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Winery-Derived By-Products: Valorization and Potential

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Abstract

The food industry always generates solid wastes as well as high volumes of effluents, the handling of which constitutes a considerable challenge. Currently, efforts are focused on the optimization of food processing technology, trying to minimize the by-products and waste that are generated. The use of the by-products also known as by-product valorization is a crucial subject nowadays that not only confers added value to the waste products but also allows food companies to have a sustainable development.

In the present chapter, we describe the wine industry, the main by-products and the waste that are produced, the handling of them and the possible uses they may have. In fact, waste from food industry constitutes a vast resource of a myriad of bioactive compounds. Furthermore, the use of them can in turn reduce the environmental impact derived from the accumulation of such compounds. Particularly, we focus in polyphenols from grape and in the beneficial properties they have. Furthermore, we describe how these phenolic compounds interact with proteins related to neurodegenerative diseases such as acetylcholinesterase and α-synuclein.

Keywords: winery byproducts, winemaking wastes, valorization, reutilization, polyphenols, neurodegenerative diseases

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1. INTRODUCTION

Grape (*Vitis vinifera*) is one of the main cultivated crops worldwide. In fact, around 60 to 70 million tons of grapes are produced every year. Approximately, half of the global production is used for winemaking, but this percentage varies among countries. For instance, China, which has the largest cultivated surface and is currently the biggest producer of grapes, only uses a small fraction for wine. Indeed. The vast majority of grapes are consumed as fresh fruit or juice in China. An even more pronounced use of grapes as fresh fruits is observed in Egypt and India, where almost none of the production is dedicated for wine. On the contrary, traditional wine producers as France, Italy and Spain have almost all the grapes dedicated to wine. The same trend is observed in Argentina, Australia and to a lesser extent South Africa. Chile and USA are important grape crop producers that have a more even distribution, with half of grapes committed to wine making and the rest for fresh and dried fruit consumption [1].

The global annual production of wines is calculated to be roughly 250 million of hectoliters, which implies that an enormous amount of waste and by-products are produced. The generation of these sub-products can be summarized as follows: a) grapes are harvested, destemmed and crushed. After that the proper wine elaboration starts and differs based on the type of wine is being produced. If red wine is elaborated, a maceration followed by alcoholic fermentation takes place before the pressing and racking of the material. A second fermentation is followed, the so-called malolactic fermentation. Then, there is a aging period before the last stages. On the other hand, for white wine production, grapes are pressed first, clarified and then the alcoholic fermentation is allowed avoiding the maceration, racking and aging steps. Once the malolactic fermentation begins, both wines are handled in a similar way. Indeed, they are clarified, stabilized by reducing tartaric salts, filtered and bottled. Important by-products are produced in each of these steps [2].

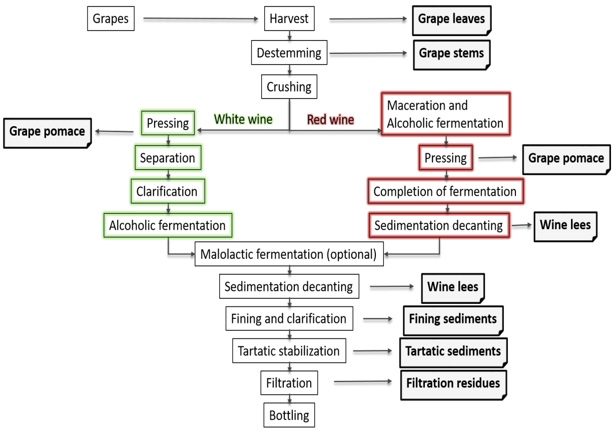
The first waste related to vineyards that should be mentioned is the pruning waste. This is estimated to be at least 1 oven dry ton of residual biomass per hectare [3, 4]. Even though most of it is just used for mulching into the vineyard or burnt on-site, there is a growing interest in using the pruning waste as a bioenergy source [5]. Moreover, grape pruning waste can be used as a source of biosurfactants, sugars and derivatives such as lactic acid [6].

The first residue generated during the elaboration of wine itself is the grape stem that is accumulated during the de-stemming step. As described above, the pressing of the material depends on the type of wine. This step can be placed before the alcoholic fermentation or after the yeast-driven fermentation for white and red wine, respectively. Pressing gives rise of the grape pomace also known as grape marc. Wine lees are produced after the racking stages, i.e. twice during the red wine elaboration and just once during white wine making. The final steps for wine involves the fining and clarification process, which typically leaves residues known as fining sediments. Then the wine is stabilized, i.e. tartaric salts that are in excess are removed by refrigeration or other strategies, which leads to the production of tartrate sediments. Finally, the filtration of the product let collect filtration residues [7]. In every step mentioned, wastewaters are generated and may contain grape pulp leftovers, skin and seeds and a number of compounds that have been used for filtration, precipitation and cleaning [8]. Wine lees and pomace, are considered by-products according to the European Council Regulation (EC) N° 479/2008 on the common organization of the market in wine (EC, 2008). Therefore, they have to be used as substrates in distilleries in order to get alcohol and tartrates. After distillation, vinasse and once again more winery wastewater are left as liquid wastes. Also, a solid residue known as exhausted marc is produced. The aerobic depuration of vinasse and wastewaters gives rise to another solid waste, the winery sludge.

The liquid and solid wastes generated in the wineries and distilleries typically have acidic pH, a high organic content, mostly composed of polyphenols. Several ions such as sodium, potassium, phosphorous and even heavy metals [9]. Even though they are not considered toxic to humans per se, they do display phytotoxic effects, and they certainly may have an important impact to the environment mainly because the organic content. Therefore, different strategies have been developed in order to reduce the potential deleterious effect on the environment and also to recycle these waste products. Indeed, alcohol, tartrates and polyphenols constitute by-products of the upmost importance because they have many applications as we are going to discuss in detail.

2. EXPERIMENTAL SETUP, RESULTS AND DISCUSSION.

Fig. 1. The winemaking global process and the generation of the main by-products.



2. WINERY RESIDUES AND BY-PRODUCTS

Currently there is a wide diversity of winemaking processes, from industrial procedures to many artisanal practices which still follow ancestral traditions. Despite that, the vinification process could be summarizing as it can be seen in scheme (Fig. 1). The type and physico-chemical properties of final residues depend on what specific technique was employed to produce the wine. The major by-products could be classified into solid and liquid residues. Among the solids, the grape marc is the most abundant waste product. It consists of grape pomace, containing skin, seeds, pulp and stalks, that remain after pressing the grapes.

2.1. Grape Pomace

Grape pomace (GP) is the most abundant by-product of winemaking. Actually, approximately 20-30% (w/w) of the total grapes production destined to winemaking ends up as this organic residue, which represents about 9 million tons generated per year in the world.

The variability produced by grape varieties, agricultural conditions of growth and different winemaking employed processes explains the variations in GP composition [10–12]. Besides, it is important to take into account that GP derived from red wine has been fermented and differs from GP derived from white and rosé wine, which have been removed before alcoholic fermentation, so they contain fermentable sugars.

Concerning the general composition of grape pomace, the water content varies from 50% to 72% depending on the grape variety, ripening state and the crushing pressure employed.

This material is a lignocellulosic complex with a lignin content ranging from 17% to 24% and protein content lower than 4%. In general, pectic substances are the main polysaccharide constituent of the cell walls present in grape pomaces, ranging from 37% to 54%. Cellulose is the second one in abundance in grape pomaces, varying from 27% to 37% [13–15]. The protein and phenols contained in this material represent a valuable organic source if they are released from the lignin-carbohydrate clusters to which they are linked. The release could be achieved by several treatments. On the one hand, GP should be submitted to additional fermentation processes in order to be used as a feed additive and avoid gastrointestinal disturbances. Another way proposed by Jin *et al*. is to treat GP with fungi of *Aspergillus, Rhizopus* and *Trichoderma* sp genera [16]. This treatment has proved not only to enhance the digestibility but also the protein content. GP is an attractive component for feed matrix since it has been found to improve sensory abilities and enhance the metabolism of livestock. Besides, there is a growing market for feed additive since the livestock production has been expanded the last years, especially in developing countries.

The hydrolyzate obtained from GP contains a mixture of xylose and glucose, which in turn, could be converted into lactic acid by different microorganisms. *Lactobacillus pentosus* and *L. rhamnosus* have proven to produce biosurfactants simultaneously with lactic acid [15, 17, 18]. Gallander and Peng (1980) found that grapes contain huge amounts of palmitic, stearic, arachidic, linoleic and linolenic acids, which may be inducers for the production of biosurfactants in lactic acid fermentation media. [19]. In another study, Portilla *et al.* (2008b) observed that biosurfactants produced by *L. pentosus* not only reduce the surface tension, but also have emulsifying properties that may facilitate the bioremediation of hydrocarbon-contaminated sites. These biosurfactants demonstrated high capacity to stabilize kerosene/water emulsions, in comparison with sodium dodecyl sulfate, SDS, or surfactin, a commercial biosurfactant produced by Bacillus subtilis [20].

