immune response, is associated with chronic inflammation, pancreatic insufficiency. Covid-19 causes metabolic complications, although studies show that natural anti-diabetic and anti-aging remedies can be used to fight Covid (Chawla, Kashyap, and Husain 2021).

Chapter 13. Phenolic Compounds

Phenolic compounds have been studied in treatment against Covid 19. The antioxidant, antiviral and immunomodulatory effects of phenolic compounds against the virus have been studied. The study demonstrated the role of phenolic compounds in the intestine microbiome sample. (Augusti et al. 2021) The most well-known flavonoids catechin, quercetin, kaempferol and non-flavonoid polyphenols, gallic acid and resveratrol, can be used in the development, treatment and formulation of a new medication for the treatment of coronavirus (Dejani et al. 2021). Studies have shown that natural phenolic compounds have several pharmacological properties, including anti-coronavirus and immunomodulatory actions. Therefore, the dual action of natural products containing these substances is considered from the perspective of using COVID-19. (Dejani et al. 2021)

The vesicles in grape seed extract are a promising technological and a kind of green solution to the problem of agricultural waste and by-product applications and creating highly valuable products for human health. The vesicles are highly biocompatible and can counteract oxidative damage caused by Caco-2 cells with hydrogen peroxide. In addition, they promote the formation of a biofilm of *Lactobacillus reuteri*, which acts as a prebiotic. Overall results indicate that glucidex-hyalutransferomes as dietary supplements have the potential to treat intestinal disorders (Manca et al. 2020).

Grape seed extract thickens the inner layer of the bowels, rebuilds the intestinal biome and reduces inflammation. (Y. H. Wang et al. 2010; H. Wang et al. 2013; G. Yang et al. 2014)

Grapes are rich in their primary and secondary metabolites. Polyphenolic compounds are most abundant in the secondary metabolites of grape seed. Their number varies depending on environmental factors as well as climate, soil, vineyards and management. Polyphenolic compounds and phenolic acids have beneficial effects on human health (Šikuten et al. 2020).

At the present stage, the demographic aging of the population is taking place all over the world. Hypertension is becoming a global health problem. Flavonoids or flavonoid-rich extracts have antihypertensive effects. They enhance the activity of antihypertensive drugs through synergism and, although they cannot replace the main drugs, they still affect changes in blood pressure (Cao et al. 2021). Chronic diseases are responsible for 71% of global mortality. They are characterized by chronic low inflammation and metabolic changes. Basically, "functional foods" are characterized by anti-inflammatory action. These functional foods, such as grapes, may show clinically relevant results (Luvián-Morales et al. 2021). Animal studies have shown that grape seed extract protects blood vessels from oxidative stress, drug poisoning, clogging and hardening of blood vessels (Pataki et al. 2002). Grape seed extract also reduces deep vein thrombosis (Olas et al. 2008; Zhang et al. 2011; Michał Bijak et al. 2011; 2013; Michal Bijak et al. 2019). The grape seed extract is effective for healthy blood circulation, and grape seed reduces the risk of heart disease (Vigna et al. 2003; Sano et al. 2007; Yamakoshi et al. 1999; Razavi et al. 2013). It also has a positive effect on arterial hypertension (Feringa et al. 2011; E. Park et al. 2016).

Oxidative stress causes many health problems. Grapeseed is one of the best sources of effective antioxidants, proanthocyanidins, which form an oligomeric proanthocyanidin complex with its unique antioxidant properties (Burton and Jauniaux 2011; J. Yang and Xiao 2013; Toden et al. 2018; Lu et al. 2018). Free radicals cause hundreds of such diseases in the human body as arthritis, hemorrhagic shock, atherosclerosis, premature aging, ischemia, Alzheimer’s and Parkinson’s disease, carcinogenesis and tumour promotion. Antioxidants bind free radicals and have a positive effect on human health and disease prevention. Grape seed extract in combination with vitamins C and E reduces the damage of tobacco-induced oxidative tissues. Grape seed extract protects the liver and kidneys from acetaminophen overdose. Taking it as a supplement improves chronic pancreatitis. Topical application of grape seed extract enhances sun protection (Debasis Bagchi et al. 2000) and prevents UV-induced skin cancer with anti-inflammatory effect and blocking oxidative damage (Sharma, Meeran, and Katiyar 2007; Katiyar 2008; Sharma and Katiyar 2010; Katiyar 2015; 2016).

Antioxidant natural toothpaste also made from grape seeds was created after wine production (Emmulo et al. 2021).

Global agro-commodity production produces a larger amount of waste and creates economic and ecological problems. Grape waste containing phenolic compounds exhibit natural antioxidant activity and anti-inflammatory effect in the treatment of ulcerative colitis (Saadoune et al. 2021).

Alzheimer's disease is a degenerative disease of the brain characterized by progressive impairment of intelligence. This disease was first described by the German doctor A. Alzheimer in 1970. Alzheimer's disease is the most common form of acquired dementia. Numerous studies have been conducted using grape seed to find a method for treating it. Animal studies have shown that grape seed extract reduces the risk of Alzheimer's disease, increases the percentage of antioxidants, prevents protein mutations, and reduces the number of free radicals. (Ono et al. 2008; J. Wang et al. 2008; Asha Devi et al. 2011; Abhijit et al. 2018)

Grape seed extract protects kidneys from toxic medications and high cholesterol (Saad, Youssef, and El-Shennawy 2009; Salem and Salem 2011; Turki et al. 2016). It strengthens kidney function, reduces creatinine, urea and uric acid. It reduces inflammation markers.

Recently, numerous nutritional supplements have been introduced to combat obesity. Studies in animals have shown that grape seed extract prevents fatty liver, promotes fat burning, lowers cholesterol levels and blood lipids. (Quesada et al. 2009; Baiges et al. 2010; Caimari et al. 2013; Downing et al. 2015)

Grape seed extract protects the liver against damages (D. Bagchi et al. 1998), like induced by acetaminophen (Debasis Bagchi et al. 2000), heavy metal poisoning (Miltonprabu, Nazimabashir, and Manoharan 2016), bile duct obstruction (Dulundu et al. 2007; Savdan et al. 2017), ischemic injury (Song et al. 2012), various chemicals (W. Liu et al. 2015).

Grape seed phenolic acids and flavonoids fight oxidative stress. (Nuttall et al. 1998) Grape seed with the ability to inhibit free radicals reduces inflammation and allergic reactions kill microbes and protect the body from toxins and radiation. (Debasis Bagchi et al. 2000; De La Iglesia et al. 2010; Ma and Zhang 2017)

Aflatoxin B1 (AFB1) is a widespread mycotoxin that contaminates food, causing severe oxidative stress damage and immunotoxicity. Grape Seed Proanthocyanidin (GSPE), a natural antioxidant with a wide range of pharmacological and healing properties, inhibits the effects of this mycotoxin and protects the body from oxidative stress (Kumar et al. 2017; Rajput et al. 2017; 2019).

Methodology: Experimental Research of Selected Materials

Based on the analyses of available data on the grapevine sorts grown in Georgia and their potential to produce biologically active compounds (Chapters 1-12 above), the following vine species were selected as the research object: Rkatsiteli, Saperavi and Isabella. The study material was obtained as the outcome of the composition of the fermented and natural seeds and skin of the grapes of the mentioned varieties. The Materials included:

1. Rkatsiteli pomace before fermentation – RNBS,
2. Rkatsiteli fermented pomace – RWBS,
3. Rkatsiteli seeds before fermentation – RNP,
4. Rkatsiteli fermented seeds – RWP,
5. Saperavi pomace before fermentation – SNBS,
6. Saperavi fermented pomace – SWBS,
7. Saperavi seeds before fermentation – SNP,
8. Saperavi fermented seeds – SWP.

Section 1. Experimental Procedures

Section 1.1 Experimental Procedures for Stage 1

Determination of vitamin and antioxidant composition of dry grape seed extract was carried out by the staff and Acad. Dr Gulnara Badridze head of the Department of Physiology at the Institute of Botany, Ilia State University. The following experiments were performed:

Plant material. The pomace of the three most common grape varieties in Georgia was used for research: *Vitis vinifera* var. *Rkatsiteli* (Further Rkatsiteli), *V. vinifera* var. *Saperavi* (Further Saperavi) and *V. labrusca* var. *Isabella* (Further Isabella). The experimental material was obtained from a private vineyard (owned by Maia Akhalkatsi, one of the co-supervisors, which is located in the village of Shilda, Kvareli district). There was squeezed juice from the grape berries to obtain the unfermented beet and berry skin of the unfermented plants. The residual seeds and berry skin were dried at room temperature and crushed into powder. As for the fermented seeds and grape berry skin, they were also provided by the same person after producing the wine in the “Kakhetian” way. All kinds of pomace are mixed together and distilled into alcohol, which is the residue after pomace distillation (further "Chacha"); This material was dried, without the separation of the skin and the seeds, and was used for further analysis. In total, 13 samples were obtained (see Table 5) in which tocopherol content and overall antioxidant activity were determined.

TABLE 2 MATERIAL SAMPLES AND THEIR ABBREVIATION

№	Samples	Code
1	Rkatsiteli skin before fermentation	RP
2	Isabella skin after fermentation	ISF
3	Saperavi skin after fermentation	SSF
4	Rkatsiteli skin after fermentation	RSF
5	Isabella seeds after fermentation	IPF
6	Isabella seeds before fermentation	IP
7	Saperavi seeds before fermentation	SP
8	Saperavi seeds after fermentation	SPF
9	Saperavi skin before fermentation	SS
10	Rkatsiteli seeds after fermentation	RPF
11	Isabella skin before fermentation	IS
12	Rkatsiteli seeds before fermentation	RS
13	Mixed waste after distillation of alcohol	MW

Anthocyanins: In order to detect the anthocyanins, 20 ml of ethanol and 2% hydrochloric acid solution was poured onto 1 g of ground experimental material, and it was filtered. The obtained extract was measured by a spectrophotometer at 529 nm (SPEKOL 11, KARL ZEISS, Germany) (Caldwell 1968).

Total phenols: 250 mg of ground grape seed was boiled for 15 minutes with 80% ethanol. After centrifugation, the supernatant was separated, and the powder residue was mixed with 60% ethanol and boiled for another 10 minutes. The extract was added to the original supernatant and evaporated. The sediment was dissolved in distilled water. 1 ml of solution was added to the Folin & Ciocalteu's phenol reagent, and the optical density was measured with a spectrophotometer at 765 nm. Chlorogenic acid was used as a control (Badridze et al. 2015).

Soluble carbohydrates: An anthrone reagent was used to determine the amount of soluble carbohydrates (Turkina and Sokolova 1971). 96% alcohol (triple extraction) was added to 100 mg of crushed material for extraction. The entire amount of the obtained extract was evaporated in a water bath and then dissolved in 5 ml of distilled water. Anthrone reagent was added to 0.5 ml of distilled water, to the extract, and placed in a water bath for 10 minutes. After that, the tubes were placed in a cold water bath and after 15 minutes the optical density of the solution was measured by a spectrophotometer at 620 nm.

Tocopherol (TPH): The amount of tocopherols was determined by the method described by Filipovich et al. (1982): 20-25 ml of pure ethanol was added to 500 mg of ground powder in order to obtain pure ethanol; The procedure was performed three times at room temperature. 20 ml of 60% potassium hydroxide was added to the combined extract and mixed in a water bath for two hours. The combined extract was purified with distilled water until complete removal of the alkaline residue; water was dried out by using Na_2SO_4; the obtained solution was evaporated on a water bath, cooled, and a mixture of alcohol-nitric acid (1 mL concentrated HNO_3: 5 mL 96% alcohol) was added to it. After 3 min of boiling, until dark red, the extract was measured by a spectrophotometer at 470 nm (Spekol 11, Karl Zeiss, Germany).

Total antioxidant action (TAA): Total antioxidant activity was measured by a modified method using diphenyl-picrylhydrazyl (DPPH) (Koleva et al. 2002). There was carried out two-fold extraction of 200 mg of experimental powder by 96% ethanol. The extract was evaporated in a water bath and the remaining sediment was dissolved in 10 ml of the water-alcohol mixture. 40 µl of 4 mL DPPH solution was added to 0.01 ml of the resulting solution and after incubation for 30 minutes in the dark, its optical density was measured with a spectrophotometer at 515 nm (Spekol 11, Karl Zeiss, Germany).

Proline (PRN): 10 ml of 3% sulfosalicylic acid is mixed with 0.1 g of ground grape seed and filtered. 2 ml of ninhydrin acid and 2 ml of glacial acetic acid were added to the 2 ml of obtained filtrate. After an hour of the water bath, 4 ml of toluene was added to the cooled extract and distributed in a separating funnel. The optical density of the upper fraction was measured by a spectrophotometer at 520 nm (Spekol 11, Karl Zeiss, Germany).

Total proteins: Total protein content was studied according to Lowry (1951). Bovine cattle serum albumin was used as standard (ZEISS, Germany) (Bates, Waldren, and Treare 1973).

Section 1.2 Experimental Procedures for Stage 2

We used pips and skin from the same sorts as in the previous experiments: *Vitis vinifera* var. *Rkatsiteli* (hereafter Rkatsiteli), and *V. vinifera* var. *Saperavi* (herafter Saperavi). We did not analyse *V. labsrusca* in this part since, usually, wineries do not use this grapevine sort. The samples were obtained from Telavi (Ikalto), Gurjaani (Vejini), and Akhmeta (Khodasheni) wineries. We collected the pomace samples in March from kvevris of these wineries, after the wine was transferred into other vessels for storage. Pomace - the pips and skin remained at the bottom of the kvevris and we took samples from this material. This samples was dried, ground into a powder, and used in analytical procedures.

Chemical analyses were conducted pomace samples differing in the following factors: three wineries, two grapevine sorts (red and white), two fractions (pips and skin), and three compounds (antioxidants, soluble phenols, anthocyans), and there were five replicates. All in all we performed 3 * 2 * 2 * 3 * 5 = 180 measurements. .

Soluble phenols in pomace: The chemical analyses were conducted using the same methods as described above in the previous section (Section 1.1) of the Methodology above, in the pharmaceutical firm “Iberia Pharm”.

Soluble phenols in wines: The soluble phenols were measured in the wines from the same kvevris where the pip and skin samples were collected. Therefore, there were samples differing in the following factors: three wineries (Akhmeta, Gurjaani and Telavi), two grapevine sorts (red and white), and two fermentation methods (with pomace - chacha - or without it); there were five replicates, in total 3 * 2 * 2 * 5 = 90 measurements.The samples for the analyses were prepared in the firm “Iberia Pharm” and chemical analyses were performed in Irma Chanturia Wine Laboratory using High Performance Liquid Chromatography (testing method - (OIV) MA-E-AS2-10-INDFOL).

Section 2. Statistical Data Analysis

During the study, a quantitative analysis of the material was carried out. Mean values, standard deviations, Minimal and Maximal values were calculated separately according to the number of samples (Table 2). The differences between the indicators were determined by the ANOVA. The multiple-path analysis (DFA) was used to determine the connection of materials within groups. Mean averages were compared by Tukey retrospective pairwise comparison test, where $\alpha = 0,05$. All analyses were performed with the software package SPSS v.16.0 for Windows (IBM Corp, NY: USA).

Results and Discussion

Chapter 1. Main Findings (Stage 1 Experimental Results)

Tocopherol: The results revealed that the content of tocopherols in unfermented grape seed is higher than in unfermented grape berry skin. This indicator is especially significant in the unfermented seeds of Rkatsiteli. After fermentation, the content of tocopherol is decreased by an average of 25-32 % both in the seeds as well as in the berry skin. However, the amount of tocopherol in the skin of Rkatsiteli berry changed insignificantly (Table 3).

Tocopherol is an antioxidant that is synthesized in plants and cyanobacteria. Its high concentration corresponds to the intensity of various abiotic factors (intense light, salinity, drought, low temperature). The synthesis of tocopherol is an important biochemical process in the evolution of seeds. This is confirmed by the fact that seeds contain it in large quantities, as well as by its synthesis (Gill and Tuteja 2010). It has been established that tocopherol boosts immunity and helps to prevent cancer, cardiovascular diseases, stroke, cataracts, and aging. It is effective in treating diabetes, has a positive effect on the nervous system, wound healing process, protects the lungs from the effects of polluted air. In the human body, tocopherol acts in combination with ascorbic acid. It binds free radicals and inhibits peroxidation processes (Shao et al. 2008). Thus, the presence of tocopherols found in winemaking waste experiments increases their practical importance as a by-product.

Vitamin E is essential for eye health, reproduction, and the health of the blood, brain, and skin. Antioxidant activity is a feature of vitamin E. It protects cells from free radicals, which are molecules released by the body as a result of food processing or tobacco consumption, as well as radiation. Free radicals play a major role in the development of heart disease, cancer and other diseases. Grape seeds, peanuts are rich in vitamin E. It can also be obtained from meat products, green leaves, and dairy products. Vitamin E deficiency causes nerve pain (neuropathy). The recommended dose for adults is 15 mg daily.

Vitamin E is used to treat a variety of diseases. As some studies show, intake of vitamin E slows the advancement of Alzheimer's disease in case of mild to moderate severity. Vitamin E is beneficial in the case of non-alcoholic fatty liver. Its 2 years of continuous consumption has also been linked to insulin resistance. Vitamin E protects a pregnant woman from shifts in blood pressure (Drug.com, n.d.).

Vitamin E is a fat-soluble vitamin that contains four tocopherols. Vitamin E deficiency mainly causes nervous problems as it is a fat-soluble antioxidant that protects the cell membrane and activates reactive oxygen species (Traber and Bruno 2020; Office of Dietary Supplements of US National Institutes of Health 2019). Vitamin E protects the body from oxidative stress.

Vitamin E improves the course of pregnancy in patients who have a thin endometrium. Vitamin E increases the thickness of the endometrium and improves ovarian function (Lédée-Bataille et al. 2002).

Chemoprotective strategies in cases of brain cancer are not well studied. Studies show the chemoprotective effect of vitamin E (Betti et al. 2006). Vitamin E and its products in cancer cells play a critical role in oxidative and non-oxidative functions (Yu, Wang, and Yang 2022).

Anthocyanins: The largest amount of anthocyanins were found in unprocessed Saperavi seeds and their amount exceeded by 2.6–3.7 times as compared to other samples. Fermentation reduced the anthocyanins content in all experimental samples. In the fermented berry skin of both Saperavi and Rkatsiteli, the rate was decreased by 25-27%. Fermentation significantly reduced anthocyanins in Saperavi seeds as well (48 %). However, their content, in this case, was still higher than in all non-fermented samples. (Table 3)

Anthocyanins are substances belonging to the flavonoid group, which are mainly concentrated in vacuoles and have strong antioxidant properties. They have the ability of binding metal ions and actively participate in the acidification process. The accumulation of anthocyanins in the vacuole prevents their direct contact with the sites of the formation of reactive oxygen species. However, it has been found that increased levels of anthocyanins are associated with various types of stress (Badridze et al. 2015). High content of anthocyanins is found in tea, vegetables, cocoa, cereals, etc. These classes of plant substances are often referred to as bioflavonoids to highlight their versatile effects on human health. Anthocyanins, along with other flavonoids, are administered with food. The daily norm ranges between 500-1000 mg. However, if one administers anthocyanins in the form of flavonoid (Grape Seed Extract, Ginkgo Biloba, etc.) dietary supplements (BAA), their amount can even reach several grams.

Common phenols: According to the results, grape seeds contain more phenols than grape berry skins. Moreover, the obtained results of Rkatsiteli and Saperavi seeds reveal similarities. As for the Isabella seeds, the phenol content is slightly lower compared to other beet species. The content of soluble phenols in the Rkatsiteli berry skin is quite high as well compared to Saperavi. Fermentation resulted in a significant reduction of phenols in both seeds and berry skin. The decrease of this indicator was especially obvious in the examined samples of Rkatsiteli (in seeds - by 68%, in grape berry skins - by 77%). The rate has decreased less in the case of Saperavi (in seeds — by 48 %, in grape berry skin — by 49 %). (Table 3)

Phenols are the most active metabolites in plants. In terms of antioxidant effect, they exceed ascorbic acid and even tocopherols (Hernández et al. 2009). Phenols neutralize the action of reactive oxygen types before they damage the cell (Løvdal et al. 2010). Phenols are the most popular group of phytonutrients as they are abundant in plants and foods. Their positive effect on certain aspects of health has been proven many times over (Kroon and Williamson 2005). The fact that scientists are trying to increase the content of phenols in plants, in order to obtain derivatives with improved pharmacological properties, points to their beneficial effect (Dimitrios 2006).

Polyphenols and their metabolites have local beneficial effects on the intestine, regardless of whether they are absorbed or not. (Choy et al. 2014) 95% of grape tannins pass through the large intestine without being absorbed. (Clifford 2004) The presence of phenolic compounds in the intestinal lumen and stimulation of the intestine increases the ability to present microbial metabolites that may be considered beneficial (Krautkramer, Fan, and Bäckhed 2021).

Broad-spectrum antibiotics can affect not only pathogenic but also commensal bacteria, although penicillins (e.g. amoxicillin) appear to have very little effect on the microbiota in general (Ianiro, Tilg, and Gasbarrini 2016). In addition to host bacterial-pathogen interactions, food composition (protein and carbohydrate content), as well as naturally originated compounds such as polyphenols, play a significant role in intestinal microbiota during eubiosis (Lee et al. 2006).

Proline: The content of the amino acid proline in the unfermented samples of Saperavi and Rkatsiteli was practically the same. In the studied samples, except for Saperavi, fermentation caused the reduction of their number. In the Rkatsiteli berry skin, it decreased by 74%, while in seeds by - 60%; For Isabella seeds, the reduction was 63%; As for Saperavi, the level of proline in the berry skins decreased relatively slightly (36%), while in the seeds it remained practically unchanged (Table 3).

Proline (its symbol is **Pro** or **P**) is an organic acid that is classified as a proteinogenic amino acid. The human body can synthesize it from the essential amino acid L-glutamate. Proline was first separated in 1900 by Richard Wilstater and in 1901 Emile Fisher separated Proline from casein (Plimmer 1908). The name proline is derived from pyrrolidine, which is one of its constituents (American Heritage Dictionary of the English Language, n.d.).

In addition to participating in the structuring of proteins, proline is one of the most widely used competing substances that accumulate in plants and bacteria under unfavourable conditions (low temperature, drought, salinity, etc.) (Kuznetsov and Shevyakova 1999; Anjum, Rishi, and Ahmad 2000). Moreover, proline is likely involved in flourishing and development as a metabolite and signalling molecule. Proline is involved in the formation of cartilage and collagen. It maintains the flexibility of muscles and joints and reduces skin laxity and wrinkling caused by UV radiation or aging. Hence, proline supplements may be beneficial for osteoarthritis, chronic back pain, and persistent soft tissue distention. Proline is derived from glutamic acid, and deficiencies are rare in healthy people who eat healthy foods. However, taking this amino acid additive as a supplement may be necessary for people recovering from various injuries, especially those with such skin damage as severe burns. People with collagen formation problems or pain from underdeveloped cartilage may also benefit from adding proline to their diet. Proline can be added to supplements used to prevent cardiovascular disease, along with vitamin C. The recommended therapeutic daily dose is 500 to 1000 mg, in combination with vitamin C. The presence of proline and other antioxidants in fermented wine waste increases the recycling value of this by-product.

Soluble carbohydrates: Among the studied grape varieties, the highest content of soluble carbohydrates was observed in unfermented Saperavi seed. Since soluble carbohydrates are the main substrate for alcoholic fermentation, a significant reduction of their concentration in fermented seed was expected (In Saperavi seeds it was reduced 4.4 times compared to non-fermented samples, while in other samples 2-2.5 times). Although only a small amount of soluble carbohydrates was found in the fermented samples, it should be noted that the carbohydrate content in the fermented Isabella seeds remained the same. (Table 3)

According to biochemical, molecular and genetic experiments, soluble carbohydrates play an important role in the regulation of plant metabolism and growth, as well as in development. The accumulation of carbohydrates under stress is increased in different parts of the plant. Soluble carbohydrates play a stress-protective role (Kolupaev and Karpets 2010). Carbohydrates have been shown to reveal a multifunctional, protective, and regulatory effect under stress, meaning both osmoprotective and antioxidant impacts on proteins and other macromolecules. The importance of carbohydrates is manifested not only in their participation in the synthesis of other substances but also in the function of membrane stabilization. They are also regulators of gene expression and signalling molecules (Pego et al. 2000).

Total proteins: High content of total proteins was detected in the unfermented seeds and grape berry skins of the studied varieties. However, in terms of this indicator, the seed is slightly behind the grape berry skin. A significant reduction of proteins was observed in fermented samples of Rkatsiteli (in berry skin - by 72.5%, in seeds – by 80%). This indicator decreased relatively less in the experimental samples of Saperavi (by 38-39%) and Isabella (by 20%). As a result, the protein content of Saperavi fermented seed and skin was higher than in Rkatsiteli. (Table 3) Because of its ability to inhibit lipid oxidation, proteins can become an excellent antioxidant dietary supplement. Recently, by enzymatic hydrolysis of various dietary proteins (such as wheat gluten, soy protein, gelatin, casein, and whey protein), the antioxidant activity of bioactive peptides has been demonstrated (Elias, Kellerby, and Decker 2008).

Retaining significant amounts of protein in the tested wine waste (especially red varieties) is another factor in the processing of this waste for further use.

TABLE 3 CHEMICAL COMPOSITION OF THE GRAPE SEED AND BERRY SKIN EXTRACTS OF THREE GRAPE VARIETIES "RKATSITELI", "SAPERAVI" AND "ISABELLA"

(Data are in milligrams)

Specifications	Data	TPH	ANC	PRN	PRT	PHS	CBH	ANO
RNBS	Mean	3,5767	2,4233	4,3767	131,4533	362,0333	7,4667	21,69
	Mean deviation	0,1079	0,353	0,1079	1,2307	10,2627	0,2517	0,3568
	Minimal	3,5	2,1	4,3	130,2	350,2	7,2	21,3
	Maximal	3,7	2,8	4,5	132,66	368,5	7,7	22,0
RWBS	Mean	3,26	1,74	1,2	36,5767	83,5667	3,0	12,45
	Mean deviation	0,2425	0,2506	0,1	0,402	1,1015	0,1	0,1609
	Minimal	3,0	1,5	1,1	36,2	82,5	2,9	12,27
	Maximal	3,48	2,0	1,3	37,0	84,7	3,1	12,58
RNGS	Mean	9,33	2,89	4,3933	99,47	567,4333	3,5033	83,3067
	Mean deviation	0,1539	0,3568	0,3523	0,3559	0,5859	0,395	0,1901
	Minimal	9,2	2,5	4,0	99,1	567	3,11	83,12
	Maximal	9,5	3,2	4,68	99,81	568,1	3,9	83,5
RWGS	Mean	6,27	2,8	1,5533	19,3567	181,1167	1,7067	24,5333
	Mean deviation	0,2524	0,3	0,0503	0,2228	0,852	0,1901	0,1155
	Minimal	6,0	2,5	1,5	19,1	180,3	1,52	24,4
	Maximal	6,5	3,1	1,6	19,5	182	1,9	24,6
SNBS	Mean	4,8967	3,7567	3,4667	124,9	135,1	2,31	91,1333
	Mean deviation	0,1762	0,2836	0,2309	0,3606	0,3606	0,2007	0,162
	Minimal	4,7	3,43	3,2	124,5	134,8	2,1	91,03
	Maximal	5,04	3,94	3,6	125,2	135,5	2,5	91,32
SWBS	Mean	3,6867	2,4033	2,0367	77,1833	68,4233	1,35	39,6733
	Mean deviation	0,1026	0,1818	0,0513	0,0981	1,157	0,15	0,0252
	Minimal	3,6	2,2	1,98	77,07	67,2	1,2	39,65
	Maximal	3,8	2,55	2,08	77,24	69,5	1,5	39,7
SNGS	Mean	7,43	8,64	4,4433	89,4167	551,31	11,6333	91,3333
	Mean deviation	0,3897	0,3816	0,1401	0,1041	0,5986	0,1528	0,1528
	Minimal	7,0	8,2	4,33	89,3	550,93	11,5	91,2
	Maximal	7,76	8,88	4,6	89,5	552,0	11,8	91,5
SWGS	Mean	5,3333	4,8033	4,2333	54,5533	282,95	2,7667	80,0233
	Mean deviation	0,3512	0,2608	0,1155	0,3281	1,0476	0,2887	0,0681
	Minimal	5,0	4,61	4,1	54,33	281,8	2,6	79,97
	Maximal	5,7	5,1	4,3	54,93	283,85	3,1	80,1
INGS	Mean	4,6067	2,72	2,6167	82,5667	451,31	4,9	44,05
	Mean deviation	0,1901	0,0854	0,1041	0,3512	0,5986	0,3606	0,4822
	Minimal	4,42	2,63	2,5	82,2	450,93	4,6	43,7
	Maximal	4,8	2,8	2,7	82,9	452	5,3	44,6
IWGS	Mean	3,1333	-	1,2133	65,5667	-	4,35	43,7333
	Mean deviation	0,1528	-	0,2203	0,3055	-	0,1803	0,4726
	Minimal	3	-	1	65,3	-	4,2	43,2
	Maximal	3,3	-	1,44	65,9	-	4,55	44,1

Abbreviations: RNBS: Natural Rkatsiteli berry skin; RWBS: Rkatsiteli berry skin while producing wine; RNGS: Natural Rkatsiteli seeds; RWGS: Rkatsiteli seeds while producing wine; SNBS: Natural Saperavi berry skin; SWBS: Saperavi berry skin while producing wine; SNGS: Natural Saperavi seeds; SWGS: Saperavi seeds while producing wine; INGS: Natural Isabella seeds; TPH: Tocopherol; ANC: Anthocyanins; PRT: Proteins; PHS: Phenols; CBH: Carbohydrates; PRN: Proline; ANO: Antioxidant action.

Total antioxidant action: Based on the results of the experiment, we can conclude that Saperavi and Rkatsiteli unfermented seeds and unfermented Saperavi berry skins are characterized by high antioxidant activity (Table 4).

Fermentation significantly reduced this indicator in the experimental samples. In particular, the antioxidant effect of Rkatsiteli berry skin, which was not high even in non-fermented samples, was reduced 1.7 times after fermentation, while in the case of seeds it was reduced 3.4 times. The antioxidant activity of Saperavi skin was reduced by 2.3 times after fermentation, while in seeds this index was slightly reduced (1.1 times). As for Isabella seeds, fermentation did not affect its antioxidant action (Table 4). The total antioxidant activity is a significant integral indicator that considers data on the total antioxidant activity of the test material without specifying the class of the substance. Several publications have shown the relationship between the content of hydrophilic antioxidants and overall antioxidant activity (Wu et al. 2004).

TABLE 4 ANTIOXIDANT ACTIVITY OF THE GRAPE SEED AND BERRY SKIN EXTRACTS OF THREE GRAPE VARIETIES "RKATSITELI", "SAPERAVI" AND "ISABELLA"

(Studied by ANOVA)

Material		Sum of squares	do	Mean square	F	Sig
TPH	Among groups	109.722	9	12.191	228.259	0.0001
	Within groups	1.068	20	0.053		
	Total	110.790	29			
ANC	Among groups	139.701	9	15.522	210.007	0.0001
	Within groups	1.478	20	0.074		
	Total	141.179	29			
PRN	Among groups	51.711	9	5.746	193.717	0.0001
	Within groups	0.593	20	0.030		
	Total	52.304	29			
PRT	Among groups	34586.443	9	3842.938	16503.777	0.0001
	Within groups	4.657	20	0.233		
	Total	34591.100	29			
PHS	Among groups	1150421.327	9	127824.592	11527.301	0.0001
	Within groups	221.777	20	11.089		
	Total	1150643.104	29			
CBH	Among groups	264.695	9	29.411	492.255	0.0001
	Within groups	1.195	20	0.060		
	Total	265.890	29			
ANO	Among groups	25051.567	9	2783.507	39021.132	0.0001
	Within groups	1.427	20	0.071		
	Total	25052.994	29			

Based on the data obtained, it can be assumed that the total antioxidant activity of the studied samples is mainly due to the content of hydrophilic anthocyanins and total phenols.

The total antioxidant properties are so unevenly distributed among the samples of the three grape varieties that, among the 13 tested samples, 10 groups with significantly different total antioxidant effects can be distinguished (Diagram 1). In general, fermentation reduces the content of antioxidants (for example, as in the Saperavi seeds and berry skin, as well as in the Rkatsiteli berry skin). In addition, fermentation can increase the antioxidant effect in the Isabella seed and berry skin, and even more in the Rkatsiteli berry skin. In general, the red varieties (Isabella, Saperavi) turned out to be somehow richer in tocopherols than the white varieties of Rkatsiteli. Finally, the lowest levels of total antioxidant activity were found in mixed residues after distillation of alcohol (black column in Diagram 1).

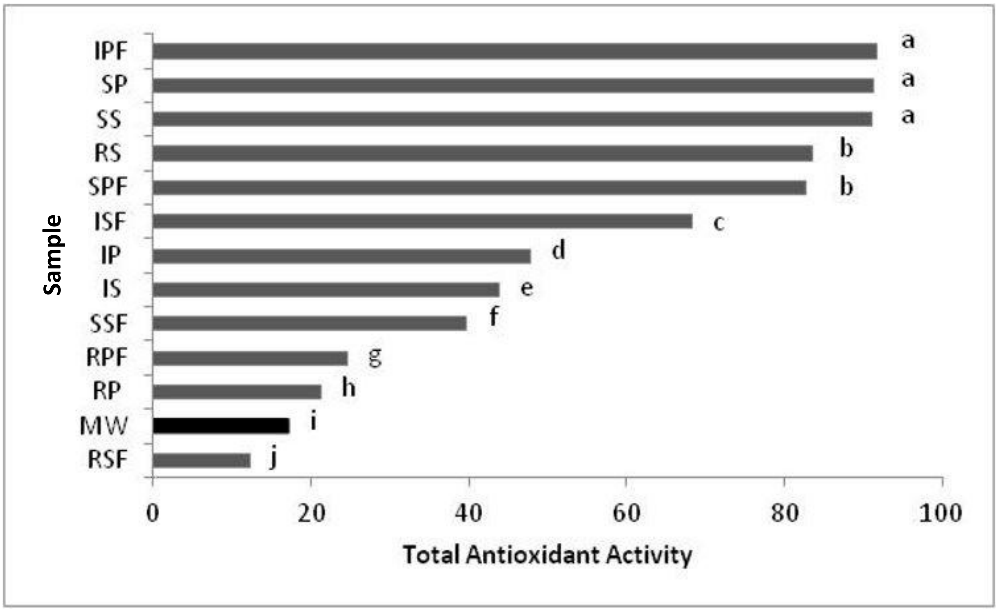

DIAGRAM 1 TOTAL ANTIOXIDANT ACTIVITY IN SAMPLES OF VARIOUS GRAPE VARIETIES.

IP: Isabella seeds (Unprocessed), IPF: Isabella Fermented seeds; IS: Isabella berry skin (Unprocessed); ISF: Isabella berry fermented skin; MW: Mixed waste (Distilled); RP: Rkatsiteli seeds (Unprocessed); RPF: Rkatsiteli fermented seeds; RS: Rkatsiteli berry skin (Unprocessed); RSF: Rkatsiteli berry fermented skin; SP: Saperavi seeds (Unprocessed); SPF: Saperavi fermented seeds; SS: Saperavi berry skin SSF: Saperavi berry fermented skin. The letters to the right indicate homogeneous groups (Tukey retrospective pairwise comparison test, where α = 0,05).

Tocopherols were also unevenly distributed among the studied grape samples, and nine groups were identified with significantly different levels of tocopherol content (Diagram 2). The highest tocopherol content was found in the fermented Rkatsiteli seeds, followed by the unfermented Saperavi berry skin. Fermentation can increase (for example, as in the case of Isabella and Rkatsiteli berry skin) as well as decrease (for example, Rkatsiteli seeds) the tocopherol content in samples. Red and white varieties do not differ significantly in tocopherol content. Interestingly, the distillation of alcohol reduced, albeit slightly, the tocopherol content in the mixed sample (black column on Diagram 2).

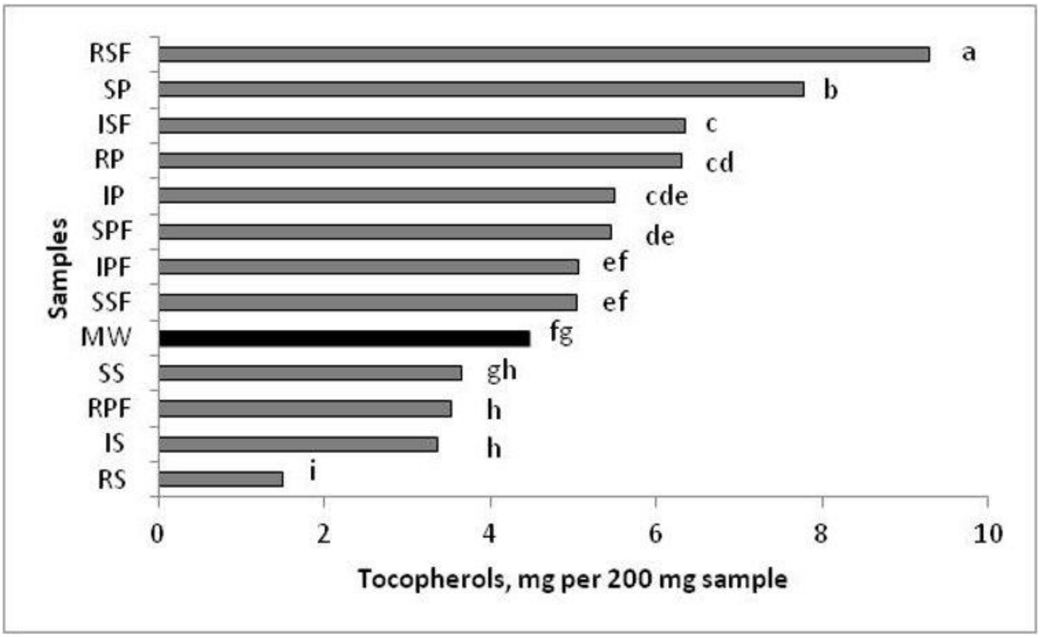

DIAGRAM 2 TOTAL TOCOPHEROL ACTIVITY IN SAMPLES OF VARIOUS GRAPE VARIETIES.

IP: Isabella seeds (Unprocessed), IPF: Isabella fermented seeds; IS: Isabella berry skin (Unprocessed); ISF: Isabella fermented berry skin; MW: Mixed waste (distilled); RP: Rkatsiteli seeds (Unprocessed); RPF: Rkatsiteli fermented seeds; RS: Rkatsiteli berry skin (Unprocessed); RSF: Rkatsiteli fermented berry skin; SP: Saperavi seeds (Unprocessed); SPF: Saperavi fermented seeds; SS: Saperavi berry skin; SSF: Saperavi berry fermented skin;. The letters to the right indicate homogeneous groups (Tukey retrospective pairwise comparison test, where α = 0,05).

The results show that wine production waste can be a valuable source of such active ingredients as tocopherols and antioxidants.

Tocopherols are a class of lipophilic methylated phenols with vitamin E activity. The main source of these substances is vegetable oil. Although Georgia has a good resource base for the industrial production of tocopherol, it is not produced in the country. On the other hand, wine waste can be a very cheap raw material for the commercial production of tocopherols, which can be used for many purposes. Recent studies have shown that tocopherols may act as chemical protection against hepatotoxicity (Al-Jammas and Al-Saraj 2020; Ibrahim et al. 2020). Tocopherols can be used as a topical anti-inflammatory agent against skin infections (Praça et al. 2020). Tocopherol can significantly reduce the risk of heart attack (Han et al. 2020). The evidence shows that they may have anti-tumour effects (Constantinou, Charalambous, and Kanakis 2020). In general, tocopherols have an antioxidant and anti-inflammatory effect, which allows these substances to protect cells from oxidative stress (Casati et al. 2020). Research results confirm that grape pomace contains measurable amounts of tocopherols. Manufacturers and businesses can use this resource to produce valuable tocopherol-containing products used in medicine and cosmetics.

Grape seeds have a strong antioxidant effect, while grape pomace is rich in antioxidants (Goloshvili, Akhalkatsi, and Badridze 2018). The results of the present study are consistent with these data, but the antioxidant effect was also found to be significantly reduced after alcohol distillation. However, experiments have shown that grape pomace, despite the distillation of alcohol, still has a sufficient antioxidant effect that can be used in pharmaceutical production. These products are widely used in medicine, pills, ointments, etc. Grape seed extracts have antioxidant properties and may have a hepatoprotective effect (Abu-Serie and Habashy 2020), as well as a protective effect against oxidative stress (Hasona and Morsi 2019). There is evidence that grape seed oil is a good remedy for colitis in patients with colorectal colitis (Chartier, Howarth, and Mashtoub 2019). It is also used as an anti-inflammatory and antioxidant agent in case of kidney failure (Boozari and Hosseinzadeh 2017). The research findings confirm that grape pomace contains significant amounts of antioxidants, and this resource can be used by manufacturers for producing a valuable pharmaceutical product with antioxidant effects.

Oxidative stress is one of the signs of diabetes, hypercalcemia increases ROS production from glucose-induced oxidation and produces mitochondrial superoxide (Qin et al. 2012).

Systemic research confirms that antioxidant supplementation improves sperm parameters. In addition, it provides indications for antioxidant treatment in specific clinical conditions, including varicocele, unexplained, and idiopathic infertility, and cases of sperm quality changes have also been studied (Agarwal et al. 2021).

Infertility in men is always a difficult problem. Its pathophysiology and possible treatments are poorly represented. Numerous studies have shown positive results in changing sperm parameters (Cardoso, Cocuzza, and Elterman 2019).

Chapter 2. Comparison of Main Finding with Data Available in the Literature

We compared data available from the literature on the levels of several bioactive compounds of our interest. Not all combinations of factors that we researched could be found. For example, not all compounds that we studied were reported and we were able to collect sufficient data from the published papers only for three classes of substance: antioxidants, soluble phenols, and anthocyans. Literature on the content of these three compounds in red grapevine pomace are summarized in the Table 5, 6, 7 below.

TABLE 5 REPORTED ANTIOXIDANT CONTENT (%) IN RED GRAPEVINE POMACE

Grapevine sort	Fraction	Antioxidant, %	Reference	Country
Saperavi	Natural seeds	*91.3333	Goloshvili, Akhalkatsi, and Badridze 2018	Georgia
Red Globe	Natural seeds	89.191	Özcan et al. 2017	Türkiye
Çınarlı karası	Natural seeds	86.88	Özcan et al. 2017	Türkiye
Çavuş Vitis vinifera	Natural seeds	90.096	Özcan et al. 2017	Türkiye
Kalecik karası	Natural seeds	90.469	Özcan et al. 2017	Türkiye
Yapıncak	Natural seeds	87.966	Özcan et al. 2017	Türkiye
Yalova incisi	Natural seeds	90.841	Özcan et al. 2017	Türkiye
Trakya ilkeren	Natural seeds	90.974	Özcan et al. 2017	Türkiye
Saperavi	Fermented seeds	*43.7333	Goloshvili, Akhalkatsi, and Badridze 2018	Georgia
Pinot Noir	Fermented seeds	0.16925	Rockenbach et al. 2011	Brazil
Isabel	Fermented seeds	2.694	Rockenbach et al. 2011	Brazil
Sangiovese	Fermented seeds	8.144	Rockenbach et al. 2011	Brazil
Negro Amaro	Fermented seeds	7.265	Rockenbach et al. 2011	Brazil
Cabernet Sauvignon	Fermented seeds	8.281	Rockenbach et al. 2011	Brazil

Primitivo	Fermented seeds	7.795	Rockenbach et al. 2011	Brazil
Average pomace	Fermented seeds	8.517	Rockenbach et al. 2011	Brazil
Saperavi	Natural skin	*91.1333	Goloshvili, Akhalkatsi, and Badridze 2018	Georgia
Red Globe	Natural skin	90.948	Özcan et al. 2017	Türkiye
Çınarlı karası	Natural skin	82.588	Özcan et al. 2017	Türkiye
Çavuş	Natural skin	88.392	Özcan et al. 2017	Türkiye
Kalecik karası	Natural skin	79.925	Özcan et al. 2017	Türkiye
Yapıncak	Natural skin	80.085	Özcan et al. 2017	Türkiye
Yalova incisi	Natural skin	30.298	Özcan et al. 2017	Türkiye
Trakya ilkeren	Natural skin	90.735	Özcan et al. 2017	Türkiye
Saperavi	Fermented skin	*39.6733	Goloshvili, Akhalkatsi, and Badridze 2018	Georgia
Sangiovese	Fermented skin	1.466	Rockenbach et al. 2011	Brazil
Negro Amaro	Fermented skin	1.3055	Rockenbach et al. 2011	Brazil
Cabernet Sauvignon	Fermented skin	2.032	Rockenbach et al. 2011	Brazil
Primitivo skin	Fermented skin	2.897	Rockenbach et al. 2011	Brazil
Pinot Noir skin	Fermented skin	1.113	Rockenbach et al. 2011	Brazil
Average pomace	Fermented skin	2.076	Rockenbach et al. 2011	Brazil

*Reference for One-sample t-test within the given fraction.