Grape skins constitute the major component of GP, accounting for about 50% of it mass [21]. This tissue has been described as a rich organic source of phenolic compounds, containing the highest amounts of anthocyanins and tannins with a high polymerization degree. The phenolic composition of the skin is strongly dependent on the variety and cultivation conditions, and in this particular case, on the specific vinification process [22, 23]. Skins from red pomace are generally richer in phenolic acids than the white ones. Grape skins are rich in hydroxycinnamic acids and especially in tartaric esters of these acids, mainly caftaric acid and coutaric acid [24, 25].

The phytochemical profile of this agro-industrial residue supports its use as a promising source of bioactive phytochemicals. Nevertheless, the lack of appropriate valorization processes forced its main use as compost or its dumping in open areas which might have a substantial environmental impact. There is an urgent need of research on extraction conditions and strategies for optimization of the release of phenolics from GP to maximize the properties of the wine pomace [23]. In this sense, Martinez et al. have proposed the development of a multi-purpose GP biorefinery scheme. The scheme suggests four consecutive processes. The recovery of polyphenols by supercritical CO_2 extraction constitutes the first step, followed by the production of volatile fatty acids (VFAs) by anaerobic acidogenic digestion, continuing with the production of the biopolymer polyhydroxyalkanoate, using the produced VFAs as the precursors, by aerobic fermentation and finally the production of a biomethane gas by the anaerobic methanogenic digestion of solid leftovers obtained from the second process [26]. This biorefinery scheme constitutes a novel and interesting GP valorization scheme in which all steps are integrated, obtaining great profit from this agro-industrial by-product in terms of the final products and the great value added to the GP. Another efforts to recover phenols from grape marc, using ultrasound and solvents (ethanol, methanol), membrane filters and supercritical fluid consecutive extraction method, have been made [27–29].

The relative proportion of seeds in the GP is determined, once again, by the specific vinification process, but it ranges from 38% to 52% of the dry GP [30, 31]. The final composition also depends on the material management as well as the variety, state of ripeness, climate growing conditions. Grape seeds contain up to 40% fiber, 11% proteins, 20% essential oil, 8% of polyphenolic compounds (like tannins) and other components like carbohydrates and minerals.

Seed oil is an unsaturated fatty acids rich-oil, with high concentrations of linoleic acid ranging from 72 to 76%, and significant amounts of tocopherols and tocotrienols [32–36]. The essential oil can be extracted by pressing, solvent extraction or combination of both techniques. Mechanical pressing is used only for small production because of its low yield. Better yields were obtained with solvent extraction. Diethyl ether and hexane produced the highest oil yields, whereas ethanol and methanol produced the lowest yields [36]. The use of ultrasound-assisted extraction in the extraction of oil from grape seeds can greatly improve the efficiency of solvent-mediated extraction [33]. Another method used to enhance the yield of oil is treatment with enzymes (cellulose, xylanase, and proteases) to release the oil from the seed structure [37, 38]. Grape-seed oil is employed for culinary, pharmaceutical, and cosmetic applications. Another potential use is as a biofuel.

Special attention has been paid to the phenolic content of seeds because they represent about 70% of total extractable polyphenolic compounds from GP. Polyphenolics in grape seeds are mainly flavonoids, including flavan-3-ols and proanthocyanidin oligomers and polymers [39, 40]. The high phenolic content is due to the minimal proportion extracted during pressing in winemaking process.

2.2. Grape stems

Grape stems comprise the woody part of grape clusters and constitute a waste of winemaking industry. In traditional wine making, stems were often left with grapes during crushing, pressing, and even during fermentation, especially for the production of red wine [41]. This may improve the drainage during pressing and added more tannins in a poor vintage. However, this practice is no longer common since their presence during fermentation increases astringency, negatively affecting the organoleptic characteristics of the produced wines. Nowadays, producers tend to separate the processes of de-stemming and crushing in order to minimize the excessive uptake of phenols and lipids from vine parts [41]. As stated before, large amounts of solid wastes are generated during the wine making process which corresponds to 20-30% (*w/w*) of the grapes used [42]. Stems represent approximately 2%–8% [43], and even though they are not a detrimental waste, once again the high content of organic matter and their seasonal production can contribute to potential pollution problems, especially regarding the chemical and biological oxygen demand of groundwater [44].

Llobera and Cañellas studied the composition of *Manto Negro* grape by-products, grape stalks and grape pomace, and found out that both of them are remarkable rich in dietary fiber (DF). They have compared the general compositions of both, revealing important differences in sugar and oil values and, to a less extent, in protein and pectin values [43]. As it has been described in the previous section, pomace is richer in oil, proteins, pectins and sugars, whereas the stems mainly have rich fiber content. It constitutes up to 70% of its dry matter comprising mainly neutral sugars and lignin (43% and 32% of the dry matter, respectively). It has been established that DF promotes beneficial physiological effects, including laxation, blood cholesterol and glucose attenuation, among others [45]. The distinguished presence of total DF in the molecular structure of GP and stems opens the possibility of using them as ingredients in the food industry, due to the known effect related to the high DF content. In fact, in agreement with the definition of antioxidant dietary fiber established by Saura-Calixto [46], the Manto Negro grape stem and pomace, would comply with the proposed requirements: DF content above 50% on a dry matter basis (74% for pomace and 77% for stem), a free radical-scavenging capacity equivalent to, at least, 50 mg of vitamin E (162 mg for pomace and 495 mg for stem) and, finally, the antioxidant capacity must be an intrinsic property, derived from natural constituents of the material. Therefore, both by-products can be considered excellent antioxidant dietary fiber products that could be used as ingredients in the food and pharmacological industries. Lignin in the grape stem contains important amounts of condensed tannins which could explain its excellent ability to scavenge free radicals. In a more recent study of the carbohydrate composition of stems from 10 different grape varieties, González-Centeno et al revealed that cellulose was the major component followed by pectin, ranging from 40-48 and 27-37 mol%, respectively. The most important pectin polysaccharides contain, homogalacturonan (about 68 mol% of total pectin in fresh grape), followed by rhamnogalactoronan I (26 mol% of total pectin) and rhamnogalactoronan II (about 7 mol% of total pectin) [13].

Llobera and Cañellas also determined total polyphenols quantity. For that purpose, total soluble polyphenols were extracted from the samples sequentially with methanol: water (50:50 *v:v*) and acetone: water (70:30 *v:v*) at room temperature for 60 min in each case. The supernatants were combined, concentrated at 40°C and lyophilized. Total soluble polyphenols (TP) were spectrophotometrically measured in the polyphenolic extracts obtained from both by-products by reading the absorbance at 765 nm (Folin–Ciocalteau method), using gallic acid as standard [47] and expressing the results as gallic acid equivalents (GAE).They have concluded that phenolic compounds are the second most abundant chemical component found in the grape stem and can amount to more than 10% of its dry matter [43]. Moreover, Anastasiadi *et al*. have studied grape stems from six native Greek red and white *V. vinifera* cultivars and found the total phenolic content ranged from 367 to 587 and 372 to 574 mg/g, respectively [48]. In consonance with Barros et al. [49], they found that the phenolic content of stems from red varieties was greater than that in white ones. The predominant phenolic compounds in both red and white grape stems were (+)-catechin, followed by procyanidin B3, ε-viniferin, and trans-resveratrol [48].

In order to present the possible uses of one of the most important by-products in wine production, many studies have investigated the use of waste derived from grape stems as a source of natural antioxidants [50, 51]. In fact, the antioxidant activity provided by the high amount of polyphenols components in grape stems is currently the most studied and profitable. Barros et al. have analyzed the correlation between the concentrations of extracted phenolic compounds and antioxidant activity as measured by the DPPH, ORAC, ABTS, FRAP, and oxygen radical absorbance capacity. They found that procyanidin dimer B, isorhamnetin- 3-O-(6-O-feruloyl)-glycoside, quercetin-3-O-glucoside, and malvidin-3-O-(6-O-caffeoyl)-glucoside were highly correlated to antioxidant activities [49]. Furthermore, Prozil *et al.* found out that stem extracts are three-fold more powerful antioxidants compared with GP extracts [52]. Besides, an interesting study performed by Goutzourelas *et al.* revealed the antioxidant role of a grape stem extract at a cellular level: extracts derived from the stalks of three Greek grape varieties (Moshomayro, Mavrotragano and Mandilaria) in endothelial (EA.hy926) and muscle (C2C12) cells. The oxidative stress markers were thiobarbituric acid reactive substances (TBARS), protein carbonyl (CARB) levels, reactive oxygen species (ROS) levels and glutathione (GSH) levels. The outcomes revealed that treatment of the EA.hy926 cells with Mandilaria extract significantly decreased the TBARS levels by 15% and the CARB levels by 26%, while it increased the GSH levels by 16% compared to the controls. Moreover, treatment of the EA.hy926 cells with Mavrotragano extract significantly increased the GSH levels by 20%, while it significantly decreased the TBARS and CARB levels by 12% and 17%, respectively. Treatment of the C2C12 cells with Mandilaria extract significantly decreased the TBARS levels by 47 %, the CARB levels by 39% and the ROS levels by 22%, whereas it increased the GSH levels by 23% compared to the controls. In the same trend, treatment of the C2C12 cells with Mavrotragano significantly decreased the TBARS, CARB and ROS levels by 36%, 36% and 16%, respectively. In conclusion, their results demonstrated for the first time that treatment with grape stem extracts at low concentrations improves the redox status of endothelial and muscle cells [53]. In this way, grape stem extracts may be used for developing antioxidant food supplements or bio-functional foods.