TABLE 6 REPORTED ANTIOXIDANT CONTENT (%) IN RED GRAPEVINE POMACE

Fraction	Grapevine sort	Antocyans, mg/g	Reference	Country
Natural seeds	Saperavi	*8.64	Goloshvili et al. 2021	Georgia
Natural seeds	Shiraz Thailand	5.06	Butkhup et al. 2010	Slovenia
Natural skin	Saperavi	*3.7567	Goloshvili, Akhalkatsi, and Badridze 2018	Georgia
Natural skin	Pusa Navrang	4.9	Doshi et al. 2015)	India
Natural skin	Merlot	1	Doshi et al. 2015	India
Fermented skin	Saperavi	*2.4033	Goloshvili, Akhalkatsi, and Badridze 2018	Georgia
Fermented skin	Pinot Noir	3.8593	Rockenbach et al. 2011	Brazil
Fermented skin	Isabel	4.5652	Rockenbach et al. 2011	Brazil
Fermented skin	Sangiovese	3.0157	Rockenbach et al. 2011	Brazil
Fermented skin	Negro Amaro	2.8946	Rockenbach et al. 2011	Brazil
Fermented skin	Cabernet Sauvignon	9.3467	Rockenbach et al. 2011	Brazil
Fermented skin	Primitivo	8.3292	Rockenbach et al. 2011	Brazil

*Reference for One-sample t-test within the given fraction.

TABLE 7 REPORTED SOLUBLE PHENOLS (MG PER GRAM) IN RED GRAPEVINE POMACE

Fraction	Grapewine sort	Phenols mg/g	Colour	Authors	Country
Natural seeds	Saperavi	551.31	Red	Goloshvili et al. 2021	Georgia
Natural seeds	Red Globe	4.73125	Red	Özcan et al. 2017	Türkiye
Natural seeds	Çınarlı karası	4.87813	Red	Özcan et al. 2017	Türkiye
Natural seeds	Çavuş	4.90625	Red	Özcan et al. 2017	Türkiye
Natural seeds	Kalecik karası	4.21563	Red	Özcan et al. 2017	Türkiye
Natural seeds	Yapıncak	4.29688	Red	Özcan et al. 2017	Türkiye
Natural seeds	Yalova incisi	4.32813	Red	Özcan et al. 2017	Türkiye
Natural seeds	Trakya ilkeren	4.44063	Red	Özcan et al. 2017	Türkiye
Natural seeds	Pusa Navrang	65.8	Red	Doshi et al. 2015	India
Natural seeds	Merlot	41.7	Red	Doshi et al. 2015	India
Natural seeds	Shiraz, Thailand	0.2932	Red	Doshi et al. 2015	India
Natural seeds	Pusa Navrang	65.8	Red	Doshi et al. 2015	India
Natural seeds	Merlot	41.7	Red	Doshi et al. 2015	India
Natural seeds	Nero d'Avola	85.92	Red	Lucarini et al. 2020	Italy
Natural seeds	Cesanese d' Affile	57.8	Red	Lucarini et al. 2020	Italy
Fermented seeds	Saperavi	*282.95	Red	Goloshvili, Akhalkatsi, and Badridze 2018	Georgia
Fermented seeds	Pinot Noir	0.16518	Red	Rockenbach et al. 2011	Brazil
Fermented seeds	Isabel	21.28	Red	Rockenbach et al. 2011	Brazil
Fermented seeds	Sangiovese	76.82	Red	Rockenbach et al. 2011	Brazil
Fermented seeds	Negro Amaro	72.37	Red	Rockenbach et al. 2011	Brazil
Fermented seeds	Cabernet Sauvignon	82.49	Red	Rockenbach et al. 2011	Brazil
Fermented seeds	Primitivo	89.63	Red	Rockenbach et al. 2011	Brazil
Fermented seeds	Average pomace	84.63	Red	Rockenbach et al. 2011	Brazil
Fermented seeds	Barbera	20	Red	(Guaita and Bosso 2019)	Italy
Fermented seeds	Grignolino	37.5	Red	Guaita and Bosso 2019	Italy
Fermented seeds	Cabernet sauvignon	11.3	Red	Guaita and Bosso 2019	Italy
Fermented seeds	Nebbiolo	25.1	Red	Guaita and Bosso 2019	Italy
Fermented seeds	Barbera	24.5	Red	Guaita and Bosso 2019	Italy
Fermented seeds	Grignolino	47.6	Red	Guaita and Bosso 2019	Italy
Fermented seeds	Nebbiolo	44.5	Red	Guaita and Bosso 2019	Italy
Fermented seeds	Uvalino	60.1	Red	Guaita and Bosso 2019	Italy
Fermented seeds	Barbera	20.1	Red	Guaita and Bosso 2019	Italy
Fermented seeds	Grignolino 2	37.5	Red	Guaita and Bosso 2019	Italy
Fermented seeds	Nebbiolo 2	25.1	Red	Guaita and Bosso 2019	Italy
Fermented seeds	Uvalino 2	22.8	Red	Guaita and Bosso 2019	Italy
Natural skin	Saperavi	*135.1	Red	Goloshvili, Akhalkatsi, and Badridze 2018	Georgia

Natural skin	Red Globe	1.70313	Red	Özcan et al. 2017	Türkiye
Natural skin	Çınarlı karası	1.27813	Red	Özcan et al. 2017	Türkiye
Natural skin	Çavuş	1.46641	Red	Özcan et al. 2017	Türkiye
Natural skin	Kalecik karası	1.19531	Red	Özcan et al. 2017	Türkiye
Natural skin	Yapıncak	1.21016	Red	Özcan et al. 2017	Türkiye
Natural skin	Yalova incisi	0.44063	Red	Özcan et al. 2017	Türkiye
Natural skin	Trakya ilkeren	1.99063	Red	Özcan et al. 2017	Türkiye
Natural skin	Pusa Navrang	12.5	Red	Özcan et al. 2017	Türkiye
Natural skin	Merlot	6.1	Red	Özcan et al. 2017	Türkiye
Fermented skin	Saperavi	*68.4233	Red	Goloshvili, Akhalkatsi, and Badridze 2018	Georgia
Fermented skin	Pinot Noir	6.6	Red	Rockenbach et al. 2011	Brazil
Fermented skin	Isabel skin	18.39	Red	Rockenbach et al. 2011	Brazil
Fermented skin	Sangiovese	7.5	Red	Rockenbach et al. 2011	Brazil
Fermented skin	Negro Amaro	6.86	Red	Rockenbach et al. 2011	Brazil
Fermented skin	Cabernet Sauvignon	10.65	Red	Rockenbach et al. 2011	Brazil
Fermented skin	Primitivo	13.28	Red	Rockenbach et al. 2011	Brazil
Fermented skin	Average pomace	10.55	Red	Rockenbach et al. 2011	Brazil
Fermented skin	Cabernet sauvignon 2	0.71	Red	Rockenbach et al. 2011	Brazil

*Reference for One-sample t-test within the given fraction.

Even in these cases, not all factors were present: for example, antioxidants and anthocyans were reported only for red sorts of grapevine. In some cases data were available only for pips, on others only for skin. All in all, we analysed 94 data extracted from 13 references (see Tables 4-6). We used one-sample I-test for comparisons, where the sample was represented by data reported in references, and the given mean was the value obtained by us in our samples. The level of significance was α=0.05.

Antioxidants were analysed only in the red sorts of grapevine and compared to our Saperavi. As it appeared, the contents of antioxidants in natural pips were slightly higher in Saperavi (Figure 4, the difference was statistically significant). In fermented pips we see a very sharp drop in the content of antioxidants reported in references, while it dropped but not so strongly in our samples of Saperavi (Figure 5). As a result, fermented pips of Saperavi contained much higher antioxidants, than the red grapevines reported in the references. A very similar pattern was found for the natural versus fermented skin (Figures 9 and 10): there was a dramatic reduction of antioxidants in reference data, while the drop was milder in Saperavi resulting in a strong difference between our grapevine and the reported samples. The dramatic drop in antioxidant content in reported data probably was caused by the same process that we found in the samples from the industrial wineries (see the previous section): the storage conditions can strongly reduce the antioxidants in pips and skin after fermentation, while we chemically analysed our samples very soon after the fermentation.

Soluble phenols appeared to be considerably higher in Saperavi samples as compared to the levels reported in the references in all fractions (Figures 8-12). Similar results were obtained in the case of white grapevine pips (Rkatsiteli versus the reference data, Figures 12-13). The observed difference is not easy to explain. In part, it can reflect the high variability of reference data (Coefficient of Variation was 60 to 110% in reported data). In part, the cause might be the different methods used. Finally, it is also possible that, in fact, our grapevines are richer in phenols. In any case, soluble phenols require further study.

Anthocyans could be compared only in three cases: natural pips, natural skin and fermented skin between Saperavi and reported red sorts of grapevine (Figures 14-16). We could not detect any difference in the levels of anthocyans between our and reference data.

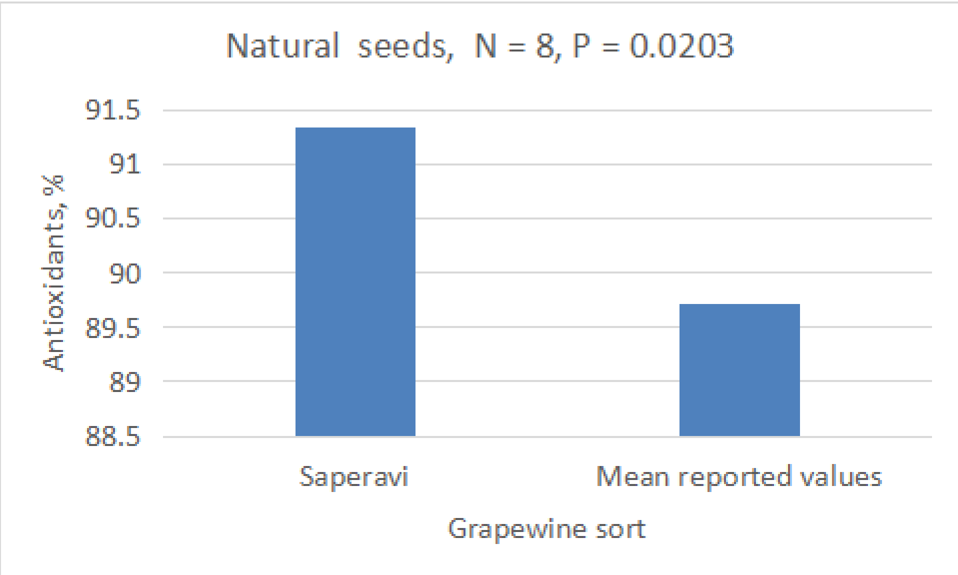

FIGURE 4 COMPARISON OF ANTIOXIDANT CONTENT IN NATURAL PIPS BETWEEN SAPERAVI AND REPORTED IN REFERENCES.
The left bar shows the mean obtained for our sort of grapevine, and the right bar shows the mean value calculated from the data reported in references (Mean reported values). Sample size *N* and the *P*-value are reported in the figure title.

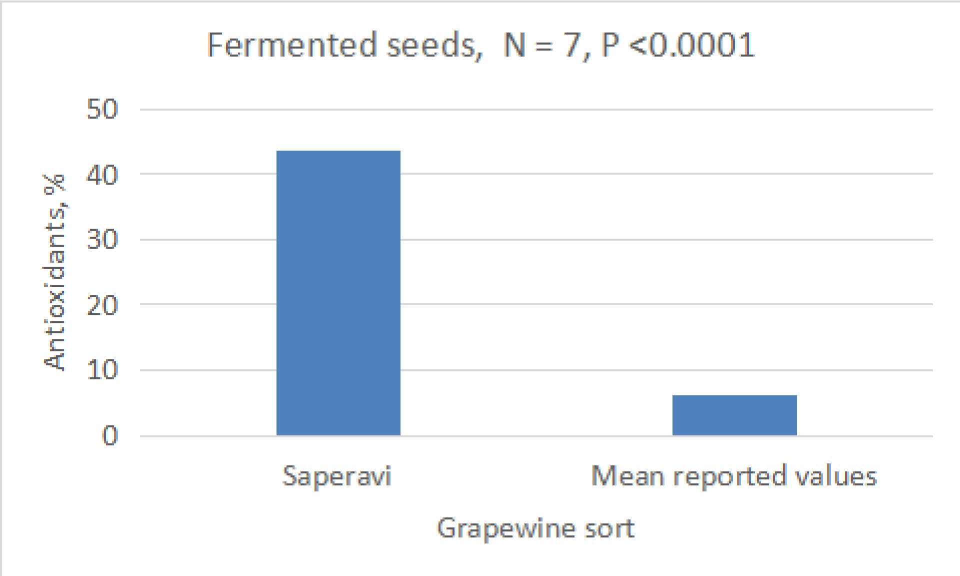

Figure 5 Comparison of Antioxidant Content in Fermented Pips Between Saperavi and Reported in References.
The left bar shows the mean obtained for our sort of grapevine, and the right bar shows the mean value calculated from the data reported in references (Mean reported values). Sample size N and the P-value are reported in the figure title.

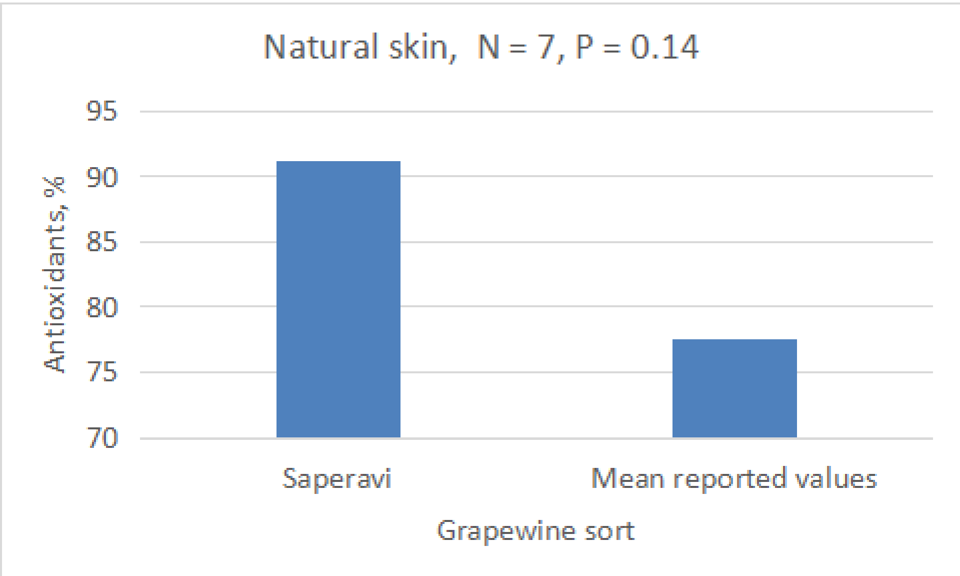

Figure 6 Comparison of Antioxidant Content in Natural Skin Between Saperavi and Reported in References.
The left bar shows the mean obtained for our sort of grapevine, and the right bar shows the mean value calculated from the data reported in references (Mean reported values). Sample size N and the P-value are reported in the figure title.

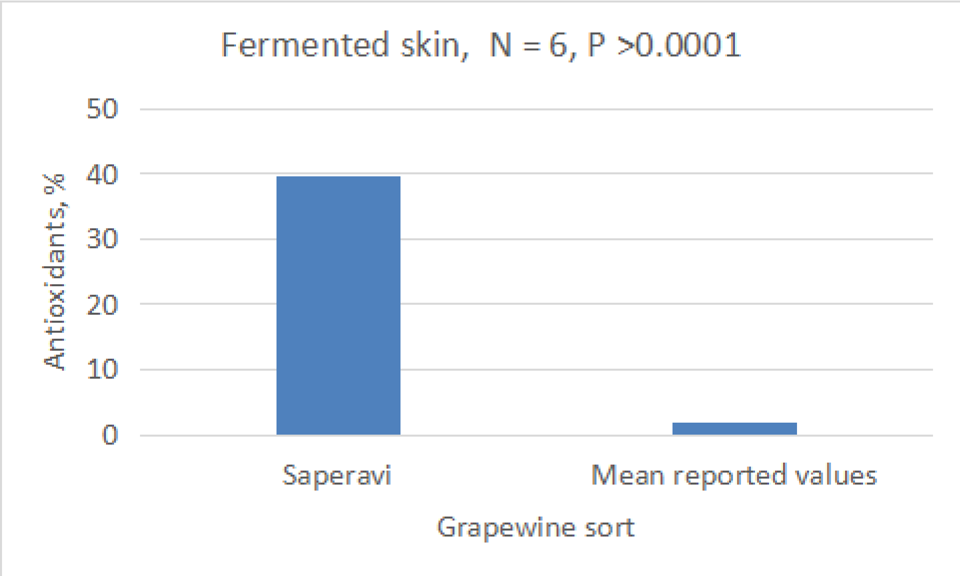

FIGURE 7 COMPARISON OF ANTIOXIDANT CONTENT IN FERMENTED SKIN BETWEEN SAPERAVI AND REPORTED IN REFERENCES.

The left bar shows the mean obtained for our sort of grapevine, and the right bar shows the mean value calculated from the data reported in references (Mean reported values). Sample size *N* and the *P*-value are reported in the figure title.

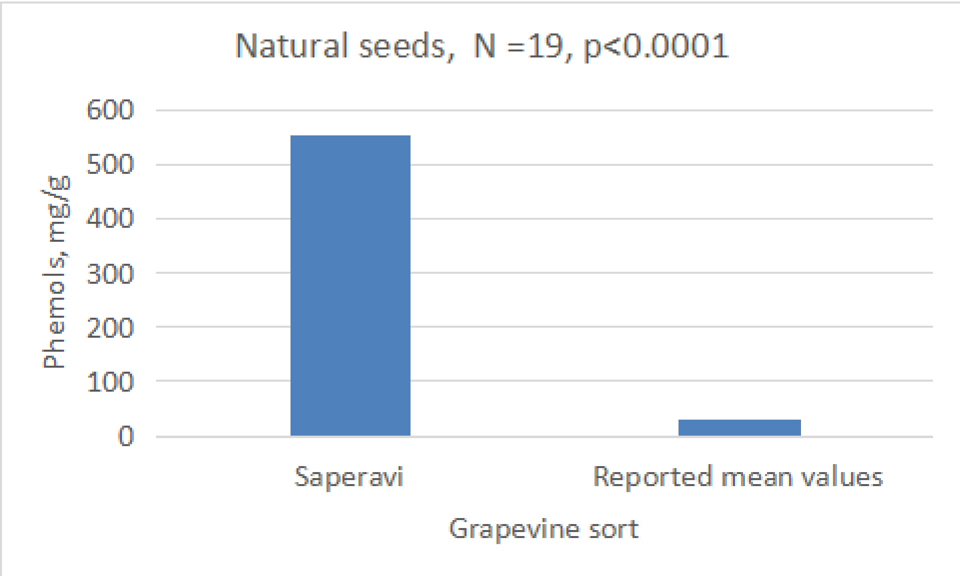

FIGURE 8 COMPARISON OF SOLUBLE PHENOL CONTENT IN NATURAL PIPS BETWEEN SAPERAVI AND REPORTED IN REFERENCES.

The left bar shows the mean obtained for our sort of grapevine, and the right bar shows the mean value calculated from the data reported in references (Mean reported values). Sample size *N* and the *P*-value are reported in the figure title.

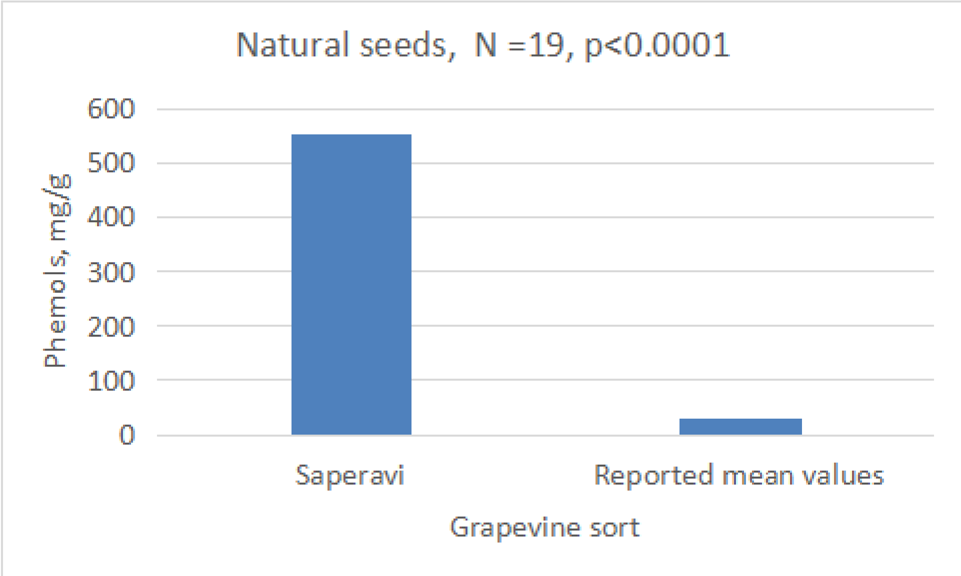

FIGURE 9 COMPARISON OF SOLUBLE PHENOL CONTENT IN FERMENTED PIPS BETWEEN SAPERAVI AND REPORTED IN REFERENCES.

The left bar shows the mean obtained for our sort of grapevine, and the right bar shows the mean value calculated from the data reported in references (Mean reported values). Sample size *N* and the *P*-value are reported in the figure title.

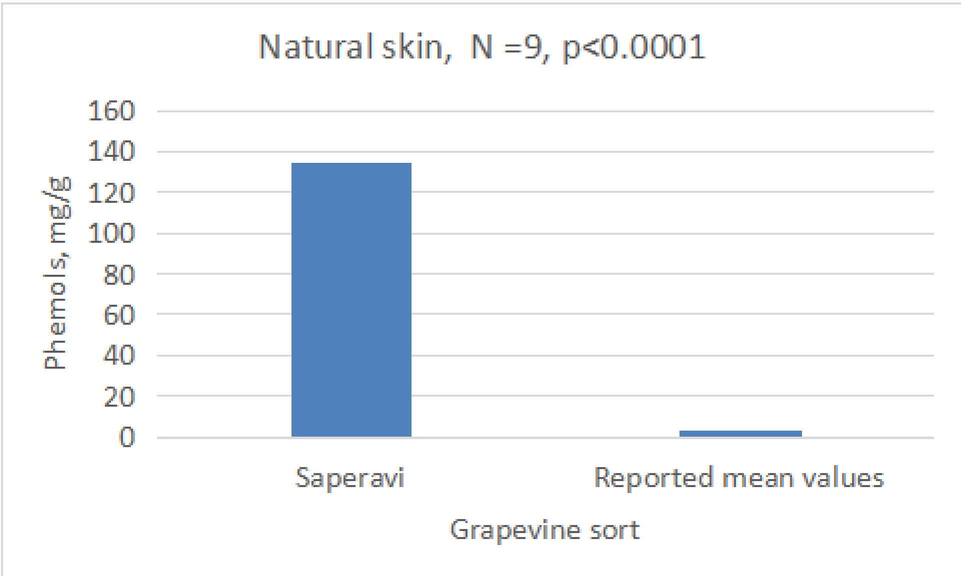

FIGURE 10 COMPARISON OF SOLUBLE PHENOL CONTENT IN NATURAL SKIN BETWEEN SAPERAVI AND REPORTED IN REFERENCES.