It has been demonstrated that grape stem extracts have important antioxidant and antimicrobial activities, which certainly increases the added value to this wine waste and may be applied as replacement of sulfur dioxide (SO_2) or at least to help reduce this preservative in winemaking [54]. SO_2 is the most used preservative in the wine industry. It exhibits an important antioxidant function that helps to reduce the effects of dissolved oxygen and inhibit oxidase enzymes, which are endogenous to grapes [55]. Moreover, SO_2 inhibits the development of all types of microorganisms, such as yeasts, lactic acid bacteria and, to a lesser extent, acetic acid bacteria [56]. Grape stem extract showed a lower inhibitory effect than SO_2 for Saccharomyces cerevisiae, *Hanseniaspora uvarum, Dekkera bruxellensis* and *Pediococcus damnosus*, whereas stem extracts seem to be more efficient against *Candida stellata* and *Botryotinia fuckeliana* [57]. Several human health risks, including dermatitis, urticaria, angioedema, diarrhea, abdominal pain, bronchoconstriction and anaphylaxis, have been associated with SO_2 [58]. Consequently, the International Organization of Vine and Wine (OIV) has established limits for SO_2 content in wines, being 150–200 mg/L for dry wines, whereas sweet wines may have exceptionally up to 400 mg/L [59]. Thus, there is great interest in the search for other preservatives that can replace and/or reduce SO_2 content in wines. Another important reason that has increased the interest in searching for alternatives to SO_2 in wines is the fact that only molecular SO_2 (a percentage of free SO_2) possesses antioxidant and antimicrobial properties. The percentage of free SO_2 depends on the pH, a high pH decreases its proportion, and therefore its effectiveness. In the last few years, wine pH has increased due to the changing climate, and thus wines are becoming more vulnerable to spoilage [60].

Another possible application of grape stalks can be compost production, being the main use carried out in these days, (a high-quality fertilizer and soil amendment) by mixing them with winery sludge digested aerobically and centrifuged [61]. This agricultural use has an important added value and is particularly suitable for the soils of the vineyards which have very low organic matter content.

Studies made by Villaescusa *et al.* revealed another conspicuous use of grape stalks in the removal of metal ions from aqueous solutions [62].

The use of grape stalks in the form of single cell protein, as ruminant feed or feeding component has also been proposed after solid state fermentation [63]. It has been determined that after biological lignin removal, the cellulose is better accessible to rumen micro-organisms, due to its good protein value and low lignin content, has a similar value of digestibility as forages (54-60%).

Finally, another green use of grape stalks is the production of lactic acid, which is an important compound in food and pharmaceutical applications [52]. Vine shoots, which also contain stems, consist of lignocellulose material. Chemical and/or enzymatic hydrolysis can degrade the polymers to monomers that can be used for the lactic acid, used as a buffering agent, flavoring agent, or preserver to inhibit spoilage. The production of lactic acid can be achieved by fermentation using *L. pentosus* as was previously discussed. The same technology can be used to produce biosurfactants that have wide applications as emulsifiers.

2.3. Wine lees

Based on the European Union regulation Nº 337/79, lees are defined as “the residue that forms at the bottom of receptacles containing wine, after fermentation, during storage or after authorized treatments, as well as the residue obtained following the filtration or centrifugation of this product.” They represent 2–6% of wine production; thus, there is a global production of lees between 2.5-15 million hectoliters approximately. Lees are separated from the wine by the racking i.e. the decanting steps during wine elaboration, and they can divided in heavy and light lees according to settling duration. The heavy lees are composed by particles with sizes between 100 µm and 2 mm that settle within 24 h. On the other hand, light lees contain particles of approximately 1-50 µm that settle in more than 24 h [64]. The composition is quite variable and the concentration of each substance heavily depends on the grapes, the conditions of vinification and the duration of the aging stage. However, yeasts and the debris that are formed upon autolysis of these cells are the major components of the wine lees. This solid residue contains roughly 50% moisture and around 5% alcohol. Moreover, tartrates are also present at relatively high concentrations [65]. Taking into account the large volumes of wine lees that are produced every year and the content of tartrates and alcohol, lees arise as a great source for this two components that can be commercialized, generating added value to this wine residue. Among the other substances that can be found in lees, fatty acids, which are mainly released from the grape seeds [66], and particularly polyphenols are worth to be mentioned. As a matter of fact, lees can both adsorb polyphenols from the wine and release these phenolic compounds to the wine. On the other hand, lees also provide mannoproteins that have been released during yeast autolysis. These proteins can bind polyphenols, regulating the astringency of the final product [67]. It had been reported that up to 16 g of phenolic compounds per Kg of lees can be obtained. Once again, the large amount of lees that are produced indicates that thousands of tons of polyphenols can be gotten from wine lees every year [9]. Therefore, attempts are being made to collect alcohol, tartrates and polyphenols from lees (and pomace as well), as well as fatty acids, although to a lesser extent. A standard protocol includes a first step of centrifugation, where liquid and solid fractions can be separated. The liquid fraction can then be distilled in order to obtain alcohol, that can be commercialized as such or it can be used later in the same facility to purify polyphenols [68]. Actually, water:ethanol mixture can be used for extraction of phenolic compounds from the lees solid fraction, once the extraction is completed, the solid fraction is separated by centrifugation. This precipitate is the source of tartrates that are purified by a simple 2-step procedure: first the solid is acidified with HCl in order to solubilize tartaric salts and then calcium chloride and calcium carbonate are added for inducing the formation of calcium tartrate that can be finally separated by centrifugation o filtration. Even though lees and also pomace are good sources of tartrates by means of distillation, they can also be obtained by an easier and cheaper way during the stabilization step, where wines are cooled down till -4ºC (see below).

2.4. Lees and pomace distillation wastes

As it was mentioned above, distillation of pomace and lees leaves vinasse and wastewater. Actually, wastewater is produced throughout the entire process and can be as much as 5 kL per ton of crushed grapes. They can be readily used as fertilizers to a certain extent because of the organic content, but an indiscriminate and continuous application of vinasse and wastewaters to the soil may have negative impact mainly because of the salt accumulation that may cause soil dispersion [69]. The usual treatment they receive can be: evaporation in ponds, chemical oxidation that can be either wet oxidation or ozonitation, or biological digestion. The latter strategy can be divided in turn in anaerobic and aerobic digestion, depending on the conditions and microorganisms used [70]. All of them are useful because they reduce the negative impact on the environment, but they are associated to rather high costs and all of them still leave a solid waste, the sludge. One of the soundest strategies for using winery wastes and particularly wine-associated distillery wastes is the preparation of compost. As a matter of fact, it has been shown that winery and distillery wastes can constitute partial or even total substitutes of peat, because they have similar physic-chemical properties. Moreover, because of the phenolic compounds they may still have, they can control a number of plant pathogens [71, 72]. For instance, a promising result was obtained by mixing grape stalks with sludge [61].

3. Products Obtained From Grape Processing Residues

Among the main affordable products that might be obtained after several valorization processes are:

3.1. Tartrates

Tartaric acid and its salts are a good example of how important can be to invest in wine by-products. As a matter of fact, the wine industry is the only source for commercial tartrates nowadays. Tartaric acid can be obtained in a relatively easy way during the stabilization of the wine, what have 2 positive outcomes: it eliminates the possibility of having insoluble particles in the bottled wine and let's get tartaric acid for commercial purposes.

L-(+) tartaric acid alongside citric acid and malic acids is the major acids in grapes. Particularly, tartaric acid is present at high concentrations in the wine mainly as potassium bitartrate but also as calcium tartrate. Moreover, the grape juice is usually supersaturated with the former salt, which tends to precipitate. Actually, the precipitation is stimulated by alcohol since it reduces the solubility of bitartrate [73]. This precipitation is a slow and uncontrolled process that needs to be avoided because it could spoil the quality of the final product. A cold treatment (~ -4°C) is usually applied in the step known as stabilization with the purpose of inducing the removal of the excess of potassium bitartrate by precipitation. The insoluble material is easily removed by filtration. On the other hand, calcium tartrate can also be formed during wine production and it is also prone to precipitation. The concentration of this salt depends on the amount of calcium that is used. For instance, calcium carbonate is often added in deacidification of wine that in turn may lead to calcium tartrate formation. The removal of this salt represents a challenge because precipitation is not induced by refrigeration and other strategies have to be followed [74]. There are some alternative strategies for getting tartaric acid from wine with high efficiencies that can be classified based on the principle used: adsorption, extraction, ion exchange, and electrodialysis [75].

Indeed, tartaric acid is an important by-product of the wine industry since the acid and its salts have a number of applications [76]. For instance, they are extensively used as food additives since they confer a characteristic tartar flavor and also may act as a food preservative. Moreover, tartaric acid is frequently used to improve the taste of medications. In addition, tartaric acid and its salts are used as antioxidants and emulsifiers. Other uses include the making blue ink for blueprints, dye fabrics and for the tanning leather, for naming a few. Potassium sodium tartrate tetrahydrate (Rochelle salt) is used in the process of silvering mirrors. This salt is also used in piezoelectricity and electronics and as a combustion accelerator in cigarette paper [77].

3.2. Polyphenolic compounds

As it was previously mentioned, phenolic composition of GP has been extensively described by several authors with substantial quantitative and qualitative differences [24, 25]. These differences are correlated with two factors: one the one hand, there is a strong influence of the environmental and genetic factors on the grape composition [78]. On the other, the effect of the diverse enological practices on the extraction of phenolics during the vinification process [79].

Phenolic compounds derived from GP are attractive products for its greater beneficial properties, which justify the use of grape residues as an inexpensive organic source for phenol recovery.

There is a large amount of papers about the extraction of polyphenolic compounds from grape residues, as well as their activity and characterization. In general, the extraction of these compounds from grape by-products has been proposed using conventional (solid liquid extraction, heating, enzymatic treatment, etc.) and nonconventional (pulsed electric fields, ultrasounds, microwave-assisted extractions, high-voltage electrical discharges, pulsed ohmic heating, sub- and supercritical fluid extractions, as well as pressurized liquid extraction) methods with diverse yields.

3.2.1. Main biological activities of polyphenols

-Antioxidant activity

Polyphenols have been widely described as potent antioxidants. As it was referred above, the major polyphenolic compounds in grape seeds are flavan-3-ols, with catechin as the predominant component. Flavanols are being extensively studied due to their biological and beneficial properties, especially for their antioxidant activities [80]. This remarkable antioxidant power explains the potential applications proposed for these phenolics in pharmaceutical and food and beverages processing industries.

As a result of the aerobic metabolism, cells produce toxic and aggressive metabolites known as reactive oxygen species (ROS). Under physiological conditions, ROS are considered an important part of the signaling network of living cells. Among their functions, the promoting cell growth and differentiation role, the adaptation to physiological stresses, immune response as well as protection against pathogen invasion could be mentioned. However, the over-accumulation of ROS produced by several factors exposes the tissues to aggressive conditions of oxidative stress, which is related to the development of a wide range of pathologies and diseases, including diabetes, neurodegenerative diseases, cancer, liver and cardiovascular diseases, and precipitate aging [81–83].

The therapeutic treatment for avoiding and combating oxidative damage involves the use or consumption of antioxidants. The molecules with antioxidant activity can act in different ways. They may; a- inhibit the free radical formation (preventive antioxidants), b- interrupt auto-oxidation chain reactions (chain braking antioxidants), c- up-regulate cellular antioxidant defenses (indirect antioxidants), d- neutralize the action of metal pro-oxidant ions (metal chelators) and e- inhibit pro-oxidative enzymes (enzyme inhibitors) [84].

Winemaking residues-phenolics, especially flavonoids, in vitro have probed to act as both, preventive and chain breaking antioxidants, preventing the LDL oxidation as well as scavenging free radicals as superoxide, peroxyl, alkoxyl and hydroxyl [85–87]. In addition, flavonoids can inhibit enzymes involved in ROS generation as xanthine oxidase; protein kinase C; cyclooxygenase; lipoxygenase; glutathione S-transferase; microsomal monooxygenase; mitochondrial succinoxidase and NADH oxidase [88]. They have been described also as ferric and cupric ions chelators [89]. In addition to these activities, in vivo research has described flavonoids as indirect antioxidants since they can up-regulate the antioxidant defense system [90].

Schrieks *et al*. have demonstrated that the increase of antioxidant activity of plasma after the consumption of red wine might be achieved by the consumption of dealcoholized red wine, which has the same flavonoid composition as red wine, but it is free of alcohol and in consequence, free of the prejudicial effects of it [91].

The exceptional combination and quantities of polyphenols with antioxidant properties in grape residues, mainly in GP, makes them a promising source for the development of novel nutraceutical products [25, 92]. The currently commercially available presentations of phenolics derived from winemaking residues include phenolic-rich extracts, for example ExGrape seeds, ExGrape total (http://lalilab.com/botanicals/), grape skin powder, dry seed powder capsulated or bulk, pomace powder, colorants rich in anthocyanins. Moreover, Mildner-Szkudlarz *et al.* proposed the powdered grape pomace as a gluten-free additive for baked products which increased not only the antioxidants but also the fiber content [93].

Phenolics have been proposed also for its use in meat and oil industries. The lipid oxidation is one of the major problems in these industries. Meat products or oils that are constituted of lipid and polyunsaturated fatty acids tend to deteriorate due to lipid oxidation, affecting color, flavor, odor, texture, and nutritional value during processing and storage. The development of rancidity rapidly occurred especially when the products are exposed to air and cooked in frying oil. Therefore, phenolic compounds might replace current synthetic antioxidants, such as butylated hydoxyanisole (BHA) and butylated hydroxytolune (BHT) which use has been restricted because of the carcinogenic properties that have been reported [94]. Grape seed, skin, and pomace phenolic extracts (in powder or liquid forms) have all been used as antioxidants in meat products. The effective level used in order to prevent oxidation in these products was in the range 0.03–0.86 g/kg of tissue [95–97]. In general, grape phenolics in various meat formulations were found to inhibit lipid oxidation upon precooking, during storage in different bags, temperature and atmosphere conditions [97, 98].

Grape phenolics have been used as effective antioxidants for preserving seafood and fish products, which contain high concentrations of polyunsaturated fatty acids, thus they are very susceptible to loss of quality through lipid oxidation [99, 100].

Cosmetic industry has also made use of antioxidant polyphenolic compounds from winery wastes. An example is the product named “PhytoCellTec Solar Vitis/Vitis vinifera”, a natural additive for skin caring obtained by methods of modern high-end plant biotechnology, which profits not only the phenolic compounds contained in grape pomace, but the biomass from cell suspension of V. vinifera.

Resveratrol, one of the dominant polyphenols in grapes, is believed to improve the appearance of wrinkled, lined, dry, flaky, aged or photodamaged skin and improving skin thickness, elasticity, flexibility, radiance, glow, and plumpness. This stilbene inhibits proliferation keratinocytes of skin and stimulates their differentiation [101].

A particular attention should be given to vitamin E, which is abundant in grape seed, composed by eight isoforms, with four tocopherols (α-tocopherol, β-tocopherol, γ-tocopherol, and δ-tocopherol) and four tocotrienols (α-tocotrienol, β- tocotrienol, γ-tocotrienol, and δ-tocotrienol). Among them, α-tocopherol is the most powerful biological antioxidant [102]. In cosmetics, vitamin E is commonly used in day and night creams, acting as chain-breaking antioxidant preventing the aging of skin [103].

In addition, as stated before, high amount of linoleic acid are present in grape seeds which is useful for moisturizing of skin and its protection, as well as in antiaging and skin-lightening cosmetics [104, 105].

-Anti-aging activity

One of the most studied properties of wine in general and resveratrol in particular is the anti-aging effect that has been proposed for the red wine and this stilbene [106]. As a matter of fact, resveratrol seems to have a myriad of beneficial properties. Among them, resveratrol may favor longevity and it is related to cardiovascular protection [107]. It is believed that the cardiovascular effect is achieved through the modulation of different signalling pathways as well as regulating the expression of key proteins. Briefly, it has been shown that resveratrol increases phosphorylated ERK1/2 and induces NOS expression [108]. At the same time, it inhibits the vascular cell adhesion molecule-1 (VCAM-1) and the intercellular adhesion molecule-1 (ICAM-1) [107], thus efficiently reducing atherogenic lesions. Interestingly, resveratrol is thought to increase the lifespan via activation of the NAD-dependent deacetylase SIRT1, showing similar properties of the calorie restriction [109]. Based on molecular dynamics, it has been proposed that resveratrol may act as a protein-substrate stabilizer of SIRT1 and can enhance the N-terminal domain-substrate interaction for “loose-binding” substrates [110].

-Antimicrobial Activity

Several studies have shown antimicrobial activity of grape seed extracts, against several pathogenic and spoilage bacteria, such as *Bacillus cereus, Enterobacter aerogenes, Aeromonas hydrophila, Enterococcus faecalis, Escherichia coli*, including *E. coli* O157:H7, *Klebsiella pneumoniae, Mycobacterium smegmatis, Proteus vulgaris, Pseudomonas aeruginosa, Pseudomonas fluorescens, Salmonella Enteritidis, Salmonella Typhimurium, Staphylococcus aureus* and *Yersinia enterocolitica* [111–113].