The left bar shows the mean obtained for our sort of grapevine, and the right bar shows the mean value calculated from the data reported in references (Mean reported values). Sample size *N* and the *P*-value are reported in the figure title.

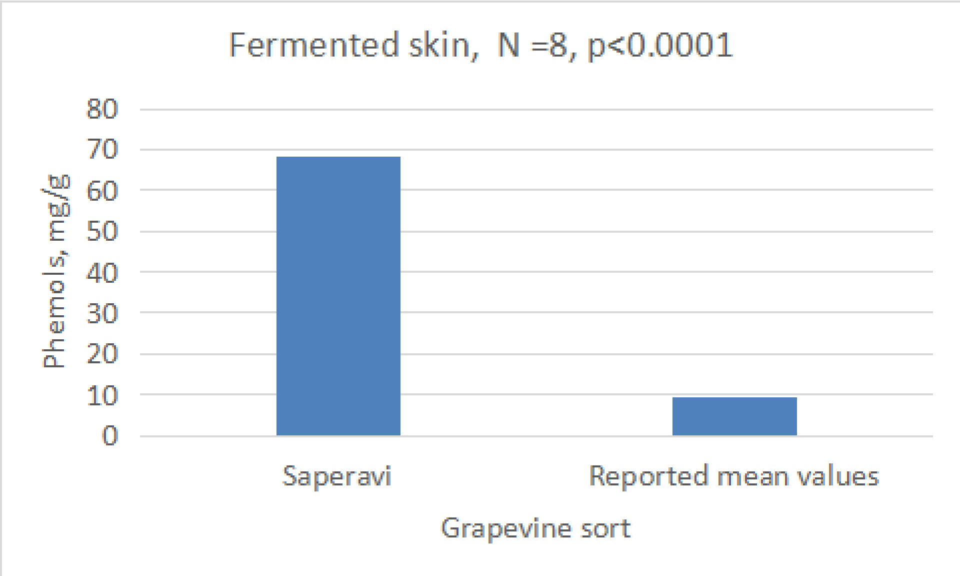

FIGURE 11 COMPARISON OF SOLUBLE PHENOL CONTENT IN FERMENTED SKIN BETWEEN SAPERAVI AND REPORTED IN REFERENCES.
The left bar shows the mean obtained for our sort of grapevine, and the right bar shows the mean value calculated from the data reported in references (Mean reported values). Sample size *N* and the *P*-value are reported in the figure title.

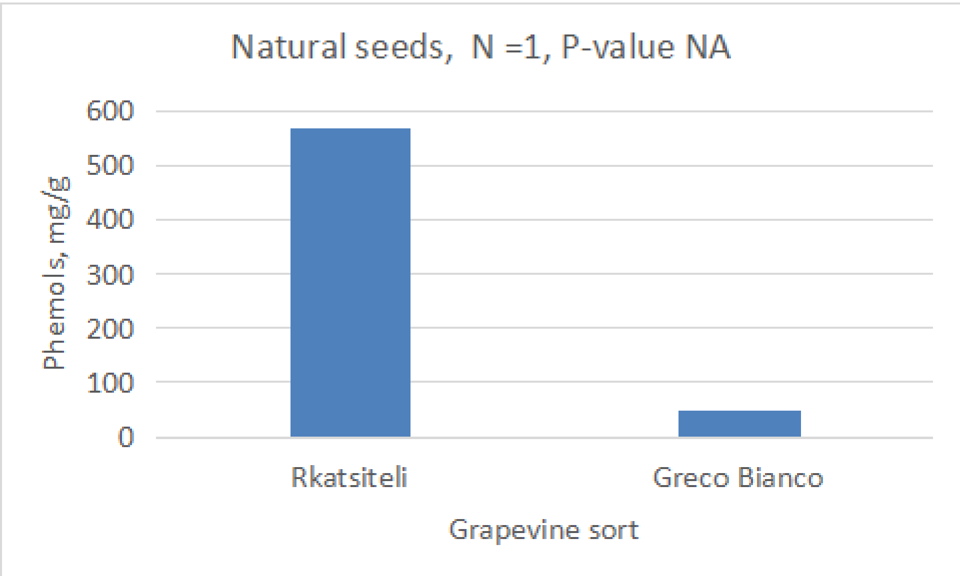

FIGURE 12 COMPARISON OF SOLUBLE PHENOL CONTENT IN NATURAL PIPS BETWEEN RKATSITELI AND REPORTED IN REFERENCES.
Sample size *N* and the *P*-value are reported in the figure title.

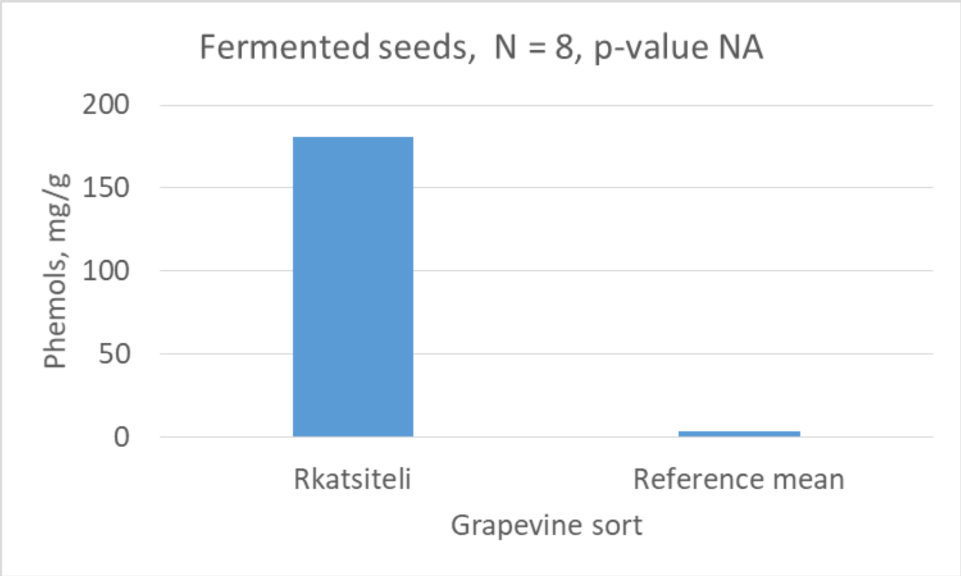

FIGURE 13 COMPARISON OF SOLUBLE PHENOL CONTENT IN FERMENTED PIPS BETWEEN RKATSITELI AND REPORTED IN REFERENCES.

The left bar shows the mean obtained for our sort of grapevine, and the right bar shows the mean value calculated from the data reported in references (Mean reported values). Sample size *N* and the *P*-value are reported in the figure title.

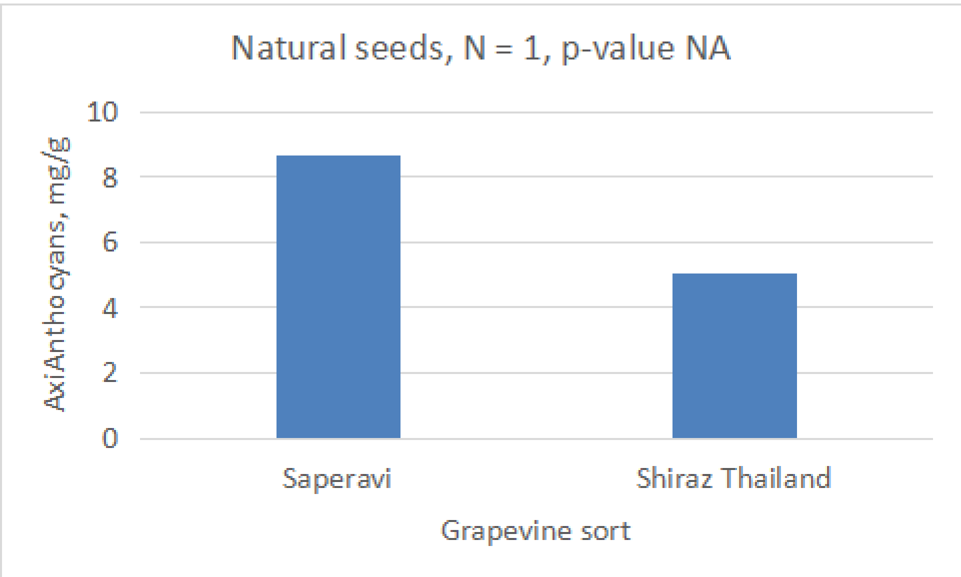

FIGURE 14 COMPARISON OF ANTHOCYAN CONTENT IN NATURAL PIPS BETWEEN SAPERAVI AND REPORTED IN REFERENCES.

Sample size *N* and the *P*-value are reported in the figure title.

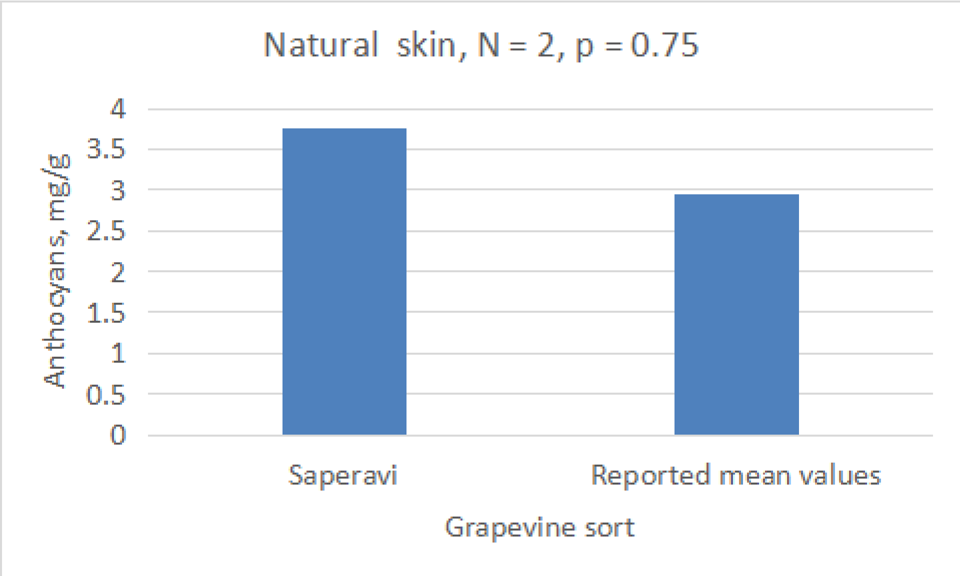

FIGURE 15 COMPARISON OF ANTHOCYAN CONTENT IN NATURAL SKIN BETWEEN SAPERAVI AND REPORTED IN REFERENCES.

The left bar shows the mean obtained for our sort of grapevine, and the right bar shows the mean value calculated from the data reported in references (Mean reported values). Sample size *N* and the *P*-value are reported in the figure title.

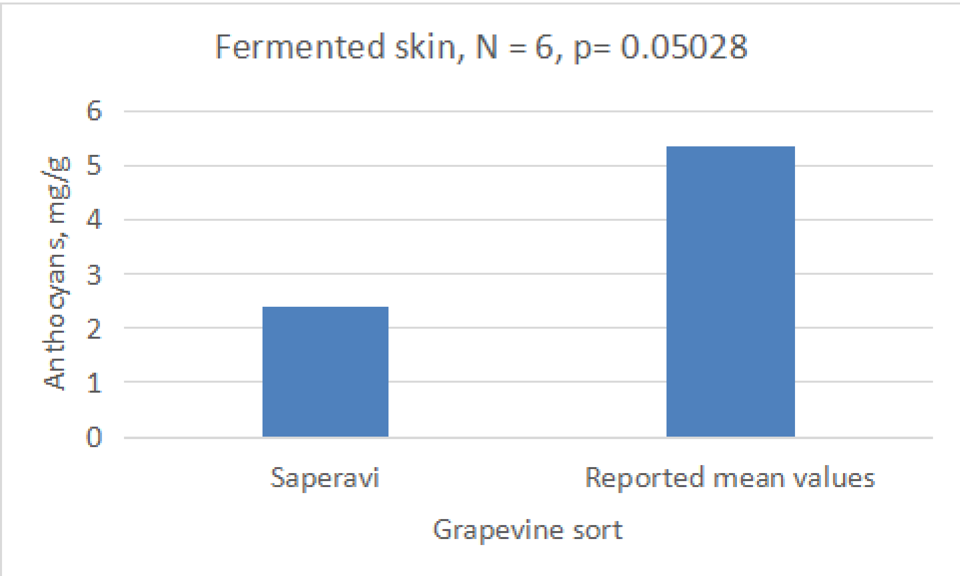

FIGURE 16 COMPARISON OF ANTHOCYAN CONTENT IN FERMENTED SKIN BETWEEN SAPERAVI AND REPORTED IN REFERENCES.

The left bar shows the mean obtained for our sort of grapevine, and the right bar shows the mean value calculated from the data reported in references (Mean reported values). Sample size *N* and the *P*-value are reported in the figure title.

Chapter 3. Comparison of bioactive compounds in pomace and wines (Stage 2 Experimental Results)

Our analyses could not detect the target compounds in any of sample or fraction, even after repeated analyses in the pips and skin fractions of the pomace that was stored in kvevris after the fermenting young wine was moved to other vessels. Thus these compounds either were decomposed during the storage in the kvevris, or were extracted by the wine during the storage. To assess to what extent the phenolic compounds moved from the pips and skin into the wine, we analysed the soluble phenols in the produced wines (below).

The location of a winery (vineyeard) was not a free factor as it was strongly linked to the grapevine sort (Telavi provided only red wine, while Akhmeta and Gurjaani - only white wine). Therefore, we used One- and Two-Way ANOVA for data analyses. These tests have shown that the contents of soluble phenols were particularly high in the red wine fermented with chacha. In the white wines (irrespective of the fermentation method), as well as in the red wine fermented without chacha, the phenolic content was lower and did not vary considerably even though the differences were statistically significant, as was shown by the One-Way ANOVA with subsequent Tukey´s test (Figure 17 with the ANOVA results). Two-Way ANOVA produced similar results, with statistically significant differences among grapevine sorts and fermentation methods (Figure 18 with the ANOVA results table). When the grape juice was fermented without pomace, the phenolic compounds in red wine were slightly higher than in white wines. There were also certain differences between white wines, yet the level of soluble phenols varied inconsistently between the wine types, winery locations, and fermentation methods. In any case, these differences were not large in physical terms and could be accounted by the natural variation that is always associated with the grape quality and wine production process.

Our results show that the phenolic compounds were absent in the fractions of pomace (pips or skin) after they were stored in kvevris. Some parts of these compounds undoubtedly were extracted and moved to wine. The remaining phenols were most probably decomposed during the storage: usually, wine is separated from the pomace in December and over three or four months of storage a full decomposition of phenols was likely. Remarkably, soluble phenols were not detected either in the pomace fractions that were not fermented together with juice; in this case, decomposition is an even a more plausible explanation. The major agent decomposing pomace components probably are air-born bacteria. In any case, if the waste of winemaking is to be recycled, it is important to use it immediately after pressing the juice or at least by the end of fermentation avoiding any lengthy storage of pomace.

We also found that red wine fermented with pomace contains remarkably high levels of phenolic substances and thus might have considerably higher antioxidant potential than the other wines. This fact indicates a higher nutritional value of traditional red Kakheti wines and the potential of pomace to increase this value.

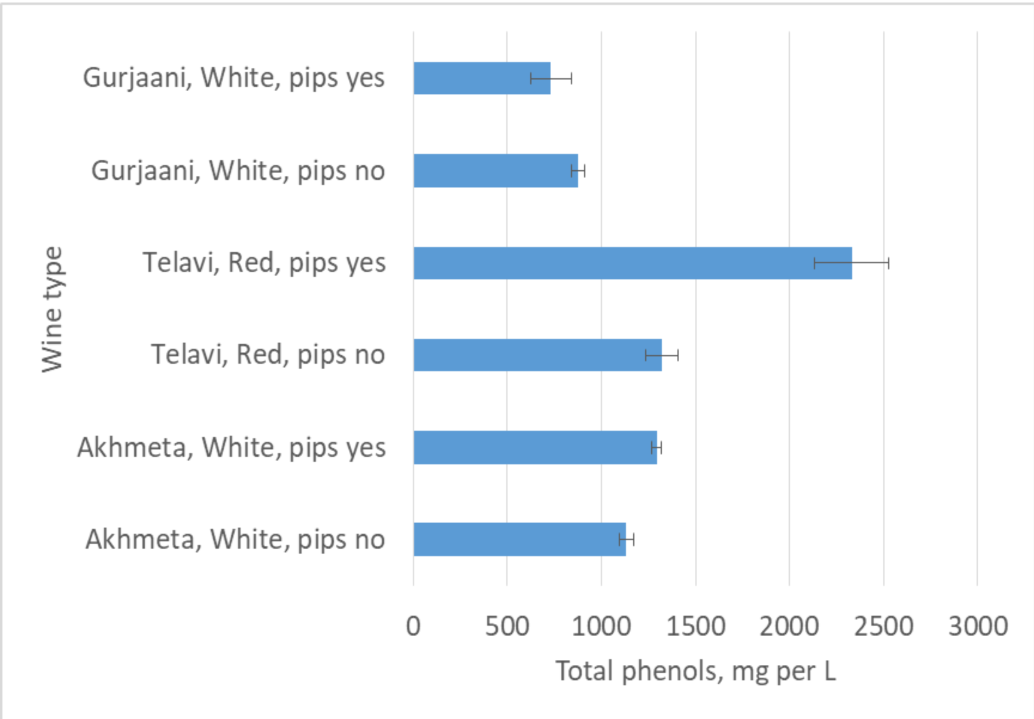

FIGURE 17. SOLUBLE PHENOLES IN DIFFERENT WINES. SEE THE ANOVA RESULTS TABLE.

ANOVA	Sum of sqrs	df	Mean square	F	p (same)
Between groups:	7.95E+06	5	1.59E+06	30.53	<0.0001
Within groups:	1.25E+06	24	52084.1	Permutation p (n=99999)	
Total:	9.20E+06	29			<0.0001

Tukey´s test at α = 0.05	Akhmeta, white, pips no				
Akhmeta, White, pips yes	0.867	Akhmeta, white, pips yes			
Telavi, Red, pips no	0.772	0.99	Telavi, red, pips no		
Telavi, Red, pips yes	**<0.0001**	**<0.0001**	**<0.0001**	Telavi, red, pips yes	
Gurjaani, White, pips no	0.498	0.076	**0.0496**	**<0.0001**	Gurjaani, white, pips no

Gurjaani, White, pips yes	0.09736	**0.008102**	0.004999	**<0.0001**	0.9155

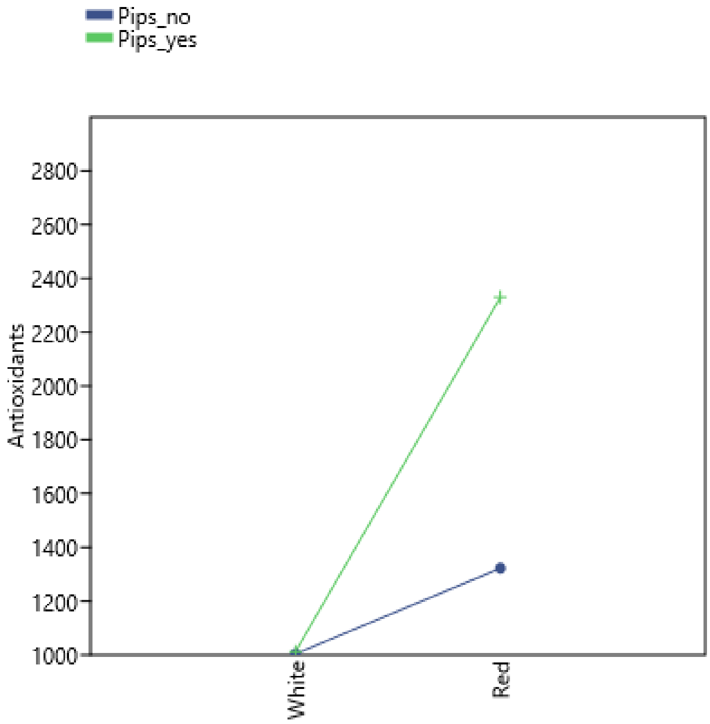

FIGURE 18 TWO-WAY ANOVA OF THE SOLUBLE PHENOLS ("ANTIOXIDANTS", MG PER L) IN THE WINES FROM DIFFERENT GRAPEVINE SORTS (RED VS. WHITE) AND FERMENTED IN TWO DIFFERENT WAYS (WITH CHACHA OR WITHOUT). SEE THE ANOVA RESULTS TABLE BELOW.

	Sum of sqrs	df	Mean square	F	p (same)
Sort:	4.46E+06	1	4.46E+06	52.66	<0.0001
Pips:	876546	1	876546	10.35	0.003
Interaction:	1.66E+06	1	1.66E+06	19.64	0.0002
Within:	2.20E+06	26	84692		
Total:	9.20E+06	29			

Conclusions and Recommendations

In order to ensure food product supply of the country and high-quality natural food products and food supplements to the international market, determination of the main directions of winemaking and its processed waste products development and the related production promotion is still urgent. The annual increase in wine consumption has led to an increase in the quantity of wine by-products, consequently, a significant amount of wine waste products are obtained during grape processing (15 – 20 %). Due to the high content of phenols, pesticides, heavy metals, as well as high concentrations of nitrogen, phosphates, potassium and organic compounds, convenient waste disposal is necessary and important to avoid environmental problems. Their processing also has a commercial interest, as the organic compounds present in winemaking waste can be important in the form of additives, ingredients and substrates in the food and pharmaceutical industries. That is why one of the current tasks of winemaking is different in nature and considers developing complex processing technology for such winemaking waste as a stalk of the bunch, chacha (grape skins and pips after pressing), seeds and sediment to obtain useful components, which may be used in food and animal feed production, medicine, as well as solving environmental problems.

The search for new natural sources for the production of biologically active compounds is one of the priorities of public health. At the same time, there is a problem of utilization of biotechnological waste, which could be considered for further use as a natural raw material. This recycling method can be very attractive from an economic point of view, as it offers cheap (or completely free) natural raw materials and at the same time ensures waste disposal. In wine-growing countries, the grape pomace is a material that can be processed, and at the same time, it contributes to the development of small and medium-sized industries. The experiment showed that the by-products left over from wine production, which are used to extract ethanol, are still valuable materials for the medical, cosmetic and food industries.

Based on the data concerning the chemical activity of fermented samples, we can conclude that fermented seeds of all the varieties studied, left after producing wine in the “Kakhetian” way, can be used for the production of dietary supplements. Thus, the presence of antioxidants and other groups of organic substances in wine waste, produced in the "Kakhetian" way is a sensible reason for using this waste in food additives, cosmetics, or for other purposes. However, phenolic substances can rapidly decompose if the pomace is stored for long time, therefore, the best approach is to use winery waste immediately after fermentation.