The inhibitory activity of 1% grape seed extract and nisin, alone and combined, against *Listeria monocytogenes*, both in tryptic soy broth with yeast extract (TSBYE) and on the surface of full-fat turkey frankfurters, was evaluated by Sivarooban *et al*. The combination of GSE and nisin had the greatest inhibitory activity in both media, with reductions of *L. monocytogenes* populations to undetectable levels [114]. They proposed the combination of these two natural antimicrobials as a potent way to control the growth of *L. monocytogenes*, avoiding the recontamination of ready-to-eat meat products with this food-borne pathogen.

The antimicrobial activity of whole grape and fermented GP extracts against *Streptococcus mutans* was assessed [115]. Despite major differences in phenolic content, GP extracts were either as effective as, or significantly better, than whole fruit grape extracts. The better antimicrobial activity, in general, is exerted by extracts obtained from grape seed and GP. The ability of grape processing by-products to control the growth of some bacteria can be successfully applied in food preservation.

Furthermore, given their great antimicrobial potential, functional feed containing processed winemaking by-products are effective in modifying the intestinal microbiota, enhancing the growth of specific beneficial bacteria strains in the intestinal tract while competitively excluding certain pathogenic bacteria.

Among other factors, antibacterial effect depends on the grape variety. White grape skin extracts presented lower MICs against both Gram-positive (*S. aureus* and *B. cereus*) and Gram-negative bacteria (*E. coli, Salmonella Infantis, Campylobacter coli*) than red ones [116].

The procedures used for obtaining the grape pomace–derived products also affect their antimicrobial activity.

-Other biological activities

Polyphenols derived from winery wastes exhibit anticarcinogenic, antimutagenic, antiinflammatory, antiulcer, antiallergic, and antitoxic effects [80]. Recent studies have been focused the characterization of phenolics from grape seeds for different diseases, for treatment for high blood pressure [117], as protector in the oxidative stress-mediated pancreatic dysfunction [80], bleomycin-induced lung oxidative stress in lung fibrosis [118], preventive effects of calcium oxalate monohydrate calculus formations, induced by cytotoxic compounds with oxidative capacity [119], and so on.

-Wine-derived polyphenols and neuropathologies

There is a growing body of evidence indicating that grape-derived polyphenols may play a positive role in Alzheimer's disease (AD), ameliorating the cognitive deterioration observed in these patients. Polyphenols are important because the protection they confer against the oxidative stress that is always present in Alzheimer’s disease and other pathologies [127]. In fact, it has been proposed that polyphenols can scavenge reactive oxygen species, ameliorating the oxidative damage in the brain that is typically found in Alzheimer’s [128]. However, this is not the only mechanism they have. Indeed, the neuroprotection observed could also be explained by the impairment of the β-amyloid peptide (Aβ) generation induced by polyphenols and also by the blockage of the assembly of this peptide into neurotoxic oligomeric aggregated species [129]. In addition, modulation of tau neuropathology with a concomitant reduction of tau aggregation has also been proposed [130]. In this regard, a careful study demonstrated that wine-derived metabolites selectively accumulate in the brain. Particularly, quercetin-3-O-glucuronide proved to be very efficient in reducing the generation Aβ peptides by primary neuron cultures generated from the Tg2576 AD mouse model. In fact, quercetin-3-O-glucuronide seems to interfere with the protein-protein interaction between Aβ peptides, a critical step during the formation of the neurotoxic oligomeric Aβ species [131]. Another study demonstrated that the polyphenol penta-O-galloyl-β-D-glucose also blocks the oligomerization of Aβ by interacting with the N-terminal metal binding regions of the peptides, suppressing the formation of the Aβ1-42 dodecamer [132]. In addition to these polyphenols acting alone, it has been reported that a commercially available grape seed polyphenolic extract (GSPE) that is rich in gallic acid, catechins, and proanthocyanidins inhibited Aβ aggregation in vitro and also reduced Aβ plaques and attenuated AD-type cognitive deterioration in a mouse model of AD [133, 134]. Interestingly enough, GSPE also inhibited aggregation of tau and was able to dissociate preformed tau aggregates, possibly via non-covalent interactions between GSPE polyphenols with tau residues [135]. Moreover, the interaction of tau protein and procyanidins has been studied in detail by means 2D-NOESY and then modelized by molecular dynamics, determining that procyanidin presented affinity towards the proline-rich region of tau. Interestingly enough, two regions are crucial in the interaction: the one containing the threonine 205 and the region with threonine 212–217. These are residues that get phosphorylated in Alzheimer, thus decreasing the capacity of tau to associate with tubulin in the microtubules. This finding gives insights to explain how procyanidin reduces hyperphosphorylation [136].

Besides interacting with Aβ peptides, polyphenols can also activate signaling pathways such as the c-Jun N-terminal kinases and the mitogen-activated protein kinase pathways, which in turn have positive effects in the hippocampal synaptic transmission and the long-term potentiation [131].

Last but not least, wine polyphenols have been proposed to interact and even inhibit acetylcholinesterase (AChE), an important enzyme related to Alzheimer’s. As it is well-known, the hallmarks of the AD are not only the amyloid deposition and the neurofibrillary tangles composed of hyperphosphorylated tau protein that have been mentioned above, but also the neuronal and synaptic loss in the central nervous system. One of the first neurons affected are the cholinergic neurons; hence, acetylcholinesterase inhibitors are usually prescribed for Alzheimer’s subjects. At present, few inhibitors are available: donepezil, rivastigmine, galantamine. Among natural products that have promising properties relevant to AChE, polyphenols seem to be good candidates for medical applications [137]. Most of the studies devoted to search for new inhibitors of AChE use a soluble form of the enzyme that is commercially available [138, 139]. However, this approach may underestimate the activity of some potential inhibitors because the brain isoform of AChE is associated with cell membranes. In this regard, there are some reports that have tested inhibitors using a rat brain isoform [140, 141], which would be a better approach. In a recent paper, we proposed the red blood cell isoform of AChE-E as a model for studying inhibitors because this is also a membrane-bound enzyme. It differs from the brain isoform in the way it is attached to plasma membrane. Brain isoform is associated to membrane via PriMA protein, whereas the erythrocitic AChE is a GPI-anchored protein [142]. We did find an important inhibition of the erythrocyte membrane-bound acetylcholinesterase (AChE) by the flavonoid epigallocatechin gallate, which can be present at relatively high concentrations in the grape seeds [143]. This polyphenol seems to interact with the membrane surface and the extent of interaction heavily depends on the concentration of cholesterol that the red blood cells may have (Salazar, unpublished results). Importantly, the inhibition was less efficient when the enzyme was solubilized, suggesting that epigallocatechin gallate (EGCG) might approach more efficiently to AChE if there is a previous interaction with membrane surface. Moreover, these results indicate the usual approach with the soluble form of the enzyme may underestimate the activity of some potential inhibitors. Our group carried out a fractionation of grape marc obtained from an Argentinean winery, which elaborates wines from vineyards located at high altitude. Interestingly, the ethyl acetate fractions turned out to have the highest activity as AChE inhibitors. Moreover, polyphenol fraction from white grape pomace proved to be the best source of inhibitors (Salazar, unpublished results).

Parkinson's disease (PD) disease is another neurodegenerative disorder where polyphenols could be of some help as well. The accumulation of α-synuclein aggregates is the hallmark of Parkinson's disease, this protein gets phosphorylated and aggregated in the so-called Lewy bodies in the subcortical regions of the brain [144]. A number of polyphenols from grapes have shown to be promising candidates for the treatment of Parkinson's patients. Phenolic compounds are all beneficial in PD because of the antioxidative activity they have, but they also have other mechanisms that differ from each other. For instance, resveratrol increases the viability of neurons by activation of the human sirtuin (SIRT1) [145] and inducing autophagy [146]. However, resveratrol was unable to inhibit α- synuclein fibril formation in an efficiently way [147]. On the contrary, EGCG turned out to be a good inhibitor of α- synuclein amyloidogenesis by redirecting α-synuclein to non-amyloid, spherical aggregates that are less toxic to cells. This effect is achieved because of direct interaction of EGCG with this protein, reducing its ability to form intermolecular b-sheets and fibrils [148]. More importantly, EGCG is also able to bind to oligomers of α-synuclein, destabilizing them and preventing the interaction of these toxic oligomers with membranes, hence reducing the α-synuclein cytotoxicity [149]. Another important polyphenol from grapes is gallic acid that also proved to be a potent inhibitor of α-synuclein oligomerization by stabilizing the random coil state of this protein [150]. At low concentrations, gallic acid seems to stimulate oligomer formation though. However, these oligomers proved to be non-toxic to neurons [151].

3. CONCLUSION

Winery-derived by-products possess several beneficial properties. So, it is possible reuse these for pharmaceutical industry, without involving a risk to human health.