References

Abhijit, S., Sunil Jamuna Tripathi, V. Bhagya, B. S. Shankaranarayana Rao, Muthangi V. Subramanyam, and S. Asha Devi. 2018. "Antioxidant Action of Grape Seed Polyphenols and Aerobic Exercise in Improving Neuronal Number in the Hippocampus Is Associated with Decrease in Lipid Peroxidation and Hydrogen Peroxide in Adult and Middle-Aged Rats." *Experimental Gerontology* 101 (October 2017): 101–12. https://doi.org/10.1016/j.exger.2017.11.012.

Abu-Serie, Marwa M., and Noha H. Habashy. 2020. "Vitis Vinifera Polyphenols from Seedless Black Fruit Act Synergistically to Suppress Hepatotoxicity by Targeting Necroptosis and Pro-Fibrotic Mediators." *Scientific Reports* 10 (1): 1–15. https://doi.org/10.1038/s41598-020-59489-z.

Agarwal, Ashok, Kristian Leisegang, Ahmad Majzoub, Ralf Henkel, Renata Finelli, Manesh Kumar Panner Selvam, Nicholas Tadros, et al. 2021. "Utility of Antioxidants in the Treatment of Male Infertility: Clinical Guidelines Based on a Systematic Review and Analysis of Evidence." *World Journal of Men's Health* 39 (2): 1–58. https://doi.org/10.5534/WJMH.200196.

Ahmad, Sheikh Fayaz, Khairy M.A. Zoheir, Hala E. Abdel-Hamied, Abdelkader E. Ashour, Saleh A. Bakheet, Sabry M. Attia, and Adel R.A. Abd-Allah. 2013. "Grape Seed Proanthocyanidin Extract Has Potent Anti-Arthritic Effects on Collagen-Induced Arthritis by Modifying the T Cell Balance." *International Immunopharmacology* 17 (1): 79–87. https://doi.org/10.1016/j.intimp.2013.05.026.

Aktan, Gülşen, Semra Doğru-Abbasoğlu, Canan Küçükgergin, Ateş Kadioğlu, Gül Özdemirler-Erata, and Necla Koçak-Toker. 2013. "Mystery of Idiopathic Male Infertility: Is Oxidative Stress an Actual Risk?" *Fertility and Sterility* 99 (5): 1211–15. https://doi.org/10.1016/j.fertnstert.2012.11.045.

Al-Jammas, Saif, and Ayad Al-Saraj. 2020. "The Histological Changes Induced by Cytarabine on Rabbits Livers (With and without Vitamin E Administration).” *Iraqi Journal of Veterinary Sciences* 34 (1): 9–13. https://doi.org/10.33899/ijvs.2020.163564.

Ali, B. H. 2002. “The Effect of Treatment with the Medicinal Plant Rhazya Stricta Decne on Gentamicin Nephrotoxicity in Rats.” *Phytomedicine* 9 (5): 385–89. https://doi.org/10.1078/09447110260571607.

Ali, Doaa A., Nariman K. Badr El-Din, and Rania F. Abou-El-magd. 2015. “Antioxidant and Hepatoprotective Activities of Grape Seeds and Skin against Ehrlich Solid Tumor Induced Oxidative Stress in Mice.” *Egyptian Journal of Basic and Applied Sciences* 2 (2): 98–109. https://doi.org/10.1016/j.ejbas.2015.02.003.

American Heritage Dictionary of the English Language. n.d. “Proline.” In , 4th ed.

Anand, R., B. K. Binukumar, and Kiran Dip Gill. 2011. “Aluminum Phosphide Poisoning: An Unsolved Riddle.” *Journal of Applied Toxicology* 31 (6): 499–505. https://doi.org/10.1002/jat.1692.

Anjum, Farah, Vikas Rishi, and Faizan Ahmad. 2000. “Compatibility of Osmolytes with Gibbs Energy of Stabilization of Proteins.” *Biochimica et Biophysica Acta - Protein Structure and Molecular Enzymology* 1476 (1): 75–84. https://doi.org/10.1016/S0167-4838(99)00215-0.

Apollonius of Rhodes. 1948. *არგონავტიკა [Argonautica]*. Edited by Akaki Urushadze. Tbilisi: Sakhelgami.

Archetti, Marco, Thomas F. Döring, Snorre B. Hagen, Nicole M. Hughes, Simon R. Leather, David W. Lee, Simcha Lev-Yadun, et al. 2009. “Unravelling the Evolution of Autumn Colours: An Interdisciplinary Approach.” *Trends in Ecology and Evolution* 24 (3): 166–73. https://doi.org/10.1016/j.tree.2008.10.006.

Asha Devi, S., B. K. Sagar Chandrasekar, K. R. Manjula, and N. Ishii. 2011. “Grape Seed Proanthocyanidin Lowers Brain Oxidative Stress in Adult and Middle-Aged Rats.” *Experimental Gerontology* 46 (11): 958–64. https://doi.org/10.1016/j.exger.2011.08.006.

Augusti, Paula R., Greicy M.M. Conterato, Cristiane C. Denardin, Inês D. Prazeres, Ana Teresa Serra, Maria R. Bronze, and Tatiana Emanuelli. 2021. “Bioactivity, Bioavailability, and Gut Microbiota Transformations of Dietary Phenolic Compounds: Implications for COVID-19." *Journal of Nutritional Biochemistry* 97: 108787. https://doi.org/10.1016/j.jnutbio.2021.108787.

Aversi Rationale. n.d. Phenovin (ფენოვინი).

Babbush, Kayla M., Remy A. Babbush, and Amor Khachemoune. 2021. "Treatment of Melasma: A Review of Less Commonly Used Antioxidants." *International Journal of Dermatology* 60 (2): 166–73. https://doi.org/10.1111/ijd.15133.

Badavi, Mohammad, Hassan Ali Abedi, Mahin Dianat, and Ali Reza Sarkaki. 2013. "Exercise Training and Grape Seed Extract Co-Administration Improves Lipid Profile, Weight Loss, Bradycardia, and Hypotension of STZ-Induced Diabetic Rats." *International Cardiovascular Research Journal* 7 (4): 111–17.

Badavi, Mohammad, Hassan Ali Abedi, Ali Reza Sarkaki, and Mahin Dianat. 2013. "Co-Administration of Grape Seed Extract and Exercise Training Improves Endothelial Dysfunction of Coronary Vascular Bed of STZ-Induced Diabetic Rats." *Iranian Red Crescent Medical Journal* 15 (10). https://doi.org/10.5812/ircmj.7624.

Badridze, G., N. Kacharava, E. Chkhubianishvili, L. Rapava, M. Kikvidze, S. H. Chanishvili, and L. Chigladze. 2015. "Influence of Ultraviolet Irradiation and Acid Precipitations on the Content of Antioxidants in Wheat Leaves." *Applied Ecology and Environmental Research* 13 (4): 993–1013. https://doi.org/10.15666/aeer/1304_9931013.

Bagchi, D., A. Garg, R. L. Krohn, M. Bagchi, D. J. Bagchi, J. Balmoori, and S. J. Stohs. 1998. "Protective Effects of Grape Seed Proanthocyanidins and Selected Antioxidants against TPA-Induced Hepatic and Brain Lipid Peroxidation and DNA Fragmentation, and Peritoneal Macrophage Activation in Mice." *General Pharmacology* 30 (5): 771–76. https://doi.org/10.1016/S0306-3623(97)00332-7.

Bagchi, Debasis, Manashi Bagchi, Sidney J. Stohs, Dipak K. Das, Sidhartha D. Ray, Charles A. Kuszynski, Shantaram S. Joshi, and Harry G. Pruess. 2000. "Free Radicals and Grape Seed Proanthocyanidin Extract: Importance in Human Health and Disease Prevention." *Toxicology* 148 (2–3): 187–97. https://doi.org/10.1016/S0300-483X(00)00210-9.

Bagchi, Debasis, Manashi Bagchi, and Sidney J Stohs. 2002. “Cellular Protection with Proanthocyanidins.” *Annals of the New York Academy of Sciences* 270: 260–70. http://www.ncbi.nlm.nih.gov/pubmed/12074978.

Baiges, Isabel, Johan Palmfeldt, Cinta Bladé, Niels Gregersen, and Lluís Arola. 2010. “Lipogenesis Is Decreased by Grape Seed Proanthocyanidins According to Liver Proteomics of Rats Fed a High Fat Diet.” *Molecular and Cellular Proteomics* 9 (7): 1499–1513. https://doi.org/10.1074/mcp.M000055-MCP201.

Baravoi, V.A. 1984. *Растительные Фенолы и Здоровье Человека [Plant Phenolics and Human Health]*. Moscow: Nauka.

Bates, L.S., R.P. Waldren, and I.D. Treare. 1973. “Short Communication. Rapid Determination of Free Proline for Water- Stress Studies.” *Plant and Soil* 39: 205–7.

Begunova, R.D. 1953. “Динамика Накопления Красящих Веществ в Ягодах Винограда При Их Созревании [The Dynamics of the Accumulation of Dyes in Grapes during Their Ripening].” *Магарач. Виноградарство и Виноделие [Magarach. Viticulture and Winemaking]* 4: 169–74.

Berashvili, D., M. Gonashvili, B. Chumburidze, A. Bakuridze, T Chikviladze, J Phutkaradze, and N Kurdiani. 2006. “ზოგიერთი ქართული ღვინის ანტიოქსიდანტური აქტიურობის შესწავლა [Study of Antioxidant Activity of Some Georgian Wines].” *საქართველოს ქიმიური ჟურნალი [Georgian Chemical Journal]* 6 (5): 553–56.

Beridze, Tamar. 2012. “ქართული ვაზის ჯიშები [Georgian Vine Species].” Tbilisi. https://studentresearch.iliauni.edu.ge/wp-content/uploads/2016/05/Tberidze.pdf.

Betti, Michele, Andrea Minelli, Barbara Canonico, Pasqualina Castaldo, Simona Magi, M. Cristina Aisa, Marta Piroddi, Valentina Di Tomaso, and Francesco Galli. 2006. “Antiproliferative Effects of Tocopherols (Vitamin E) on Murine Glioma C6 Cells: Homologue-Specific Control of PKC/ERK and Cyclin Signaling.” *Free Radical Biology and Medicine* 41 (3): 464–72. https://doi.org/10.1016/j.freeradbiomed.2006.04.012.

Beygi, Z, S Forouhari, E Mahmoudi, SMG Hayat, and F Nourimand. 2021. “Role of Oxidative Stress and Antioxidant Supplementation in Male Fertility.” *Curr Mol Med* 21 (4): 265–

82. https://doi.org/10.2174/1566524020999200831123553.

Bijak, Michał, Mateusz Bobrowski, Marta Borowiecka, Anna Podsędek, Jacek Golański, and Paweł Nowak. 2011. "Anticoagulant Effect of Polyphenols-Rich Extracts from Black Chokeberry and Grape Seeds." *Fitoterapia* 82 (6): 811–17. https://doi.org/10.1016/j.fitote.2011.04.017.

Bijak, Michał, Joanna Saluk, Michał Błazej Ponczek, and Paweł Nowak. 2013. "Antithrombin Effect of Polyphenol-Rich Extracts from Black Chokeberry and Grape Seeds." *Phytotherapy Research* 27 (1): 71–76. https://doi.org/10.1002/ptr.4682.

Bijak, Michal, Agnieszka Sut, Anna Kosiorek, Joanna Saluk-Bijak, and Jacek Golanski. 2019. "Dual Anticoagulant/Antiplatelet Activity of Polyphenolic Grape Seeds Extract." *Nutrients* 11 (1): 1–9. https://doi.org/10.3390/nu11010093.

Boozari, Motahareh, and Hossein Hosseinzadeh. 2017. "Natural Medicines for Acute Renal Failure: A Review." *Phytotherapy Research* 31 (12): 1824–35. https://doi.org/10.1002/ptr.5943.

Brasky, Theodore M., Alan R. Kristal, Sandi L. Navarro, Johanna W. Lampe, Ulrike Peters, Ruth E. Patterson, and Emily White. 2011. "Specialty Supplements and Prostate Cancer Risk in the VITamins and Lifestyle (VITAL) Cohort." *Nutrition and Cancer* 63 (4): 573–82. https://doi.org/10.1080/01635581.2011.553022.

Burton, Graham J., and Eric Jauniaux. 2011. "Oxidative Stress." *Best Practice and Research: Clinical Obstetrics and Gynaecology* 25 (3): 287–99. https://doi.org/10.1016/j.bpobgyn.2010.10.016.

Butkhup, L., S. Chowtivannakul, R. Gaensakoo, P. Prathepha, and S. Samappito. 2010. "Study of the Phenolic Composition of Shiraz Red Grape Cultivar (Vitis Vinifera L.) Cultivated in Northeastern Thailand and Its Antioxidant and Antimicrobial Activity." *South African Journal of Enology and Viticulture* 31 (2): 89–98. https://doi.org/10.21548/31-2-1405.

Caimari, A., J. M. Del Bas, A. Crescenti, and L. Arola. 2013. "Low Doses of Grape Seed Procyanidins Reduce Adiposity and Improve the Plasma Lipid Profile in Hamsters."

International Journal of Obesity 37 (4): 576–83. https://doi.org/10.1038/ijo.2012.75.

Caldwell, Martyn M. 1968. “Solar Ultraviolet Radiation as an Ecological Factor for Alpine Plants.” *Ecological Monographs* 38 (3): 243–68. https://doi.org/10.2307/1942430.

Cao, Yi, Long Xie, Kai Liu, Youdan Liang, Xiaolin Dai, Xian Wang, Jing Lu, Xumin Zhang, and Xiaofang Li. 2021. “The Antihypertensive Potential of Flavonoids from Chinese Herbal Medicine: A Review.” *Pharmacological Research* 174 (December): 105919. https://doi.org/10.1016/J.PHRS.2021.105919.

Cardoso, Joao Paulo, Marcello Cocuzza, and Dean Elterman. 2019. “Optimizing Male Fertility: Oxidative Stress and the Use of Antioxidants.” *World Journal of Urology* 37 (6): 1029–34. https://doi.org/10.1007/s00345-019-02656-3.

Casati, Martina, Virginia Boccardi, Evelyn Ferri, Laura Bertagnoli, Patrizia Bastiani, Simona Ciccone, Marta Mansi, et al. 2020. “Vitamin E and Alzheimer’s Disease: The Mediating Role of Cellular Aging.” *Aging Clinical and Experimental Research* 32 (3): 459–64. https://doi.org/10.1007/s40520-019-01209-3.

Cejudo-Bastante, María Jesús, Melanie Oliva-Sobrado, M. Lourdes González-Miret, and Francisco J. Heredia. 2022. “Optimisation of the Methodology for Obtaining Enzymatic Protein Hydrolysates from an Industrial Grape Seed Meal Residue.” *Food Chemistry* 370. https://doi.org/10.1016/j.foodchem.2021.131078.

Chand, N., S. Tyagi, A. S. Sirohi, N. V. Patil, A. Sharma, and S. Sarika. 2021. “Effect of Vitamin E and Selenium Supplementation on Oxidative Markers and Semen Quality Parameters in Breeding Bulls.” *Indian Journal of Animal Sciences* 91 (10): 826–29.

Chartier, Lauren C., Gordon S. Howarth, and Suzanne Mashtoub. 2019. “Combined Nutraceuticals: A Novel Approach to Colitis-Associated Colorectal Cancer?” *Nutrition and Cancer* 71 (2): 199–206. https://doi.org/10.1080/01635581.2019.1578391.

Chavchavadze, Ilia. 1887. *ღვინის ქართულად დაყენება. გამოყენებულია: რჩეული ნაწარმოებები, 1956 [Making Wine in Georgian. Used: Featured Works, 1956]*. Vol. VII. Tbilisi: Sabchota Sakartvelo.

Chawla, Udeep, Manoj Kumar Kashyap, and Amjad Husain. 2021. “Aging and Diabetes Drive the COVID-19 Forwards; Unveiling Nature and Existing Therapies for the Treatment." *Molecular and Cellular Biochemistry* 476 (11): 3911–22. https://doi.org/10.1007/s11010-021-04200-7.

Chen, Shihui, Xiaolan Zhao, Li Ran, Jing Wan, Xiaofang Wang, Yu Qin, Furong Shu, et al. 2015. "Resveratrol Improves Insulin Resistance, Glucose and Lipid Metabolism in Patients with Non-Alcoholic Fatty Liver Disease: A Randomized Controlled Trial." *Digestive and Liver Disease* 47 (3): 226–32. https://doi.org/10.1016/j.dld.2014.11.015.

Chilashvili, Levan. 2004. "ვენახი, ღვინო და ქართველები [Vineyard, Wine and Georgians]." Tbilisi: Petite.

Cho, Mi La, Yu Jung Heo, Mi Kyung Park, Hye Jwa Oh, Jin Sil Park, Yun Ju Woo, Ji Hyeon Ju, Sung Hwan Park, Ho Youn Kim, and Jun Ki Min. 2009. "Grape Seed Proanthocyanidin Extract (GSPE) Attenuates Collagen-Induced Arthritis." *Immunology Letters* 124 (2): 102–10. https://doi.org/10.1016/j.imlet.2009.05.001.

Choy, Ying Yng, Paola Quifer-Rada, Dirk M. Holstege, Steven A. Frese, Christopher C. Calvert, David A. Mills, Rosa M. Lamuela-Raventos, and Andrew L. Waterhouse. 2014. "Phenolic Metabolites and Substantial Microbiome Changes in Pig Feces by Ingesting Grape Seed Proanthocyanidins." *Food and Function* 5 (9): 2298–2308. https://doi.org/10.1039/c4fo00325j.

Clifford, M. N. 2004. "Diet-Derived Phenols in Plasma and Tissues and Their Implications for Health." *Planta Medica* 70 (12): 1103–14. https://doi.org/10.1055/s-2004-835835.

Constantinou, Constantina, Christiana Charalambous, and Dimitrios Kanakis. 2020. "Vitamin E and Cancer: An Update on the Emerging Role of γ and δ Tocotrienols." *European Journal of Nutrition* 59 (3): 845–57. https://doi.org/10.1007/s00394-019-01962-1.

Costa, Gislaine N.S., Renata V. Tonon, Caroline Mellinger-Silva, Melicia C. Galdeano, Marcello Iacomini, Manuela C.P.A. Santiago, Eveline L. Almeida, and Suely P. Freitas. 2019. "Grape Seed Pomace as a Valuable Source of Antioxidant Fibers." *Journal of the Science of Food and Agriculture* 99 (10): 4593–4601. https://doi.org/10.1002/jsfa.9698.

Davies, Kevin M. 2004. "Plant Pigments and Their Manipulation." *Annual Plant Reviews* 14.

Dejani, Naiara Naiana, Hatem A. Elshabrawy, Carlos da Silva Maia Bezerra Filho, and Damião Pergentino de Sousa. 2021. "Anticoronavirus and Immunomodulatory Phenolic Compounds: Opportunities and Pharmacotherapeutic Perspectives." *Biomolecules* 11 (8). https://doi.org/10.3390/biom11081254.

Devesa-Rey, R., X. Vecino, J. L. Varela-Alende, M. T. Barral, J. M. Cruz, and A. B. Moldes. 2011. "Valorization of Winery Waste vs. the Costs of Not Recycling." *Waste Management* 31 (11): 2327–35. https://doi.org/10.1016/j.wasman.2011.06.001.

Dhariwala, Maria Yusuf, and Padmini Ravikumar. 2019. "An Overview of Herbal Alternatives in Androgenetic Alopecia." *Journal of Cosmetic Dermatology* 18 (4): 966–75. https://doi.org/10.1111/jocd.12930.

Dimitrios, Boskou. 2006. "Sources of Natural Phenolic Antioxidants." *Trends in Food Science and Technology* 17 (9): 505–12. https://doi.org/10.1016/j.tifs.2006.04.004.

Dinicola, Simona, Alessandra Cucina, Alessia Pasqualato, Fabrizio D'Anselmi, Sara Proietti, Elisabetta Lisi, Gabriella Pasqua, Donato Antonacci, and Mariano Bizzarri. 2012. "Antiproliferative and Apoptotic Effects Triggered by Grape Seed Extract (GSE) versus Epigallocatechin and Procyanidins on Colon Cancer Cell Lines." *International Journal of Molecular Sciences* 13 (1): 651–64. https://doi.org/10.3390/ijms13010651.

Domínguez, Jorge, Juan C. Sanchez-Hernandez, and Marta Lores. 2017. "Vermicomposting of Winemaking By-Products." *Handbook of Grape Processing By-Products: Sustainable Solutions*, 55–78. https://doi.org/10.1016/B978-0-12-809870-7.00003-X.

Doshi, Pooja, Pandurang Adsule, Kaushik Banerjee, and Dasharath Oulkar. 2015. "Phenolic Compounds, Antioxidant Activity and Insulinotropic Effect of Extracts Prepared from Grape (Vitis Vinifera L) Byproducts." *Journal of Food Science and Technology* 52 (1): 181–90. https://doi.org/10.1007/s13197-013-0991-1.

Downing, Laura E., Rebecca M. Heidker, Gianella C. Caiozzi, Brian S. Wong, Kelvin Rodriguez, Fernando Del Rey, and Marie Louise Ricketts. 2015. "A Grape Seed Procyanidin Extract Ameliorates Fructose-Induced Hypertriglyceridemia in Rats via Enhanced Fecal Bile Acid and Cholesterol Excretion and Inhibition of Hepatic Lipogenesis." *PLoS ONE* 10 (10): 1–19. https://doi.org/10.1371/journal.pone.0140267.

Drug.com. n.d. “Grape Seed.” https://www.drugs.com/mtm/grape-seed.html.

Dulundu, Ender, Yahya Ozel, Umit Topaloglu, Hale Toklu, Feriha Ercan, Nursal Gedik, and Goksel Şener. 2007. “Grape Seed Extract Reduces Oxidative Stress and Fibrosis in Experimental Biliary Obstruction.” *Journal of Gastroenterology and Hepatology (Australia)* 22 (6): 885–92. https://doi.org/10.1111/j.1440-1746.2007.04875.x.

Dumoulin, Marion, David Gaudout, and Benoit Lemaire. 2016. “Clinical Effects of an Oral Supplement Rich in Antioxidants on Skin Radiance in Women.” *Clinical, Cosmetic and Investigational Dermatology* 9: 315–24. https://doi.org/10.2147/CCID.S118920.

Durmishidze, S.V. 1955. “Дубильные Вешества и Антоцианы Виноградной Лозы и Вина [Tanning Agents and Anthocyanins of Vines and Wines].” Moscow: Academy of Sciences of the SSSR.

Durmishidze, S.V., and N.N. Nutsubidze. 1954. “Хроматографические Исследования Дубильных Веществ Виноградной Лозы [Chromatographic Studies of Vine Tannins].” *Report of the Academy of Sciences of the Georgian SSR* 96 (6): 1197–99.