REFERENCES

[1] OIV Vitiviniculture situation https://bit.ly/2AJ3K4t

[2] Dávila, I., Robles, E., Egüés, I., Labidi, J., Gullón, P. (2017) The Biorefinery Concept for the Industrial Valorization of Grape Processing By-Products. In: Galanakis, C.M. (ed.), Handbook of Grape Processing By-Products, pp. 29-54.

[3] Moreira, M. M., Barroso, M. F., Porto, J. V., Ramalhosa, M. J., Švarc-Gajić, J., Estevinho, L., … Delerue-Matos, C. (2018) Potential of Portuguese vine shoot wastes as natural resources of bioactive compounds. The Science of the Total Environment, 634, pp. 831–842.

[4] Ye, Z., Harrison, R., Cheng, V.J., Berkhi, A.In: M. B. (2016) Valorization of Wine Making By-Products. In: Bordiga, M. (ed.), Valorization of wine making by-products, pp. 73-116.

[5] Spinelli, R., Magagnotti, N., Nati, C. (2010) Harvesting vineyard pruning residues for energy use. Biosystems Engineering, 105(3), pp. 316–322.

[6] Moldes, A. B., Bustos, G., Torrado, A., Domínguez, J. M. (2007) Comparison between different hydrolysis processes of vine-trimming waste to obtain hemicellulosic sugars for further lactic acid conversion. Applied Biochemistry and Biotechnology, 143(3), pp. 244–256.

[7] Navarro, P., Sarasa, J., Sierra, D., Esteban, S., Ovelleiro, J. L. (2005) Degradation of wine industry wastewaters by photocatalytic advanced oxidation. Water Science and Technology: A Journal of the International Association on Water Pollution Research, 51(1), pp. 113–120.

[8] Bustamante, M. A., Said-Pullicino, D., Agulló, E., Andreu, J., Paredes, C., Moral, R. (2011) Application of winery and distillery waste composts to a Jumilla (SE Spain) vineyard: Effects on the characteristics of a calcareous sandy-loam soil. Agriculture, Ecosystems & Environment, 140(1), pp. 80–87.

[9] Bustamante, M. A., Moral, R., Paredes, C., Pérez-Espinosa, A., Moreno-Caselles, J., Pérez-Murcia, M. D. (2008) Agrochemical characterisation of the solid by-products and residues from the winery and distillery industry. Waste Management, 28(2), pp. 372–380.

[10] Kliewer, W. M. (1977) Influence of temperature, solar radiation and nitrogen on coloration and composition of Emperor grapes. American Journal of Enology and Viticulture, 28(2), pp. 96-103.

[11] Freeman, B. M., Lee, T. H., Turkington, C. R. (1979) Interaction of Irrigation and Pruning Level on Growth and Yield of Shiraz Vines. American Journal of Enology and Viticulture, 30(3), pp. 218–223.

[12] Gonzalez-San Jose, M. L., Santa-Maria, G., Diez, C. (1990) Anthocyanins as parameters for differentiating wines by grape variety, wine-growing region, and wine-making methods. Journal of Food Composition and Analysis, 3(1), pp. 54–66.

[13] González-Centeno, M. R., Rosselló, C., Simal, S., Garau, M. C., López, F., Femenia, A. (2010) Physico-chemical properties of cell wall materials obtained from ten grape varieties and their byproducts: grape pomaces and stems. LWT - Food Science and Technology, 43(10), pp. 1580–1586.

[14] Sousa, E. C., Uchôa-Thomaz, A. M. A., Carioca, J. O. B., Morais, S. M. de, Lima, A. de, Martins, C. G., … Rodrigues, L. L. (2014) Chemical composition and bioactive compounds of grape pomace (Vitis vinifera L.), Benitaka variety, grown in the semiarid region of Northeast Brazil. Food Science and Technology, 34(1), pp. 135–142.

[15] Devesa-Rey, R., Vecino, X., Varela-Alende, J. L., Barral, M. T., Cruz, J. M., Moldes, A. B. (2011) Valorization of winery waste vs. the costs of not recycling. Waste Management, 31(11), pp. 2327–2335.

[16] Jin, B., Zepf, F., Bai, Z., Gao, B., Zhu, N. (2016) A biotech-systematic approach to select fungi for bioconversion of winery biomass wastes to nutrient-rich feed. Process Safety and Environmental Protection, 103, pp. 60–68.

[17] Rivera, O. M. P., Moldes, A. B., Torrado, A. M., Domínguez, J. M. (2007). Lactic acid and biosurfactants production from hydrolyzed distilled grape marc. Process Biochemistry, 42(6), pp. 1010–1020.

[18] Bustos, G., Moldes, A. B., Cruz, J. M., Domínguez, J. M. (2005) Influence of the metabolism pathway on lactic acid production from hemicellulosic trimming vine shoots hydrolyzates using Lactobacillus pentosus. Biotechnology Progress, 21(3), pp. 793–798.

[19] Gallander, J. F., and Peng, A. C. (1980) Lipid and Fatty Acid Compositions of Different Grape Types. American Journal of Enology and Viticulture, 31(1), pp. 24–27.

[20] Portilla-Rivera, O., Torrado, A., Domínguez, J. M., Moldes, A. B. (2008) Stability and emulsifying capacity of biosurfactants obtained from lignocellulosic sources using Lactobacillus pentosus. Journal of Agricultural and Food Chemistry, 56(17), pp. 8074–8080.

[21] Mendes, J. A. S., Prozil, S. O., Evtuguin, D. V., Lopes, L. P. C. (2013) Towards comprehensive utilization of winemaking residues: Characterization of grape skins from red grape pomaces of variety Touriga Nacional. Industrial Crops and Products, 43, pp. 25–32.

[22] Escarpa, A., and González, M. C. (1998) High-performance liquid chromatography with diode-array detection for the determination of phenolic compounds in peel and pulp from different apple varieties. Journal of Chromatography. A, 823(1–2), pp. 331–337.

[23] Pinelo, M., Arnous, A., Meyer, A. S. (2006) Upgrading of grape skins: Significance of plant cell-wall structural components and extraction techniques for phenol release. Trends in Food Science & Technology, 17(11), pp. 579–590.

[24] Kammerer, D., Claus, A., Carle, R., Schieber, A. (2004) Polyphenol screening of pomace from red and white grape varieties (Vitis vinifera L.) by HPLC-DAD-MS/MS. Journal of Agricultural and Food Chemistry, 52(14), pp. 4360–4367.

[25] Teixeira, A., Baenas, N., Dominguez-Perles, R., Barros, A., Rosa, E., Moreno, D. A., Garcia-Viguera, C. (2014) Natural bioactive compounds from winery by-products as health promoters: a review. International Journal of Molecular Sciences, 15(9), pp. 15638–15678.

[26] Martinez, G. A., Rebecchi, S., Decorti, D., Domingos, J. M. B., Natolino, A., Rio, D. D., … Fava, F. (2015) Towards multi-purpose biorefinery platforms for the valorisation of red grape pomace: production of polyphenols, volatile fatty acids, polyhydroxyalkanoates and biogas. Green Chemistry, 18(1), pp. 261–270.

[27] Goula, A. M., Thymiatis, K., Kaderides, K. (2016) Valorization of grape pomace: Drying behavior and ultrasound extraction of phenolics. Food and Bioproducts Processing, 100, pp. 132–144.

[28] Guerrero, M. S., Torres, J. S., Nuñez, M. J. (2008) Extraction of polyphenols from white distilled grape pomace: optimization and modelling. Bioresource Technology, 99(5), pp. 1311–1318.

[29] Aizpurua-Olaizola, O., Ormazabal, M., Vallejo, A., Olivares, M., Navarro, P., Etxebarria, N., Usobiaga, A. (2015) Optimization of supercritical fluid consecutive extractions of fatty acids and polyphenols from Vitis vinifera grape wastes. Journal of Food Science, 80(1), pp. E101-107.

[30] Ghafoor, K., Choi, Y. H., Jeon, J. Y., Jo, I. H. (2009) Optimization of ultrasound-assisted extraction of phenolic compounds, antioxidants, and anthocyanins from grape (Vitis vinifera) seeds. Journal of Agricultural and Food Chemistry, 57(11), pp. 4988–4994.

[31] Nawaz, H., Shi, J., Mittal, G. S., Kakuda, Y. (2006) Extraction of polyphenols from grape seeds and concentration by ultrafiltration. Separation and Purification Technology, 48(2), pp. 176–181.

[32] Martinello, M., Hecker, G., Carmen Pramparo, M. del. (2007) Grape seed oil deacidification by molecular distillation: Analysis of operative variables influence using the response surface methodology. Journal of Food Engineering, 81(1), pp. 60–64. doi:10.1016/j.jfoodeng.2006.10.012

[33] Da Porto, C., Porretto, E., Decorti, D. (2013) Comparison of ultrasound-assisted extraction with conventional extraction methods of oil and polyphenols from grape (Vitis vinifera L.) seeds. Ultrasonics Sonochemistry, 20(4), pp. 1076–1080.