Ebelashvili, N. 2006. “ბიოლოგიურად აქტიური ნივთიერებების გამოკვლევა ვარდისფერი და ცქრიალა ღვინოების დამზადების პროცესში მათი ტექნოლოგიების სრულყოფის მიზნით [Study of Biologically Active Substances in Order to Improve Their Technologies in the Process of Making Rosé and Sparklin.” Institute of Horticulture, Viticulture and Enology.

Ebralidze, T. 2009. “სოფ. ზვარეს ისტორიიდან [From the History of the Village Zvare].” In *საერთაშორისო სამეცნიერო კონფერენცია „დიდაჭარობა“ [International Scientific Conference “Didacharoba”]*, 375–80.

Ekhvaia, Jana, and Maia Akhalkatsi. 2006. “Comparative Study of the Quantitative Parameters of Berries and Seeds in the Autochthonous Red Grape Varieties of the Kolkhis (Western Georgia),” no. March 2016.

———. 2010. “Morphological Variation and Relationships of Georgian Populations of Vitis Vinifera L. Subsp. Sylvestris (C.C. Gmel.) Hegi.” *Flora: Morphology, Distribution, Functional Ecology of Plants* 205 (9): 608–17. https://doi.org/10.1016/j.flora.2009.08.002.

Ekhvaia, Jana, Maia Gurushidze, Frank R. Blattner, and Maia Akhalkatsi. 2014. "Genetic Diversity of Vitis Vinifera in Georgia: Relationships between Local Cultivars and Wild Grapevine, V. Vinifera L. Subsp. Sylvestris." *Genetic Resources and Crop Evolution* 61 (8): 1507–21. https://doi.org/10.1007/s10722-014-0125-2.

Elias, Ryan J., Sarah S. Kellerby, and Eric A. Decker. 2008. "Antioxidant Activity of Proteins and Peptides." *Critical Reviews in Food Science and Nutrition* 48 (5): 430–41. https://doi.org/10.1080/10408390701425615.

Emmulo, Emanuela, Brunella Ceccantoni, Andrea Bellincontro, and Fabio Mencarelli. 2021. "Use of Water and Ethanol Extracts from Wine Grape Seed Pomace to Prepare an Antioxidant Toothpaste." *Journal of the Science of Food and Agriculture* 101 (14): 5813–18. https://doi.org/10.1002/jsfa.11232.

Eng, Elizabeth T., Jing Jing Ye, Dudley Williams, Sheryl Phung, Roger E. Moore, Mary K. Young, Ugis Gruntmanis, Glenn Braunstein, and Shiuan Chen. 2003. "Suppression of Estrogen Biosynthesis by Procyanidin Dimers in Red Wine and Grape Seeds." *Cancer Research* 63 (23): 8516–22.

Feringa, Harm H.H., Dayne A. Laskey, Justine E. Dickson, and Craig I. Coleman. 2011. "The Effect of Grape Seed Extract on Cardiovascular Risk Markers: A Meta-Analysis of Randomized Controlled Trials." *Journal of the American Dietetic Association* 111 (8): 1173–81. https://doi.org/10.1016/j.jada.2011.05.015.

Filippovich, U.B., T.A. Egorova, and G.A. Sevastyanova. 1982. *Практикум По Общей Биохимии [Workshop on General Biochemistry]*. Moscow: Prosveshenie.

Fronza, Marcio, Denise Coutinho Endringer, Rodrigo Scherer, Débora Rigamonti Gomes Cruz Freire, Camile Zanichelli da Costa Cassiano, Karla Lírio Soares, Mayara Fumiere Lemos, and Elisângela Flávia Pimentel-Schmitt. 2022. "Cancer Chemopreventive and Antioxidant Activities of Seed, Skin, and Pulp of Maximo Hybrid Grapes (Iac 138-22) at Five Different Ripening Stages." *Ciencia Rural* 52 (3): 1–11. https://doi.org/10.1590/0103-8478cr20200962.

Gal, Roland, Laszlo Deres, Kalman Toth, Robert Halmosi, and Tamas Habon. 2021. "The Effect of Resveratrol on the Cardiovascular System from Molecular Mechanisms to

Clinical Results." *International Journal of Molecular Sciences* 22 (18). https://doi.org/10.3390/ijms221810152.

Gelashvili, N. 1961. "მეღვინეობა [Winemaking]." Georgian Agricultural Institute.

Gelashvili, N.N., and K.M. Jmukhadze. 1970. "Состав Катехинов Винограда Ркацители [Composition of Rkatsiteli Grape Catechins]." *Communications of the Academy of Sciences of the Georgian SSR* 58 (1): 22–23.

Ghafarizadeh, Ali Asghar, Mahdi Malmir, Samira Naderi Noreini, Tayebeh Faraji, and Zeynab Ebrahimi. 2021. "The Effect of Vitamin E on Sperm Motility and Viability in Asthenoteratozoospermic Men: In Vitro Study." *Andrologia* 53 (1): 1–6. https://doi.org/10.1111/and.13891.

Giashvili, M.D. 1979. "Исследование Технологических Процессов и Разработка Способа Приготовления Ординарного Столового Вина Кахетинского Типа [Research of Technological Processes and Development of a Method for Preparing Ordinary Table Wine of the Kakhetian Type]." Yalta.

Gill, Sarvajeet Singh, and Narendra Tuteja. 2010. "Reactive Oxygen Species and Antioxidant Machinery in Abiotic Stress Tolerance in Crop Plants." *Plant Physiology and Biochemistry* 48 (12): 909–30. https://doi.org/10.1016/j.plaphy.2010.08.016.

Glampedaki, Pelagia, and Victoria Dutschk. 2014. "Stability Studies of Cosmetic Emulsions Prepared from Natural Products Such as Wine, Grape Seed Oil and Mastic Resin." *Colloids and Surfaces A: Physicochemical and Engineering Aspects* 460: 306–11. https://doi.org/10.1016/j.colsurfa.2014.02.048.

Goloshvili, Tamar, Maia Akhalkatsi, and Gulnara Badridze. 2018. "Characterization of Grape Seed Extracts of Native to Georgia Varieties of Vitis Vinifera L." *Pakistan Journal of Botany* 50 (1): 245–50.

Goloshvili, Tamar, Maia Akhalkatsi, Gulnara Badridze, and Zaal Kikvidze. 2021. "Tocopherol Contents and Antioxidant Activity in Grape Pomace after Fermentation and Alcohol Distillation." *Cellular and Molecular Biology* 67 (1): 112–15. https://doi.org/10.14715/cmb/2021.67.1.17.

Gómez-Brandón, María, Marta Lores, Heribert Insam, and Jorge Domínguez. 2019. "Strategies for Recycling and Valorization of Grape Marc." *Critical Reviews in Biotechnology* 39 (4): 437–50. https://doi.org/10.1080/07388551.2018.1555514.

Gorgodze, Gizo. 2013. "ყურძნის წიპწის ექსტრაქტოვანი ზეთის სამრეწველო წარმოების პროცესულ – აპარატურული დამუშავება [Process-Hardware Processing of Industrial Production of Grape Seed Extract Oil]." Georgian Technical University.

Guaita, Massimo, and Antonella Bosso. 2019. "Polyphenolic Characterization of Grape Skins and Seeds of Four Italian Red Cultivars at Harvest and after Fermentative Maceration." *Foods* 8 (9). https://doi.org/10.3390/foods8090395.

Gurger, Murat, Erhan Yilmaz, Seval Yilmaz, Gokhan Once, Mustafa Konuk, Emre Kaya, Yakup Say, Gokhan Artas, and Hakan Artas. 2019. "Grape Seed Extract Supplement Increases Bone Callus Formation and Mechanical Strength: An Animal Study." *Journal of Orthopaedic Surgery and Research* 14 (1): 1–10. https://doi.org/10.1186/s13018-019-1251-5.

Hamza, Alaaeldin Ahmed, Gehan Hussein Heeba, Hanan Mohamed Elwy, Chandraprabha Murali, Raafat El-Awady, and Amr Amin. 2018. "Molecular Characterization of the Grape Seeds Extract's Effect against Chemically Induced Liver Cancer: In Vivo and in Vitro Analyses." *Scientific Reports* 8 (1): 1–16. https://doi.org/10.1038/s41598-018-19492-x.

Han, Ji, Chunyang Zhao, Jiayi Cai, and Yu Liang. 2020. "Comparative Efficacy of Vitamin Supplements on Prevention of Major Cardiovascular Disease: Systematic Review with Network Meta-Analysis." *Complementary Therapies in Clinical Practice* 39 (155): 101142. https://doi.org/10.1016/j.ctcp.2020.101142.

Harbeoui, H., A. Hichami, W. Aidi Wannes, J. Lemput, M. Saidani Tounsi, and N. A. Khan. 2019. "Anti-Inflammatory Effect of Grape (Vitis Vinifera L.) Seed Extract through the Downregulation of NF-KB and MAPK Pathways in LPS-Induced RAW264.7 Macrophages." *South African Journal of Botany* 125: 1–8. https://doi.org/10.1016/j.sajb.2019.06.026.

Hasona, Nabil, and Abdullah Morsi. 2019. "Grape Seed Extract Alleviates Dexamethasone-

Induced Hyperlipidemia, Lipid Peroxidation, and Hematological Alteration in Rats." *Indian Journal of Clinical Biochemistry* 34 (2): 213–18. https://doi.org/10.1007/s12291-018-0736-z.

Hemmati, Ali A., Nasrin Aghel, Iran Rashidi, and Ali Gholampur-Aghdami. 2011. "Topical Grape (Vitis Vinifera) Seed Extract Promotes Repair of Full Thickness Wound in Rabbit." *International Wound Journal* 8 (5): 514–20. https://doi.org/10.1111/j.1742-481X.2011.00833.x.

Hemmati, Ali Asghar, Maryam Foroozan, Gholamreza Houshmand, Zahra Beigom Moosavi, Mohammad Bahadoram, and Maram Nader Shakiba. 2015. "The Topical Effect of Grape Seed Extract 2% Cream on Surgery Wound Healing." *Global Journal of Health Science* 7 (3): 52–58. https://doi.org/10.5539/gjhs.v7n3p52.

Hernández, Ingrid, Osmany Chacón, Raisa Rodriguez, Roxana Portieles, Yunior López, Merardo Pujol, and Orlando Borrás-Hidalgo. 2009. "Black Shank Resistant Tobacco by Silencing of Glutathione S-Transferase." *Biochemical and Biophysical Research Communications* 387 (2): 300–304. https://doi.org/10.1016/j.bbrc.2009.07.003.

Huber, Kristen L., José R. Fernández, Corey Webb, Karl Rouzard, Jason Healy, Masanori Tamura, Jeffry B. Stock, Maxwell Stock, and Eduardo Pérez. 2021. "Agse: A Novel Grape Seed Extract Enriched for Pp2a Activating Flavonoids That Combats Oxidative Stress and Promotes Skin Health." *Molecules* 26 (21). https://doi.org/10.3390/molecules26216351.

Ianiro, Gianluca, Herbert Tilg, and Antonio Gasbarrini. 2016. "Antibiotics as Deep Modulators of Gut Microbiota: Between Good and Evil." *Gut* 65 (11): 1906–15. https://doi.org/10.1136/gutjnl-2016-312297.

Ibrahim, Mahrous A., Hussein M. Ibrahim, Alaa A. Mohamed, and Hany G. Tammam. 2020. "Vitamin E Supplementation Ameliorates the Hepatotoxicity Induced by Tramadol: Toxicological, Histological and Immunohistochemical Study." *Toxicology Mechanisms and Methods* 30 (3): 177–88. https://doi.org/10.1080/15376516.2019.1681043.

Imazio, Serena, David Maghradze, Gabriella de Lorenzis, Roberto Bacilieri, Valérie Laucou, Patrice This, Attilio Scienza, and Osvaldo Failla. 2013. "From the Cradle of Grapevine

Domestication: Molecular Overview and Description of Georgian Grapevine (Vitis Vinifera L.) Germplasm." *Tree Genetics and Genomes* 9 (3): 641–58. https://doi.org/10.1007/s11295-013-0597-9.

Ishikawa, Makoto, Kenshi Maki, Iwan Tofani, Kyoko Kimura, and Mitsutaka Kimura. 2005. "Grape Seed Proanthocyanidins Extract Promotes Bone Formation in Rat's Mandibular Condyle." *European Journal of Oral Sciences* 113 (1): 47–52. https://doi.org/10.1111/j.1600-0722.2004.00176.x.

Javakhishvili, Ivane. 1934. *საქართველოს ეკონომიკური ისტორი [Economic History of Georgia]*. 2nd ed. Tbilisi: Kartuli Tsigni.

Jhun, Joo Yeon, Su Jin Moon, Bo Young Yoon, Jae Kyung Byun, Eun Kyung Kim, Eun Ji Yang, Ji Hyeon Ju, et al. 2013. "Grape Seed Proanthocyanidin Extract-Mediated Regulation of STAT3 Proteins Contributes to Treg Differentiation and Attenuates Inflammation in a Murine Model of Obesity-Associated Arthritis." *PLoS ONE* 8 (11). https://doi.org/10.1371/journal.pone.0078843.

Jockers, David. 2013. "Health Benefits of Grape Seed Extract." 2013. http://www.naturalnews.com/042417_grape_seed_extract_health_benefits_antioxid ants.html#.

Joshi, Snehal S., Xiaowei Su, and Doris H. D'Souza. 2015. "Antiviral Effects of Grape Seed Extract against Feline Calicivirus, Murine Norovirus, and Hepatitis A Virus in Model Food Systems and under Gastric Conditions." *Food Microbiology* 52: 1–10. https://doi.org/10.1016/j.fm.2015.05.011.

Kadri, Safwen, Mohamed El Ayed, Pascal Cosette, Thierry Jouenne, Salem Elkhaoui, Sami Zekri, Ferid Limam, Ezzedine Aouani, and Meherzia Mokni. 2019. "Neuroprotective Effect of Grape Seed Extract on Brain Ischemia: A Proteomic Approach." *Metabolic Brain Disease* 34 (3): 889–907. https://doi.org/10.1007/s11011-019-00396-2.

Kakhidze, Amiran, and Nugzar Surmanidze. 2013. *სოფელ ჩაისუბნის "შუამთის" გორანამოსახლარის არქეოლოგიური დაზვერვის შედეგები [Archaeological Excavations of the Hill Settlement of "Shuamta" in the Village of Chaisubani]*. Batumi: Ministry of Education, Culture and Sports of the Autonomous Republic of Adjara, Ajara

Cultural Heritage Protection Agency.

Kamimura, A., T. Takahashi, M. Morohashi, and Y. Takano. 2006. "Procyanidin Oligomers Counteract TGF-B1- and TGF-B2-Induced Apoptosis in Hair Epithelial Cells: An Insight into Their Mechanisms." *Skin Pharmacology and Physiology* 19 (5): 259–65. https://doi.org/10.1159/000093981.

Kamimura, Ayako, and Tomoya Takashashi. 2002. "Procyanidin B-3, Isolated from Barley and Identified as a Hair-Growth Stimulant, Has the Potential to Counteract Inhibitory Regulation by TGF-B1." *Experimental Dermatology* 11 (6): 532–41. https://doi.org/10.1034/j.1600-0625.2002.110606.x.

Kamitani, Yoshiyuki, K. Maki, I. Tofani, Y. Nishikawa, K. Tsukamoto, and M. Kimura. 2004. "Effects of Grape Seed Proanthocyanidins Extract on Mandibles in Developing Rats." *Oral Diseases* 10 (1): 27–31. https://doi.org/10.1046/j.1354-523X.2003.00977.x.

Karrer, Von P, and Rose Widmer. 1927. "Untersuchungen Über Pflanzenfarbstoffe I. Über Die Konstitution Einiger Anthocyanidine. Teilweise Mitbearbeitet von H. Hürlimann Und O. Nievergelt." *Helvetica Chimica Acta* 10 (11): 5–33. https://doi.org/10.1002/hlca.19270100102.

Katiyar, Santosh K. 2008. "Grape Seed Proanthocyanidines and Skin Cancer Prevention: Inhibition of Oxidative Stress and Protection of Immune System." *Molecular Nutrition and Food Research* 52 (SUPPL. 1): 71–76. https://doi.org/10.1002/mnfr.200700198.

———. 2015. "Proanthocyanidins from Grape Seeds Inhibit UV-Radiation-Induced Immune Suppression in Mice: Detection and Analysis of Molecular and Cellular Targets." *Photochemistry and Photobiology* 91 (1): 156–62. https://doi.org/10.1111/php.12330.

———. 2016. "Dietary Proanthocyanidins Inhibit UV Radiation-Induced Skin Tumor Development through Functional Activation of the Immune System." *Molecular Nutrition & Food Research* 60 (6): 1374–82. https://doi.org/10.1002/mnfr.201501026.

Kaur, Manjinder, Rana P. Singh, Mallikarjuna Gu, Rajesh Agarwal, and Chapla Agarwal. 2006. "Grape Seed Extract Inhibits in Vitro and in Vivo Growth of Human Colorectal Carcinoma Cells." *Clinical Cancer Research* 12 (20 PART 1): 6194–6202.

https://doi.org/10.1158/1078-0432.CCR-06-1465.

Ketskhoveli, N., M. Ramishvili, and D. Tabidze. 1960. *საქართველოს ამპელოგრაფია [Ampelography of Georgia]*. Tbilisi: Exclusive Print Plus.

Khorshidi, Fatemeh, Anne Poljak, Yue Liu, Jessica W. Lo, John D. Crawford, and Perminder Singh Sachdev. 2021. "Resveratrol: A 'Miracle' Drug in Neuropsychiatry or a Cognitive Enhancer for Mice Only? A Systematic Review and Meta-Analysis." *Ageing Research Reviews* 65: 101199. https://doi.org/10.1016/j.arr.2020.101199.

Kijima, Ikuko, Sheryl Phung, Gene Hur, Sum Ling Kwok, and Shiuan Chen. 2006. "Grape Seed Extract Is an Aromatase Inhibitor and a Suppressor of Aromatase Expression." *Cancer Research* 66 (11): 5960–67. https://doi.org/10.1158/0008-5472.CAN-06-0053.

Kikvidze, Zaal. 2020a. *Ethnobiology of Georgia*. Tbilisi: Ilia Sttae University. https://www.dropbox.com/s/1v71vyc9oa29lbg/Dakabadonebuli_EBG_Rustaveli_ZK.pdf?dl=0&fbclid=IwAR1qW-KZOcRgaSyJcqkDLhR7kWlT4IKpE4nQ_aagcr3zO9CuxeiZp-CTRAs.

———. 2020b. *Traditional Ecological Knowledge in Georgia: A Short History of the Caucasus (1st Ed.)*. Routledge. https://doi.org/10.4324/9781003131533.

Kim, Helen, Patti Hall, Michelle Smith, Marion Kirk, Jeevan K. Prasain, Stephen Barnes, and Clinton Grubbs. 2004. "Chemoprevention by Grape Seed Extract and Genistein in Carcinogen-Induced Mammary Cancer in Rats Is Diet Dependent." *Journal of Nutrition* 134 (12 SUPPL.): 3445–52. https://doi.org/10.1093/jn/134.12.3445s.

Knudtson, Jennifer F., Fangbai Sun, R. Matthew Coward, Karl R. Hansen, Kurt T. Barnhart, James Smith, Richard S. Legro, et al. 2021. "The Relationship of Plasma Antioxidant Levels to Semen Parameters: The Males, Antioxidants, and Infertility (MOXI) Randomized Clinical Trial." *Journal of Assisted Reproduction and Genetics* 38 (11): 3005–13. https://doi.org/10.1007/s10815-021-02301-2.

Kojima, K, K Maki, I Tofani, Y Kamitani, and M Kimura. 2004. "Effects of Grape Seed Proanthocyanidins Extract on Rat Mandibular Condyle" 4 (2): 301–7.

Kolenati, F.A. 1846. *Versuch Einer Systematischen Anordnung Der in Grusien*

Einheimischen Reben, Nebst Eimen Oekonomisch-Technischen Anhange. Bulletin de La Societe Imperiale Des Naturalistes de Moscou. Moscou.

Koleva, Irina I., Teris A. Van Beek, Jozef P.H. Linssen, Aede De Groot, and Lyuba N. Evstatieva. 2002. "Screening of Plant Extracts for Antioxidant Activity: A Comparative Study on Three Testing Methods." *Phytochemical Analysis* 13 (1): 8–17. https://doi.org/10.1002/pca.611.

Kolupaev, U. E., and U. V. Karpets. 2010. "Участие Растворимых Углеводов И Низкомолекулярных Соединений Азота В Адаптивных Реакциях Растений [Participation of Soluble Carbohydrates and Low Molecular Weight Nitrogen Compounds in Adaptive Plant Reactions]." *Bulletin of Kharkiv National Agrarian University.* 2 (20): 36–53.

Kong, Fan Ting, Chen Xi He, Fan Lei Kong, Su Fen Han, Xiang Shun Kong, Wei Qiang Han, and Li Xian Yang. 2021. "Grape Seed Procyanidins Inhibit the Growth of Breast Cancer MCF-7 Cells by Down-Regulating the EGFR/VEGF/MMP9 Pathway." *Natural Product Communications* 16 (2). https://doi.org/10.1177/1934578X21991691.

Kopa, Z, M Keszthelyi, and N Sofikitis. 2021. "Administration of Antioxidants in the Infertile Male: When It May Have a Beneficial Effect?" *Curr Pharm Des.* 27 (23): 2665–68. https://doi.org/10.2174/1381612826666200303115552.

Krautkramer, Kimberly A., Jing Fan, and Fredrik Bäckhed. 2021. "Gut Microbial Metabolites as Multi-Kingdom Intermediates." *Nature Reviews Microbiology* 19 (2): 77–94. https://doi.org/10.1038/s41579-020-0438-4.

Kroon, Paul, and Gary Williamson. 2005. "Polyphenols: Dietary Components with Established Benefits to Health?" *Journal of the Science of Food and Agriculture* 85 (8): 1239–40. https://doi.org/10.1002/jsfa.2204.

Kudrin, I. K., V. L. Bihunov, and E. A. Tsimberg. 1991. "Влияни Дисперсного Диоксида Кремния На Рост Дрожжей [Effect of Dispersed Silicon Dioxide on Yeast Growth]." *Journal of Microbiology* 2.

Kumar, Pradeep, Dipendra K. Mahato, Madhu Kamle, Tapan K. Mohanta, and Sang G. Kang.

2017. “Aflatoxins: A Global Concern for Food Safety, Human Health and Their Management.” *Frontiers in Microbiology* 7 (JAN): 1–10. https://doi.org/10.3389/fmicb.2016.02170.

Kuznetsov, V.V., and N.I. Shevyakova. 1999. “Proline under Stress: Biological Role, Metabolism, and Regulation.” *Russian Journal of Plant Physiology* 46 (2): 247–87.