[34] Fiori, L., Lavelli, V., Duba, K. S., Sri Harsha, P. S. C., Mohamed, H. B., Guella, G. (2014) Supercritical CO2 extraction of oil from seeds of six grape cultivars: Modeling of mass transfer kinetics and evaluation of lipid profiles and tocol contents. The Journal of Supercritical Fluids, 94, pp. 71–80.

[35] Crews, C., Hough, P., Godward, J., Brereton, P., Lees, M., Guiet, S., Winkelmann, W. (2006) Quantitation of the main constituents of some authentic grape-seed oils of different origin. Journal of Agricultural and Food Chemistry, 54(17), pp. 6261–6265.

[36] Fernández, C. M., Ramos, M. J., Pérez, A., Rodríguez, J. F. (2010) Production of biodiesel from winery waste: extraction, refining and transesterification of grape seed oil. Bioresource Technology, 101(18), pp. 7030–7035.

[37] Passos, C. P., Yilmaz, S., Silva, C. M., Coimbra, M. A. (2009) Enhancement of grape seed oil extraction using a cell wall degrading enzyme cocktail. Food Chemistry, 115(1), pp. 48–53.

[38] Rosenthal, A., Pyle, D. L., Niranjan, K. (1996) Aqueous and enzymatic processes for edible oil extraction. Enzyme and Microbial Technology, 19(6), pp. 402–420.

[39] Ricardo da Silva, J. M., Rigaud, J., Cheynier, V., Cheminat, A., Moutounet, M. (1991) Procyanidin dimers and trimers from grape seeds. Phytochemistry, 30(4), pp. 1259–1264.

[40] Prieur, C., Rigaud, J., Cheynier, V., & Moutounet, M. (1994) Oligomeric and polymeric procyanidins from grape seeds. Phytochemistry, 36(3), pp. 781–784.

[41] Jackson, R. S. (2008) Chemical Constituents of Grapes and Wine. In: Jackson, R.S. (ed.), Wine Science (Third Edition), pp. 270–331.

[42] Makris, D. P., Boskou, G., Andrikopoulos, N. K. (2007) Polyphenolic content and in vitro antioxidant characteristics of wine industry and other agri-food solid waste extracts. Journal of Food Composition and Analysis, 20(2), pp. 125–132.

[43] Llobera, A., and Cañellas, J. (2007) Dietary fibre content and antioxidant

activity of Manto Negro red grape (Vitis vinifera): pomace and stem. Food Chemistry, 101(2), pp. 659–666.

[44] Spigno, G., Pizzorno, T., De Faveri, D. M. (2008) Cellulose and hemicelluloses recovery from grape stalks. Bioresource Technology, 99(10), pp. 4329–4337.

[45] Howlett, J. F., Betteridge, V. A., Champ, M., Craig, S. A. S., Meheust, A., Jones, J. M. (2010) The definition of dietary fiber – discussions at the Ninth Vahouny Fiber Symposium: building scientific agreement. Food & Nutrition Research, 54, 5750.

[46] Saura-Calixto, F. (1998) Antioxidant Dietary Fiber Product: A New Concept and a Potential Food Ingredient. Journal of Agricultural and Food Chemistry, 46(10), pp. 4303–4306.

[47] Singleton, V. L., Orthofer, R., Lamuela-Raventós, R. M. (1999) Analysis of total phenols and other oxidation substrates and antioxidants by means of folin-ciocalteu reagent. In: Packer, L. (ed.), Methods in Enzymology, pp. 152–178.

[48] Anastasiadi, M., Pratsinis, H., Kletsas, D., Skaltsounis, A.-L., Haroutounian, S. A. (2012) Grape stem extracts: Polyphenolic content and assessment of their in vitro antioxidant properties. LWT - Food Science and Technology, 48(2), pp. 316–322.

[49] Barros, A., Gironés-Vilaplana, A., Teixeira, A., Collado-González, J., Moreno, D. A., Gil-Izquierdo, A., … Domínguez-Perles, R. (2014) Evaluation of grape (Vitis vinifera L.) stems from Portuguese varieties as a resource of (poly)phenolic compounds: A comparative study. Food Research International, 65, pp. 375–384.

[50] Van Dyk, J. S., Gama, R., Morrison, D., Swart, S., Pletschke, B. I. (2013) Food processing waste: Problems, current management and prospects for utilisation of the lignocellulose component through enzyme synergistic degradation. Renewable and Sustainable Energy Reviews, 26, pp. 521–531.

[51] Naziri, E., Nenadis, N., Mantzouridou, F. T., Tsimidou, M. Z. (2014) Valorization of the major agrifood industrial by-products and waste from Central Macedonia (Greece) for the recovery of compounds for food applications. Food Research International, 65, pp. 350–358.

[52] Prozil, S. O., Evtuguin, D. V., Lopes, L. P. C. (2012) Chemical composition of grape stalks of Vitis vinifera L. from red grape pomaces. Industrial Crops and Products, 35(1), pp. 178–184.

[53] Goutzourelas, N., Stagos, D., Spanidis, Y., Liosi, M., Apostolou, A., Priftis, A., … Kouretas, D. (2015) Polyphenolic composition of grape stem extracts affects antioxidant activity in endothelial and muscle cells. Molecular Medicine Reports, 12(4), pp. 5846–5856.

[54] Vázquez-Armenta, F. J., Silva-Espinoza, B. A., Cruz-Valenzuela, M. R., González-Aguilar, G. A., Nazzaro, F., Fratianni, F., & Ayala-Zavala, J. F. (2017) Antibacterial and antioxidant properties of grape stem extract applied as disinfectant in fresh leafy vegetables. Journal of Food Science and Technology, 54(10), pp. 3192–3200.

[55] Izquierdo-Cañas, P. M., García-Romero, E., Huertas-Nebreda, B., Gómez-Alonso, S. (2012) Colloidal silver complex as an alternative to sulphur dioxide in winemaking. Food Control, 23(1), pp. 73–81.

[56] Santos, M. C., Nunes, C., Saraiva, J. A., Coimbra, M. A. (2012) Chemical and physical methodologies for the replacement/reduction of sulfur dioxide use during winemaking: review of their potentialities and limitations. European Food Research and Technology, 234(1), pp. 1–12.

[57] Ruiz-Moreno, M. J., Raposo, R., Cayuela, J. M., Zafrilla, P., Piñeiro, Z., Moreno-Rojas, J. M., … Cantos-Villar, E. (2015) Valorization of grape stems. Industrial Crops and Products, 63, pp. 152–157.

[58] Vally, H., Misso, N. L. A., Madan, V. (2009) Clinical effects of sulphite additives. Clinical and Experimental Allergy: Journal of the British Society for Allergy and Clinical Immunology, 39(11), pp. 1643–1651.

[59] Arapitsas, P., Guella, G., Mattivi, F. (2018) The impact of SO2 on wine flavanols and indoles in relation to wine style and age. Scientific Reports, 8.

[60] Sadras, V. O., Petrie, P. R., Moran, M. A. (2013) Effects of elevated temperature in grapevine. II juice pH, titratable acidity and wine sensory attributes. Australian Journal of Grape and Wine Research, 19(1), pp. 107–115.

[61] Bertran, E., Sort, X., Soliva, M., Trillas, I. (2004) Composting winery waste: sludges and grape stalks. Bioresource Technology, 95(2), pp. 203–208.

[62] Villaescusa, I., Fiol, N., Martínez, M., Miralles, N., Poch, J., Serarols, J. (2004) Removal of copper and nickel ions from aqueous solutions by grape stalks wastes. Water Research, 38(4), pp. 992–1002.

[63] Nicolini, L., Volpe, C., Pezzotti, A., Carilli, A. (1993) Changes in in-vitro digestibility of orange peels and distillery grape stalks after solid-state fermentation by higher fungi. Bioresource Technology, 45(1), pp. 17–20.

[64] Charpentier, C. (2010) Ageing on lees (sur lies) and the use of speciality inactive yeasts during wine fermentation. In: Reynolds, A.G. (ed.), Managing Wine Quality, pp. 164–187.

[65] Dimou, C., Kopsahelis, N., Papadaki, A., Papanikolaou, S., Kookos, I. K., Mandala, I., Koutinas, A. A. (2015) Wine lees valorization: Biorefinery development including production of a generic fermentation feedstock employed for poly(3-hydroxybutyrate) synthesis. Food Research International, 73, pp. 81–87.

[66] Prado, J. M., Dalmolin, I., Carareto, N. D. D., Basso, R. C., Meirelles, A. J. A., Vladimir Oliveira, J., … Meireles, M. A. A. (2012) Supercritical fluid extraction of grape seed: Process scale-up, extract chemical composition and economic evaluation. Journal of Food Engineering, 109(2), pp. 249–257.

[67] Guadalupe, Z., Martínez, L., Ayestarán, B. (2010) Yeast Mannoproteins in Red Winemaking: Effect on Polysaccharide, Polyphenolic, and Color Composition. American Journal of Enology and Viticulture, 61(2), pp. 191–200.