Kvlividze, D.G., and M.G. Bezhuashvili. 2005. “Исследование Антоцианов Винограда Сорта Саперави и Приготовленных Из Него Столовых Сухих Виноматериалов По Месту Их Происхождения [Research of the Anthocyanins of the Saperavi Grape Variety and of Prepared Still Dry Wine Materials by Their Place of Origin.” *Магарач. Виноградарство и Виноделие [Magarach. Viticulture and Winemaking]* 1: 25–27.

La Iglesia, Rocío De, Fermín I. Milagro, Javier Campión, Noemí Boqué, and J. Alfredo Martínez. 2010. “Healthy Properties of Proanthocyanidins.” *BioFactors* 36 (3): 159–68. https://doi.org/10.1002/biof.79.

Lédée-Bataille, N., F. Olivennes, J. L. Lefaix, G. Chaouat, R. Frydman, and S. Delanian. 2002. “Combined Treatment by Pentoxifylline and Tocopherol for Recipient Women with a Thin Endometrium Enrolled in an Oocyte Donation Programme.” *Human Reproduction* 17 (5): 1249–53. https://doi.org/10.1093/humrep/17.5.1249.

Lee, Hui Cheng, Andrew M. Jenner, Chin Seng Low, and Yuan Kun Lee. 2006. “Effect of Tea Phenolics and Their Aromatic Fecal Bacterial Metabolites on Intestinal Microbiota.” *Research in Microbiology* 157 (9): 876–84. https://doi.org/10.1016/j.resmic.2006.07.004.

Liao, Min Tser, Chia Chao Wu, Shu Fang Vivienne Wu, Mei Chen Lee, Wan Chung Hu, Kuo Wang Tsai, Chung Hsiang Yang, Chien Lin Lu, Sheng Kang Chiu, and Kuo Cheng Lu. 2021. “Resveratrol as an Adjunctive Therapy for Excessive Oxidative Stress in Aging Covid-19 Patients.” *Antioxidants* 10 (9): 1–33. https://doi.org/10.3390/antiox10091440.

Liu, Wenwen, Changshui Xu, Xi Sun, Haibin Kuang, Xiaodong Kuang, Weiying Zou, Bei Yang, et al. 2015. “Grape Seed Proanthocyanidin Extract Protects against Perfluorooctanoic Acid-Induced Hepatotoxicity by Attenuating Inflammatory Response, Oxidative Stress and Apoptosis in Mice.” *Toxicology Research* 5 (1): 224–34. https://doi.org/10.1039/c5tx00260e.

Liu, Yanqin, Tara L. Pukala, Ian F. Musgrave, Danielle M. Williams, Francis C. Dehle, and John A. Carver. 2013. “Gallic Acid Is the Major Component of Grape Seed Extract That Inhibits Amyloid Fibril Formation.” *Bioorganic and Medicinal Chemistry Letters* 23 (23): 6336–40. https://doi.org/10.1016/j.bmcl.2013.09.071.

López-Alarcón, Camilo, and Ana Denicola. 2013. “Evaluating the Antioxidant Capacity of Natural Products: A Review on Chemical and Cellular-Based Assays.” *Analytica Chimica Acta* 763 (February): 1–10. https://doi.org/10.1016/J.ACA.2012.11.051.

Løvdal, Trond, Kristine M. Olsen, Rune Slimestad, Michel Verheul, and Cathrine Lillo. 2010. “Synergetic Effects of Nitrogen Depletion, Temperature, and Light on the Content of Phenolic Compounds and Gene Expression in Leaves of Tomato.” *Phytochemistry* 71 (5–6): 605–13. https://doi.org/10.1016/J.PHYTOCHEM.2009.12.014.

Lowry, O. H., N. J. Rosebrough, A. L. Farr, and R. J. Randall. 1951. “Protein Measurement with the Folin Phenol Reagent.” *The Journal of Biological Chemistry* 193 (1): 265–75. https://doi.org/10.1016/s0021-9258(19)52451-6.

Lu, Meng Chun, Mei Due Yang, Ping Chun Li, Hsin Yuan Fang, Hui Ying Huang, Yin Ching Chan, and Da Tian Bau. 2018. “Effect of Oligomeric Proanthocyanidin on the Antioxidant Status and Lung Function of Patients with Chronic Obstructive Pulmonary Disease.” *In Vivo* 32 (4): 753–58. https://doi.org/10.21873/invivo.11304.

Lucarini, Massimo, Alessandra Durazzo, Johannes Kiefer, Antonello Santini, Ginevra Lombardi-Boccia, Eliana B. Souto, Annalisa Romani, et al. 2020. “Grape Seeds: Chromatographic Profile of Fatty Acids and Phenolic Compounds and Qualitative Analysis by FTIR-ATR Spectroscopy.” *Foods* 9 (1). https://doi.org/10.3390/foods9010010.

Luvián-Morales, Julissa, Francisco Omar Varela-Castillo, Laura Flores-Cisneros, Lucely Cetina-Pérez, and Denisse Castro-Eguiluz. 2021. “Functional Foods Modulating Inflammation and Metabolism in Chronic Diseases: A Systematic Review.” *Critical Reviews in Food Science and Nutrition* 0 (0): 1–22. https://doi.org/10.1080/10408398.2021.1875189.

Ma, Zheng Feei, and Hongxia Zhang. 2017. “Phytochemical Constituents, Health Benefits, and Industrial Applications of Grape Seeds: Amini-Review." *Antioxidants* 6 (3): 1–11. https://doi.org/10.3390/antiox6030071.

Mahmoudian-Sani, Mohammad Reza, Ali Saeedi Boroujeni, Ali Khodadadi, Sheyda Houshmandfar, Sima Tahmaseby Gandomkari, and Arash Alghasi. 2022. "Resveratrol; an Inflammasome Inhibitor and a Potential Therapy for Severe Cases of COVID-19." *Immunopathologia Persa* 8 (1): 1–7. https://doi.org/10.34172/ipp.2022.09.

Manca, Maria Letizia, Eleonora Casula, Francesca Marongiu, Gianluigi Bacchetta, Giorgia Sarais, Marco Zaru, Elvira Escribano-Ferrer, et al. 2020. "From Waste to Health: Sustainable Exploitation of Grape Pomace Seed Extract to Manufacture Antioxidant, Regenerative and Prebiotic Nanovesicles within Circular Economy." *Scientific Reports* 10 (1): 1–14. https://doi.org/10.1038/s41598-020-71191-8.

Mansouri, Esrafil, Layasadat Khorsandi, and Amin Abdollahzade Fard. 2015. "Protective Role of Grape Seed Proanthocyanidin Antioxidant Properties on Heart of Streptozotocin-Induced Diabetic Rats." *Veterinary Research Forum : An International Quarterly Journal* 6 (2): 119–11924.

Mao, Jenny T., Bingye Xue, Jane Smoake, Qing Yi Lu, Heesung Park, Susanne M. Henning, Windie Burns, et al. 2016. "MicroRNA-19a/b Mediates Grape Seed Procyanidin Extract-Induced Anti-Neoplastic Effects against Lung Cancer." *Journal of Nutritional Biochemistry* 34: 118–25. https://doi.org/10.1016/j.jnutbio.2016.05.003.

Markowska, Anna, Michał Antoszczak, Janina Markowska, and Adam Huczyński. 2021. "Role of Vitamin E in Selected Malignant Neoplasms in Women." *Nutrition and Cancer* 0 (0): 1–8. https://doi.org/10.1080/01635581.2021.1952626.

Mehrinakhi, Zohre, Ehsan Ahmadifar, Najmeh Sheikhzadeh, Mohsen Shahriari Moghadam, and Mahmoud A.O. Dawood. 2021. "Extract of Grape Seed Enhances the Growth Performance, Humoral and Mucosal Immunity, and Resistance of Common Carp (Cyprinus Carpio) against Aeromonas Hydrophila." *Annals of Animal Science* 21 (1): 217–32. https://doi.org/10.2478/aoas-2020-0049.

Melo, Priscilla Siqueira, Leandro de Oliveira Rodrigues Arrivetti, Severino Matias de Alencar, and Leif H. Skibsted. 2016. "Antioxidative and Prooxidative Effects in Food

Lipids and Synergism with α-Tocopherol of Açaí Seed Extracts and Grape Rachis Extracts." *Food Chemistry* 213: 440–49. https://doi.org/10.1016/j.foodchem.2016.06.101.

Messina, Concetta Maria, Simona Manuguerra, Giuseppe Catalano, Rosaria Arena, Massimo Cocchi, Maria Morghese, Lucia Montenegro, and Andrea Santulli. 2021. "Green Biotechnology for Valorisation of Residual Biomasses in Nutraceutic Sector: Characterization and Extraction of Bioactive Compounds from Grape Pomace and Evaluation of the Protective Effects in Vitro." *Natural Product Research* 35 (2): 331–36. https://doi.org/10.1080/14786419.2019.1619727.

Miltonprabu, Selvaraj, Nazimabashir, and Vaihundam Manoharan. 2016. "Hepatoprotective Effect of Grape Seed Proanthocyanidins on Cadmium-Induced Hepatic Injury in Rats: Possible Involvement of Mitochondrial Dysfunction, Inflammation and Apoptosis." *Toxicology Reports* 3: 63–77. https://doi.org/10.1016/j.toxrep.2015.11.010.

Minamiyama, Yukiko, Shigekazu Takemura, and Hiroshi Ichikawa. 2021. "Food Additive-Induced Oxidative Stress in Rat Male Reproductive Organs and Hippocampus." *Archives of Biochemistry and Biophysics* 701 (February): 108810. https://doi.org/10.1016/j.abb.2021.108810.

Montagut, Gemma, Cinta Bladé, Mayte Blay, Juan Fernández-Larrea, Gerard Pujadas, M. Josepa Salvadó, Lluís Arola, Montserrat Pinent, and Anna Ardévol. 2010. "Effects of a Grapeseed Procyanidin Extract (GSPE) on Insulin Resistance." *Journal of Nutritional Biochemistry* 21 (10): 961–67. https://doi.org/10.1016/j.jnutbio.2009.08.001.

Muhlack, Richard A., Ravichandra Potumarthi, and David W. Jeffery. 2018. "Sustainable Wineries through Waste Valorisation: A Review of Grape Marc Utilisation for Value-Added Products." *Waste Management* 72: 99–118. https://doi.org/10.1016/j.wasman.2017.11.011.

Nuttall, S. L., M. J. Kendall, E. Bombardelli, and P. Morazzoni. 1998. "An Evaluation of the Antioxidant Activity of a Standardized Grape Seed Extract, Leucoselect®." *Journal of Clinical Pharmacy and Therapeutics* 23 (5): 385–89. https://doi.org/10.1046/j.1365-2710.1998.00180.x.

Office of Dietary Supplements of US National Institutes of Health. 2019. "Vitamin E. Fact

Sheet for Health Professionals.” 2019. https://ods.od.nih.gov/factsheets/VitaminE-HealthProfessional/.

Ojo, Oluwatoyin Osinimega, and Olufunso Olabode Olorunsogo. 2021. “Quercetin and Vitamin E Attenuate Diabetes-Induced Testicular Anomaly in Wistar Rats via the Mitochondrial-Mediated Apoptotic Pathway.” *Andrologia* 53 (10): 1–8. https://doi.org/10.1111/and.14185.

Okman, Irem, Selhan Karagöz, Turgay Tay, and Murat Erdem. 2014. “Activated Carbons from Grape Seeds by Chemical Activation with Potassium Carbonate and Potassium Hydroxide.” *Applied Surface Science* 293: 138–42. https://doi.org/10.1016/j.apsusc.2013.12.117.

Olas, Beata, Barbara Wachowicz, Anna Tomczak, Joachim Erler, Anna Stochmal, and Wieslaw Oleszek. 2008. “Comparative Anti-Platelet and Antioxidant Properties of Polyphenol-Rich Extracts from: Berries of Aronia Melanocarpa, Seeds of Grape and Bark of Yucca Schidigera in Vitro.” *Platelets* 19 (1): 70–77. https://doi.org/10.1080/09537100701708506.

Olson, Erik R., Jennifer E. Naugle, Xiaojin Zhang, Joshua A. Bomser, and J. Gary Meszaros. 2005. “Inhibition of Cardiac Fibroblast Proliferation and Myofibroblast Differentiation by Resveratrol.” *American Journal of Physiology - Heart and Circulatory Physiology* 288 (3 57-3): 1131–38. https://doi.org/10.1152/ajpheart.00763.2004.

Ono, Kenjiro, Margaret M. Condron, Lap Ho, Jun Wang, Wei Zhao, Giulio M. Pasinetti, and David B. Teplow. 2008. “Effects of Grape Seed-Derived Polyphenols on Amyloid β-Protein Self-Assembly and Cytotoxicity.” *Journal of Biological Chemistry* 283 (47): 32176–87. https://doi.org/10.1074/jbc.M806154200.

Özcan, M. M., F. Al Juhaimi, M. Gülcü, N. Uslu, and Geçgel. 2017. “Determination of Bioactive Compounds and Mineral Contents of Seedless Parts and Seeds of Grapes.” *South African Journal of Enology and Viticulture* 38 (2): 212–20. https://doi.org/10.21548/38-2-1605.

Paknahad, Z., M. J. Tarrahi, F. Shaghaghi, H. Safinejad, L. Asadi, and Z. Mohebbi-Dehnavi. 2021. “The Role of Micronutrients in Male and Female Fertility: A Review Study.”

Iranian Journal of Obstetrics, Gynecology and Infertility 24 (1): 87–98. https://doi.org/10.22038/ijogi.2021.17997.

Park, Eunyoung, Indika Edirisinghe, Ying Yng Choy, Andrew Waterhouse, and Britt Burton-Freeman. 2016. “Effects of Grape Seed Extract Beverage on Blood Pressure and Metabolic Indices in Individuals with Pre-Hypertension: A Randomised, Double-Blinded, Two-Arm, Parallel, Placebo-Controlled Trial.” *British Journal of Nutrition* 115 (2): 226–38. https://doi.org/10.1017/S0007114515004328.

Park, Jin Sil, Mi Kyung Park, Hye Joa Oh, Yun Ju Woo, Mi Ae Lim, Jong Ho Lee, Ji Hyeon Ju, et al. 2012. “Grape-Seed Proanthocyanidin Extract as Suppressors of Bone Destruction in Inflammatory Autoimmune Arthritis.” *PLoS ONE* 7 (12). https://doi.org/10.1371/journal.pone.0051377.

Park, Mi Kyung, Jin Sil Park, Mi La Cho, Hye Jwa Oh, Yu Jung Heo, Yun Ju Woo, Yang Mi Heo, et al. 2011. “Grape Seed Proanthocyanidin Extract (GSPE) Differentially Regulates Foxp3 + Regulatory and IL-17 + Pathogenic T Cell in Autoimmune Arthritis.” *Immunology Letters* 135 (1–2): 50–58. https://doi.org/10.1016/j.imlet.2010.09.011.

Pasini Deolindo, Carolina Turnes, Pablo Inocêncio Monteiro, Jânio Sousa Santos, Adriano Gomes Cruz, Márcia Cristina da Silva, and Daniel Granato. 2019. “Phenolic-Rich Petit Suisse Cheese Manufactured with Organic Bordeaux Grape Juice, Skin, and Seed Extract: Technological, Sensory, and Functional Properties.” *Lwt* 115 (April): 108493. https://doi.org/10.1016/j.lwt.2019.108493.

Pataki, Tunde, Istvan Bak, Peter Kovacs, Debasis Bagchi, Dipak K. Das, and Arpad Tosaki. 2002. “Grape Seed Proanthocyanidins Improved Cardiac Recovery during Reperfusion after Ischemia in Isolated Rat Hearts.” *American Journal of Clinical Nutrition* 75 (5): 894–99. https://doi.org/10.1093/ajcn/75.5.894.

Pego, Jónatas V., Anne J. Kortstee, Casper Huijser, and Sjef C.M. Smeekens. 2000. “Photosynthesis, Sugars and the Regulation of Gene Expression.” *Journal of Experimental Botany* 51 (SPEC. ISS.): 407–16. https://doi.org/10.1093/jexbot/51.suppl_1.407.

Pekur, G.N. 1981. “Совершенствование Технологии Натуральных Игристых и Столовых

Вин На Основе Азотного Обмена Дрожжей [Improving the Technology of Natural Sparkling and Table Wines Based on Yeast Nitrogen Exchange].” Yalta.

Pinna, Christian, Paolo Morazzoni, and Angelo Sala. 2017. “Proanthocyanidins from Vitis Vinifera Inhibit Oxidative Stress-Induced Vascular Impairment in Pulmonary Arteries from Diabetic Rats.” *Phytomedicine* 25: 39–44. https://doi.org/10.1016/j.phymed.2016.12.015.

Plimmer, Aders Robert Henry. 1908. *The Chemical Constitution of the Proteins. Series: Monographs on Biochemistry*. Edited by R.H.A. Plimmer and F.G. Hopkins. Monographs. London: Longmans. https://doi.org/https://doi.org/10.5962/bhl.title.26449.

Poljsak, Borut, Dušan Šuput, and Irina Milisav. 2013. “Achieving the Balance between ROS and Antioxidants: When to Use the Synthetic Antioxidants.” *Oxidative Medicine and Cellular Longevity* 2013. https://doi.org/10.1155/2013/956792.

Praça, Fabíola Garcia, Juliana Santos Rosa Viegas, Hong Yong Peh, Tuane Nardacchione Garbin, Wanessa Silva Garcia Medina, and Maria Vitoria Lopes Badra Bentley. 2020. “Microemulsion Co-Delivering Vitamin A and Vitamin E as a New Platform for Topical Treatment of Acute Skin Inflammation.” *Materials Science and Engineering C* 110 (January): 110639. https://doi.org/10.1016/j.msec.2020.110639.

Priyadarshi, Ruchir, Zohreh Riahi, and Jong Whan Rhim. 2022. “Antioxidant Pectin/Pullulan Edible Coating Incorporated with Vitis Vinifera Grape Seed Extract for Extending the Shelf Life of Peanuts.” *Postharvest Biology and Technology* 183 (September 2021): 111740. https://doi.org/10.1016/j.postharvbio.2021.111740.

Qin, Fuzhong, Deborah A. Siwik, Ivan Luptak, Xiuyun Hou, Lei Wang, Akiko Higuchi, Robert M. Weisbrod, et al. 2012. “The Polyphenols Resveratrol and S17834 Prevent the Structural and Functional Sequelae of Diet-Induced Metabolic Heart Disease in Mice.” *Circulation* 125 (14): 1757–64. https://doi.org/10.1161/CIRCULATIONAHA.111.067801.

Quesada, H., J. M. Del Bas, D. Pajuelo, S. Díaz, J. Fernandez-Larrea, M. Pinent, L. Arola, M. J. Salvadó, and C. Bladé. 2009. “Grape Seed Proanthocyanidins Correct Dyslipidemia Associated with a High-Fat Diet in Rats and Repress Genes Controlling Lipogenesis and VLDL Assembling in Liver.” *International Journal of Obesity* 33 (9): 1007–12.

https://doi.org/10.1038/ijo.2009.136.

Rafique, Misbah, Syed Nisar, Hussain Shah, and Irshad Hussain. 2021. "Development of Grape Seed Extract Based Formulations by Using Non- Invasive Biophysical Technique and Its Impact on Skin Aging Development of Grape Seed Extract Based Formulations by Using Non- Invasive Biophysical Technique and Its Impact on Skin Aging," no. September: 1621–28. https://doi.org/10.36721/PJPS.2021.34.4.SUP.1621-1628.1.

Raina, Komal, Rana P. Singh, Rajesh Agarwal, and Chapla Agarwal. 2007. "Oral Grape Seed Extract Inhibits Prostate Tumor Growth and Progression in TRAMP Mice." *Cancer Research* 67 (12): 5976–82. https://doi.org/10.1158/0008-5472.CAN-07-0295.

Rajput, Shahid Ali, Lvhui Sun, Ni Ya Zhang, Mahmoud Mohamed Khalil, Zhao Ling, Li Chong, Shuai Wang, et al. 2019. "Grape Seed Proanthocyanidin Extract Alleviates Aflatoxinb 1 -Induced Immunotoxicity and Oxidative Stress via Modulation of Nf-Kb and Nrf2 Signaling Pathways in Broilers." *Toxins* 11 (1): 1–15. https://doi.org/10.3390/toxins11010023.

Rajput, Shahid Ali, Lvhui Sun, Niya Zhang, Mahmoud Mohamed Khalil, Xin Gao, Zhao Ling, Luoyi Zhu, Farhan Anwar Khan, Jiacai Zhang, and Desheng Qi. 2017. "Ameliorative Effects of Grape Seed Proanthocyanidin Extract on Growth Performance, Immune Function, Antioxidant Capacity, Biochemical Constituents, Liver Histopathology and Aflatoxin Residues in Broilers Exposed to Aflatoxin B1." *Toxins* 9 (11). https://doi.org/10.3390/toxins9110371.

Rauf, Naveed, Ayesha Nawaz, Hizb Ullah, Rahim Ullah, Ghulam Nabi, Asad Ullah, Fazal Wahab, Sarwat Jahan, and Junfen Fu. 2021. "Therapeutic Effects of Chitosan-Embedded Vitamin C, E Nanoparticles against Cisplatin-Induced Gametogenic and Androgenic Toxicity in Adult Male Rats." *Environmental Science and Pollution Research* 28 (40): 56319–32. https://doi.org/10.1007/s11356-021-14516-y.

Razavi, Seyed Mostafa, Sharareh Gholamin, Ali Eskandari, Nakta Mohsenian, Amir Ghorbanihaghjo, Abbas Delazar, Nadereh Rashtchizadeh, Maryam Keshtkar-Jahromi, and Hassan Argani. 2013. "Red Grape Seed Extract Improves Lipid Profiles and Decreases Oxidized Low-Density Lipoprotein in Patients with Mild Hyperlipidemia."

Journal of Medicinal Food 16 (3): 255–58. https://doi.org/10.1089/jmf.2012.2408.

Renaud, Serge C., René Guéguen, Jean Schenker, and Alphonse D'Houtaud. 1998. "Alcohol and Mortality in Middle-Aged Men from Eastern France." *Epidemiology* 9 (2): 184–88. https://doi.org/10.1097/00001648-199803000-00014.

Ribéreau-Gayon, P., Y. Glories, A. Maujean, and D. Dubourdieu. 2006. "Assessing the Phenol Content of Red and White Wines." In *Handbook of Enology, Vol. 2, The Chemistry of Wine Stabilization and Treatments, 2nd Edition*, 172–73. Chichester: John Wiley and Sons.

Rockenbach, Ismael Ivan, Luciano Valdemiro Gonzaga, Viviane Maria Rizelio, Any Elisa de Souza Schmidt Gonçalves, Maria Inés Genovese, and Roseane Fett. 2011. "Phenolic Compounds and Antioxidant Activity of Seed and Skin Extracts of Red Grape (Vitis Vinifera and Vitis Labrusca) Pomace from Brazilian Winemaking." *Food Research International* 44 (4): 897–901. https://doi.org/10.1016/j.foodres.2011.01.049.

Roy, Heli, and Shanna Lundy. 2005. "Resveratrol." *Pennington Nutrition Series* 7: 12.

Saad, Abir A., Mokhtar I. Youssef, and Lamiaa K. El-Shennawy. 2009. "Cisplatin Induced Damage in Kidney Genomic DNA and Nephrotoxicity in Male Rats: The Protective Effect of Grape Seed Proanthocyanidin Extract." *Food and Chemical Toxicology* 47 (7): 1499–1506. https://doi.org/10.1016/j.fct.2009.03.043.

Saadoune, Zineb, Hassiba Laribi, Yasmine Benali, Amina Brahimi, Rima Bennani, and Djamel El-Hadi. 2021. "Valorization of Algerian Grape Pomace Seeds: Extraction of Bioactive Compounds, Prevention and Treatment of Experimental Inflammatory Bowel Diseases." *Waste and Biomass Valorization* 12 (10): 5401–12. https://doi.org/10.1007/s12649-021-01400-6.

Sadogh, Azita, Narjes Gorji, and Reihaneh Moeini. 2021. "Herbal Foodstuffs in Avicenna's Recommended Diet to Improve Sperm Quality and Increase Male Fertility; An Evidence-Based Approach." *Journal of Complementary and Integrative Medicine* 98 (11): 1–24. https://doi.org/10.1515/jcim-2020-0254.

Salehi, Bahare, S. Vlaisavljevic, Charles Oluwaseun Adetunji, Juliana Bunmi Adetunji, Dorota Kregiel, Hubert Antolak, Ewelina Pawlikowska, et al. 2019. "Plants of the Genus Vitis: Phenolic Compounds, Anticancer Properties and Clinical Relevance." *Trends in Food Science and Technology* 91 (January): 362–79. https://doi.org/10.1016/j.tifs.2019.07.042.

Salem, A.N., and A.E. Salem. 2011. "Renoprotective Effect of Grape Seed Extract against Oxidative Stress Induced by Gentamicin and Hypercholesterolemia in Rats." *Renal Failure* 33 (8): 824–32. https://doi.org/10.3109/0886022X.2011.601832.

Sano, Atsushi, Riichiro Uchida, Makoto Saito, Nobuhiko Shioya, Yoshika Komori, Yasuo Tho, and Naotaka Hashizume. 2007. "Beneficial Effects of Grape Seed Extract on Malondialdehyde-Modified LDL." *Journal of Nutritional Science and Vitaminology* 53 (2): 174–82. https://doi.org/10.3177/jnsv.53.174.

Satyam, S. Mani, L. Kurady Bairy, R. Pirasanthan, and R. Lalit Vaishnav. 2014. "Grape Seed Extract and Zinc Containing Nutritional Food Supplement Prevents Onset and Progression of Age-Related Cataract in Wistar Rats." *Journal of Nutrition, Health and Aging* 18 (5): 524–30. https://doi.org/10.1007/s12603-014-0020-8.

Satyam, Shakta Mani, and KL Bairy. 2013. "Antioxidant Activity of Combination of Grape Seed Extract and Zincovit Tablets (Nutritional Food Supplement) on Free Radical Scavenging in Vitro Models." *Jokull Journal* 63 (5): 360–69.

Savdan, Mervan, Murat Cakir, Husamettin Vatansev, Tevfik Kucukkartallar, Ahmet Tekin, and Sakir Tavli. 2017. "Preventing Oxygen Free Radical Damage by Proanthocyanidin in Obstructive Jaundice." *Turkish Journal of Surgery* 33 (2): 62–68. https://doi.org/10.5152/turkjsurg.2017.3337.

Sergazy, Shynggys, Zarina Shulgau, Galina Fedotovskikh, Laura Chulenbayeva, Ayaulym Nurgozhina, Madiyar Nurgaziyev, Elena Krivyh, et al. 2020. "Cardioprotective Effect of Grape Polyphenol Extract against Doxorubicin Induced Cardiotoxicity." *Scientific Reports* 10 (1): 1–12. https://doi.org/10.1038/s41598-020-71827-9.

Shao, Hong Bo, Li Ye Chu, Zhao Hua Lu, and Cong Min Kang. 2008. "Primary Antioxidant Free Radical Scavenging and Redox Signaling Pathways in Higher Plant Cells." *International Journal of Biological Sciences* 4 (1): 8–14. https://doi.org/10.7150/ijbs.4.8.

Sharma, Som D., and Santosh K. Katiyar. 2010. "Dietary Grape Seed Proanthocyanidins Inhibit UVB-Induced Cyclooxygenase-2 Expression and Other Inflammatory Mediators in UVB-Exposed Skin and Skin Tumors of SKH-1 Hairless Mice." *Pharmaceutical Research* 27 (6): 1092–1102. https://doi.org/10.1007/s11095-010-0050-9.

Sharma, Som D., Syed M. Meeran, and Santosh K. Katiyar. 2007. "Dietary Grape Seed Proanthocyanidins Inhibit UVB-Induced Oxidative Stress and Activation of Mitogen-Activated Protein Kinases and Nuclear Factor-KB Signaling in in Vivo SKH-1 Hairless Mice." *Molecular Cancer Therapeutics* 6 (3): 995–1005. https://doi.org/10.1158/1535-7163.MCT-06-0661.

Shatirishvili, Sh., and I. Maglakelidze. 1998. "ყურძნის გადამუშავების პროდუქტებში ამინომჟავებისა და ფენოლკარბონმჟავების თხევადი ქრომატოგრაფიული განსაზღვრა [Liquid Chromatographic Determination of Amino Acids and Phenolic Acids in Grape Processing Products]." In *Republican Scientific Conference on Current Issues in Agroecology*, 80–81. Tbilisi.

Šikuten, Iva, Petra Štambuk, Željko Andabaka, Ivana Tomaz, Zvjezdana Marković, Domagoj Stupić, Edi Maletić, Jasminka Karoglan Kontić, and Darko Preiner. 2020. "Grapevine as a Rich Source of Polyphenolic Compounds." *Molecules* 25 (23). https://doi.org/10.3390/molecules25235604.

Simoes, Julia Siqueira, Eliane Teixeira Mársico, Maurice R. Marshall, Amarat Simonne, Yavuz Yagiz, Changmou Xu, Wei Yea Hsu, Roberta de Oliveira Resende Ribeiro, and Carlos Adam Conte-Junior. 2019. "Applications of Extracts from Skin and Seed Muscadine Grape (Vitis Rotundifolia Michx.) Waste on Bacterial Growth, Autoxidation, and Color in Atlantic Salmon (Salmo Salar L.)." *Journal of Food Processing and Preservation* 43 (7): 1–10. https://doi.org/10.1111/jfpp.13976.

Singletary, Keith W., and Brandon Meline. 2001. "Effect of Grape Seed Proanthocyanidins on Colon Aberrant Crypts and Breast Tumors in a Rat Dual-Organ Tumor Model." *Nutrition and Cancer* 39 (2): 252–58. https://doi.org/10.1207/S15327914nc392_15.

Singleton, V.L., and P. Esau. 1969. *Phenolic Substances in Grapes and Wine and Their Significance*. New-York: Academic Press.

Singleton, V.L., and J.A. Rossi. 1965. “Colorimetry of Total Phenolics with Phosphomolybdic-Phosphotungstic Acid Reagents.” *American Journal of Enology and Viticulture* 16: 144–58.

Somaatmadja, Dardjo, John J. Powers, and Rebecca Wheeler. 1965. “Restricted AccessAction of Leucoanthocyanins of Cabernet Grapes on Reproduction and Respiration of Certain Bacteria.” *Am J Enol Vitic* January (16): 54–61.

Song, Xiaoyu, Hongde Xu, Yanling Feng, Xiaoman Li, Meina Lin, and Liu Cao. 2012. “Protective Effect of Grape Seed Proanthocyanidins against Liver Ischemic Reperfusion Injury: Particularly in Diet-Induced Obese Mice.” *International Journal of Biological Sciences* 8 (10): 1345–62. https://doi.org/10.7150/ijbs.4699.

Sozen, Erdi, Tugce Demirel-Yalciner, M. Kutay Koroglu, Merve Acikel Elmas, Feriha Ercan, and Nesrin Kartal Ozer. 2021. “High Cholesterol Diet Activates ER Stress Mediated Apoptosis in Testes Tissue: Role of α-Tocopherol.” *IUBMB Life*, no. May: 1–8. https://doi.org/10.1002/iub.2535.

Sturua, Z.Sh., M.A. Bokuchava, G.G. Valuiko, A.N. Sophromadze, and A.I. Siashvili. 1973. “Лейкоантоцианидины Винограда и Вина [Leukoanthocyanidins of Grape and Wine].” *Прикладная Биохимия и Микробиология [Applied Biochemistry and Microbiology]* 9 (1): 94–98.

Sun, Qinru, Ning Jia, Fei Ren, and Xin Li. 2021. “Grape Seed Proanthocyanidins Improves Depression-like Behavior by Alleviating Oxidative Stress and NLRP3 Activation in the Hippocampus of Prenatally-Stressed Female Offspring Rats.” *Journal of Histotechnology* 44 (2): 90–98. https://doi.org/10.1080/01478885.2020.1861907.

Suwannaphet, Wannaporn, Aramsri Meeprom, Sirintorn Yibchok-Anun, and Sirichai Adisakwattana. 2010. “Preventive Effect of Grape Seed Extract against High-Fructose Diet-Induced Insulin Resistance and Oxidative Stress in Rats.” *Food and Chemical Toxicology* 48 (7): 1853–57. https://doi.org/10.1016/j.fct.2010.04.021.

Takahashi, Tomoya, Toshikazu Kamiya, Atsuhiro Hasegawa, and Yoshiharu Yokoo. 1999. “Procyanidin Oligomers Selectively and Intensively Promote Proliferation of Mouse Hair Epithelial Cells In Vitro and Activate Hair Follicle Growth In Vivo.” *Journal of*

Investigative Dermatology 112 (3): 310–16. https://doi.org/10.1046/j.1523-1747.1999.00532.x.

Takahashi, Tomoya, Toshikazu Kamiya, and Yoshiharu Yokoo. 1998. “Proanthocyanidins from Grape Seeds Promote Proliferation of Mouse Hair Follicle Cells in Vitro and Convert Hair Cycle in Vivo.” *Acta Dermato-Venereologica* 78 (6): 428–32. https://doi.org/10.1080/000155598442719.

Tenkumo, Taichi, Alkebaier Aobulikasimu, Yoshinori Asou, Midori Shirato, Shunichi Shishido, Taro Kanno, Yoshimi Niwano, Keiichi Sasaki, and Keisuke Nakamura. 2020. “Proanthocyanidin-Rich Grape Seed Extract Improves Bone Loss, Bone Healing, and Implant Osseointegration in Ovariectomized Animals.” *Scientific Reports* 10 (1): 1–14. https://doi.org/10.1038/s41598-020-65403-4.

Tesarik, Jan, Maribel Galán-Lázaro, and Raquel Mendoza-Tesarik. 2021. “Ovarian Aging: Molecular Mechanisms and Medical Management.” *International Journal of Molecular Sciences* 22 (3): 1–10. https://doi.org/10.3390/ijms22031371.

Todasca, Cristina, Dragos Gudovan, Mihaela Tociu, Roxana Trusca, Adrian Ionut Nicoara, Bogdan Nicolae Manolescu, and Fulvia Manolache. 2020. “Wine Industry Waste Valorisation as Repellent Support.” *Revue Roumaine de Chimie* 65 (1): 69–75. https://doi.org/10.33224/rrch.2020.65.1.07.

Toden, Shusuke, Preethi Ravindranathan, Jinghua Gu, Jacob Cardenas, Madelaine Yuchang, and Ajay Goel. 2018. “Oligomeric Proanthocyanidins (OPCs) Target Cancer Stem-like Cells and Suppress Tumor Organoid Formation in Colorectal Cancer.” *Scientific Reports* 8 (1): 1–13. https://doi.org/10.1038/s41598-018-21478-8.

Traber, MG, and RS Bruno. 2020. “Vitamin E. In BP Marriott, DF Birt, VA Stallings, AA Yates (Eds.).” In *Present Knowledge in Nutrition*, edited by BP Marriott, DF Birt, VA Stallings, and AA Yates, Eleventh E. London: Academic Press (Elsevier).

Tsertsvadze, Nugzar. 1989. *საქართველოს კულტურული ვაზის კლასიფიკაცია [Classification of Georgian Cultural Vines]*. Tbilisi: Sabchota Sakartvelo.

Tsinandali Museum Complex. 2021. “About Us.” 2021.

http://tsinandali.ge/ge/museum/chven-shesaxeb.

Turki, Khaoula, Kamel Charradi, Habib Boukhalfa, Monia Belhaj, Ferid Limam, Ezzedine Aouani, Hemodialysis Unit, Hemodialysis Unit, and Habib Bougatfa Hospital. 2016. "Original Article : GRAPE SEED POWDER IMPROVES RENAL FAILURE OF." *EXCL1 Journal* 15: 424–33.

Turkina, M.V., and S.V. Sokolova. 1971. "Методы Определения Моносахаридов и Олигосахаридов [Methods for the Determination of Monosaccharides and Oligosaccharides]." In *Биохимические Методы в Физиологии Растений [Biochemical Methods in Plant Physiology]*, edited by O. A. Pavlinova, 7–34. Moscow: Nauka.

Vakarchuk, L.T. 1990. *Технология Переработки Винограда [Grape Processing Technology]*. Moscow: Agropromizdat.

Valuiko, G.G. 1973. *Биохимия и Технология Красных Вин [Biochemistry and Technology of Red Wines]*. Moscow: Pishevaja promishlenost.

Vashakidze, L. 2006. "ვაზის ქართული გენოტიპების იდენტიფიკაციისა და ზოგიერთი ფიტოტექნიკური ღონისძიების ოპტიმიზაციის მეცნიერული საფუძვლები [Scientific Basis of Identification of Georgian Vine Genotypes and Optimization of Some Phytotechnical Measures]." Institute of Horticulture, Viticulture and Enology.

Vigna, Giovanni B., Fabrizio Costantini, Giancarlo Aldini, Marina Carini, Alberico Catapano, Fabio Schena, Arianna Tangerini, et al. 2003. "Effect of a Standardized Grape Seed Extract on Low-Density Lipoprotein Susceptibility to Oxidation in Heavy Smokers." *Metabolism: Clinical and Experimental* 52 (10): 1250–57. https://doi.org/10.1016/S0026-0495(03)00192-6.

Walter, Roland B., Theodore M. Brasky, Filippo Milano, and Emily White. 2011. "Vitamin, Mineral, and Specialty Supplements and Risk of Hematologic Malignancies in the Prospective VITamins and Lifestyle (VITAL) Study." *Cancer Epidemiology Biomarkers and Prevention* 20 (10): 2298–2308. https://doi.org/10.1158/1055-9965.EPI-11-0494.

Wang, Hui, Yansong Xue, Hanying Zhang, Yan Huang, Guan Yang, Min Du, and Mei Jun Zhu. 2013. "Dietary Grape Seed Extract Ameliorates Symptoms of Inflammatory Bowel

Disease in IL10-Deficient Mice." *Molecular Nutrition and Food Research* 57 (12): 2253–57. https://doi.org/10.1002/mnfr.201300146.

Wang, Jun, Lap Ho, Wei Zhao, Kenjiro Ono, Clark Rosensweig, Linghong Chen, Nelson Humala, David B. Teplow, and Giulio M. Pasinetti. 2008. "Grape-Derived Polyphenolics Prevent Aβ Oligomerization and Attenuate Cognitive Deterioration in a Mouse Model of Alzheimer's Disease." *Journal of Neuroscience* 28 (25): 6388–92. https://doi.org/10.1523/JNEUROSCI.0364-08.2008.

Wang, Ke, Xibang Chen, Yu Chen, Sunren Sheng, and Zhongsheng Huang. 2020. "Grape Seed Procyanidins Suppress the Apoptosis and Senescence of Chondrocytes and Ameliorates Osteoarthritis: Via the DPP4-Sirt1 Pathway." *Food and Function* 11 (12): 10493–505. https://doi.org/10.1039/d0fo01377c.

Wang, Yan Hong, Xiao Lai Yang, L. Wang, Ming Xia Cui, Yong Qing Cai, Xiao Li Li, and Yong Jie Wu. 2010. "Effects of Proanthocyanidins from Grape Seed on Treatment of Recurrent Ulcerative Colitis in Rats." *Canadian Journal of Physiology and Pharmacology* 88 (9): 888–98. https://doi.org/10.1139/Y10-071.

Weber, Holly A., Andrew E. Hodges, Jill R. Guthrie, Brandon M. O'Brien, David Robaugh, Alice P. Clark, Roger K. Harris, Joseph W. Algaier, and Cynthia S. Smith. 2007. "Comparison of Proanthocyanidins in Commercial Antioxidants: Grape Seed and Pine Bark Extracts." *Journal of Agricultural and Food Chemistry* 55 (1): 148–56. https://doi.org/10.1021/jf063150n.

Willstätter, R., and H. Ernst Zollinger. 1917. "XVI. Über Die Farbstoffe Der Weintraube Und Der Heidelbeere, II." *Justus Liebigs Ann. Chem.* 412: 195–216. https://doi.org/10.1002/jlac.19174120207.

Woo, Yun Ju, Young Bin Joo, Young Ok Jung, Ji Hyeon Ju, Mi la Cho, Hye Jwa Oh, Joo Youn Jhun, et al. 2011. "Grape Seed Proanthocyanidin Extract Ameliorates Monosodium Iodoacetate Induced Osteoarthritis." *Experimental and Molecular Medicine* 43 (10): 561–70. https://doi.org/10.3858/emm.2011.43.10.062.

Wu, Xianli, Gary R. Beecher, Joanne M. Holden, David B. Haytowitz, Susan E. Gebhardt, and Ronald L. Prior. 2004. "Lipophilic and Hydrophilic Antioxidant Capacities of

Common Foods in the United States." *Journal of Agricultural and Food Chemistry* 52 (12): 4026–37. https://doi.org/10.1021/jf049696w.

Xia, Lanlan, Changmou Xu, Kunlun Huang, Jiang Lu, and Yali Zhang. 2019. "Evaluation of Phenolic Compounds, Antioxidant and Antiproliferative Activities of 31 Grape Cultivars with Different Genotypes." *Journal of Food Biochemistry* 43 (6): 1–13. https://doi.org/10.1111/jfbc.12626.

Xu, Meng, Xiaoling Chen, Zhiqing Huang, Daiwen Chen, Mingzhou Li, Jun He, Hong Chen, et al. 2022. "Effects of Dietary Grape Seed Proanthocyanidin Extract Supplementation on Meat Quality, Muscle Fiber Characteristics and Antioxidant Capacity of Finishing Pigs." *Food Chemistry* 367 (March 2021): 130781. https://doi.org/10.1016/j.foodchem.2021.130781.

Xue, Bingye, Qing Yi Lu, Larry Massie, Clifford Qualls, and Jenny T. Mao. 2018. "Grape Seed Procyanidin Extract against Lung Cancer: The Role of Microrna-106b, Bioavailability, and Bioactivity." *Oncotarget* 9 (21): 15579–90. https://doi.org/10.18632/oncotarget.24528.

Yahara, N, I Tofani, K Maki, K Kojima, Y Kojima, and M Kimura. 2005. "Mechanical Assessment of Effects of Grape Seed Proanthocyanidins Extract on Tibial Bone Diaphysis in Rats" 5 (2): 162–69.

Yamakoshi, Jun, Shigehiro Kataoka, Takuro Koga, and Toshiaki Ariga. 1999. "Proanthocyanidin-Rich Extract from Grape Seeds Attenuates the Development of Aortic Atherosclerosis in Cholesterol-Fed Rabbits." *Atherosclerosis* 142: 139–49.

Yamakoshi, Jun, Atsushi Sano, Shoichi Tokutake, Makoto Saito, Mamoru Kikuchi, Yoshiro Kubota, Yasuhiro Kawachi, and Fujio Otsuka. 2004. "Oral Intake of Proanthocyanidin-Rich Extract from Grape Seeds Improves Chloasma." *Phytotherapy Research* 18 (11): 895–99. https://doi.org/10.1002/ptr.1537.

Yang, Guan, Hui Wang, Yifei Kang, and Mei Jun Zhu. 2014. "Grape Seed Extract Improves Epithelial Structure and Suppresses Inflammation in Ileum of IL-10-Deficient Mice." *Food and Function* 5 (10): 2558–63. https://doi.org/10.1039/c4fo00451e.

Yang, Jun, and Yang Yu Xiao. 2013. "Grape Phytochemicals and Associated Health Benefits." *Critical Reviews in Food Science and Nutrition* 53 (11): 1202–25. https://doi.org/10.1080/10408398.2012.692408.

Yonguc, Goksin Nilufer, Yavuz Dodurga, Esat Adiguzel, Gulsah Gundogdu, Vural Kucukatay, Seda Ozbal, Ismail Yilmaz, Ulker Cankurt, Yusuf Yilmaz, and Ilgaz Akdogan. 2015. "Grape Seed Extract Has Superior Beneficial Effects than Vitamin E on Oxidative Stress and Apoptosis in the Hippocampus of Streptozotocin Induced Diabetic Rats." *Gene* 555 (2): 119–26. https://doi.org/10.1016/j.gene.2014.10.052.

Yu, Zhen-Qi, Lan-Min Wang, and Wan-Xi Yang. 2022. "How Vitamin E and Its Derivatives Regulate Tumour Cells via the MAPK Signalling Pathway?'." *Gene* 808 (January): 145998. https://doi.org/10.1016/J.GENE.2021.145998.

Zhang, Yunjian, Hanping Shi, Wenjian Wang, Zunfu Ke, Ping Xu, Zhiqiang Zhong, Xiaoxi Li, and Shenming Wang. 2011. "Antithrombotic Effect of Grape Seed Proanthocyanidins Extract in a Rat Model of Deep Vein Thrombosis." *Journal of Vascular Surgery* 53 (3): 743–53. https://doi.org/10.1016/j.jvs.2010.09.017.

Zhu, Fengmei, Bin Du, Lihong Zheng, and Jun Li. 2015. "Advance on the Bioactivity and Potential Applications of Dietary Fibre from Grape Pomace." *Food Chemistry* 186: 207–12. https://doi.org/10.1016/j.foodchem.2014.07.057.

Zou, Lei Xin, Chen Chen, Xiao Yan, Qiu Yue Lin, Jiao Fang, Pang Bo Li, Xiao Han, et al. 2019. "Resveratrol Attenuates Pressure Overload-Induced Cardiac Fibrosis and Diastolic Dysfunction via PTEN/AKT/Smad2/3 and NF-KB Signaling Pathways." *Molecular Nutrition and Food Research* 63 (24): 1–12. https://doi.org/10.1002/mnfr.201900418.