[68] Kopsahelis, N., Dimou, C., Papadaki, A., Xenopoulos, E., Kyraleou, M., Kallithraka, S., … Koutinas, A. A. (2018) Refining of wine lees and cheese whey for the production of microbial oil, polyphenol-rich extracts and value-added co-products. Journal of Chemical Technology & Biotechnology, 93(1), pp. 257–268.

[69] Howell, C. L., and Myburgh, P. A. (2018) Management of Winery Wastewater by Re-using it for Crop Irrigation - A Review. South African Journal of Enology and Viticulture, 39(1), pp. 116–131.

[70] Arvanitoyannis, I. S., Ladas, D., Mavromatis, A. (2006) Wine waste treatment methodology. International Journal of Food Science & Technology, 41(10), pp. 1117–1151.

[71] Carmona, E., Moreno, M. T., Avilés, M., Ordovas, J. (2012) Composting of

wine industry wastes and their use as a substrate for growing soilless ornamental plants. Spanish Journal of Agricultural Research, 10(2), pp. 482–491.

[72] Bustamante, M. A., Paredes, C., Moral, R., Moreno-Caselles, J., Pérez-Murcia, M. D., Pérez-Espinosa, A., Bernal, M. P. (2007) Co-composting of distillery and winery wastes with sewage sludge. Water Science and Technology: A Journal of the International Association on Water Pollution Research, 56(2), pp. 187–192.

[73] Lasanta, C., and Gómez, J. (2012) Tartrate stabilization of wines. Trends in Food Science & Technology, 28(1), pp. 52–59.

[74] McKinnon, A. J., Scollary, G. R., Solomon, D. H., Williams, P. J. (1994) The mechanism of precipitation of calcium L(+)-tartrate in a model wine solution. Colloids and Surfaces A: Physicochemical and Engineering Aspects, 82(3), pp. 225–235.

[75] Kaya, C., Şahbaz, A., Arar, Ö., Yüksel, Ü., Yüksel, M. (2015) Removal of tartaric acid by gel and macroporous ion-exchange resins. Desalination and Water Treatment, 55(2), pp. 514–521.

[76] Sobiecka, A., Synoradzki, L., Hajmowicz, H., Zawada, K. (2017) Tartaric Acid and its Derivatives. Part 17. Synthesis and Applications of Tartrates. Organic Preparations and Procedures International, 49(1), pp. 1–27.

[77] Rajesh, P., Rao, G. B., Ramasamy, P. (2017) Effect of Rochelle salt on growth, optical, photoluminescence, photoconductive and piezoelectric properties of the triglycine sulphate single crystal. Journal of Crystal Growth, 468, pp. 340–344.

[78] Pérez-Magariño, S., and González-San José, M. L. (2006) Polyphenols and colour variability of red wines made from grapes harvested at different ripeness grade. Food Chemistry, 96(2), pp. 197–208.

[79] Revilla, I., and González-SanJosé, M. L. (2002) Multivariate evaluation of changes induced in red wine characteristics by the use of extracting agents. Journal of Agricultural and Food Chemistry, 50(16), pp. 4525–4530.

[80] Bashir, N., Manoharan, V., Miltonprabu, S. (2016) Grape seed proanthocyanidins protects against cadmium induced oxidative pancreatitis in rats by attenuating oxidative stress, inflammation and apoptosis via Nrf-2/HO-1 signaling. The Journal of Nutritional Biochemistry, 32, pp. 128–141.

[81] Beckhauser, T. F., Francis-Oliveira, J., De Pasquale, R. (2016) Reactive Oxygen Species: Physiological and Physiopathological Effects on Synaptic Plasticity. Journal of Experimental Neuroscience, 10(Suppl 1), pp. 23–48.

[82] Schieber, M., and Chandel, N. S. (2014) ROS Function in Redox Signaling and Oxidative Stress. Current biology : CB, 24(10), pp. R453–R462.

[83] Mittler, R. (2017). ROS Are Good. Trends in Plant Science, 22(1), pp. 11–19.

[84] Lü, J.-M., Lin, P. H., Yao, Q., Chen, C. (2010) Chemical and molecular mechanisms of antioxidants: experimental approaches and model systems. Journal of Cellular and Molecular Medicine, 14(4), pp. 840–860.

[85] Frémont, L., Belguendouz, L., Delpal, S. (1999) Antioxidant activity of resveratrol and alcohol-free wine polyphenols related to LDL oxidation and polyunsaturated fatty acids. Life Sciences, 64(26), pp. 2511–2521.

[86] Ou, H.-C., Chou, F.-P., Sheen, H.-M., Lin, T.-M., Yang, C.-H., Huey-Herng Sheu, W. (2006) Resveratrol, a polyphenolic compound in red wine, protects against oxidized LDL-induced cytotoxicity in endothelial cells. Clinica Chimica Acta; International Journal of Clinical Chemistry, 364(1–2), pp. 196–204.

[87] Aviram, M., & Fuhrman, B. (2002) Wine flavonoids protect against LDL oxidation and atherosclerosis. Annals of the New York Academy of Sciences, 957, pp. 146–161.

[88] Hussain, T., Tan, B., Yin, Y., Blachier, F., Tossou, M. C. B., Rahu, N. (2016) Oxidative Stress and Inflammation: What Polyphenols Can Do for Us? Oxidative Medicine and Cellular Longevity, 2016:7432797.

[89] Cherrak, S. A., Mokhtari-Soulimane, N., Berroukeche, F., Bensenane, B., Cherbonnel, A., Merzouk, H., Elhabiri, M. (2016) In Vitro Antioxidant versus Metal Ion Chelating Properties of Flavonoids: A Structure-Activity Investigation. PLoS ONE, 11(10).

[90] Li, Y., Cao, Z., Zhu, H. (2006) Upregulation of endogenous antioxidants and phase 2 enzymes by the red wine polyphenol, resveratrol in cultured aortic smooth muscle cells leads to cytoprotection against oxidative and electrophilic stress. Pharmacological Research, 53(1), pp. 6–15.

[91] Schrieks, I. C., van den Berg, R., Sierksma, A., Beulens, J. W. J., Vaes, W. H. J., Hendriks, H. F. J. (2013) Effect of red wine consumption on biomarkers of oxidative stress. Alcohol and Alcoholism (Oxford, Oxfordshire), 48(2), pp. 153–159.

[92] Arvanitoyannis, I. S., Ladas, D., Mavromatis, A. (2006) Potential uses and applications of treated wine waste: a review. International Journal of Food Science & Technology, 41(5), pp. 475–487.

[93] Mildner-Szkudlarz, S., Zawirska-Wojtasiak, R., Gośliński, M. (2010) Phenolic compounds from winemaking waste and its antioxidant activity towards oxidation of rapeseed oil. International Journal of Food Science & Technology, 45(11), pp. 2272–2280.

[94] Vayupharp, B., and Laksanalamai, V. (2012) Recovery of Antioxidants from Grape Seeds and its Application in Fried Food. Journal of Food Processing & Technology, 3(4), pp. 1–6.

[95] Carpenter, R., O'Grady, M. N., O'Callaghan, Y. C., O'Brien, N. M., Kerry, J. P. (2007) Evaluation of the antioxidant potential of grape seed and bearberry extracts in raw and cooked pork. Meat Science, 76(4), pp. 604–610.

[96] Kulkarni, S., DeSantos, F. A., Kattamuri, S., Rossi, S. J., Brewer, M. S. (2011) Effect of grape seed extract on oxidative, color and sensory stability of a pre-cooked, frozen, re-heated beef sausage model system. Meat Science, 88(1), pp. 139–144.

[97] Selani, M. M., Contreras-Castillo, C. J., Shirahigue, L. D., Gallo, C. R., Plata-Oviedo, M., Montes-Villanueva, N. D. (2011) Wine industry residues extracts as natural antioxidants in raw and cooked chicken meat during frozen storage. Meat Science, 88(3), pp. 397–403.

[98] Rojas, M. C., and Brewer, M. S. (2007) Effect of natural antioxidants on oxidative stability of cooked, refrigerated beef and pork. Journal of Food Science, 72(4), pp. S282-288.

[99] Pazos, M., Gallardo, J. M., Torres, J. L., Medina, I. (2005) Activity of grape polyphenols as inhibitors of the oxidation of fish lipids and frozen fish muscle. Food Chemistry, 92(3), pp. 547–557.

[100] Özen, B. Ö., Eren, M., Pala, A., Özmen, İ., Soyer, A. (2011) Effect of plant

extracts on lipid oxidation during frozen storage of minced fish muscle. International Journal of Food Science & Technology, 46(4), pp. 724–731.

[101] Bastianetto, S., Dumont, Y., Duranton, A., Vercauteren, F., Breton, L., Quirion, R. (2010) Protective Action of Resveratrol in Human Skin: Possible Involvement of Specific Receptor Binding Sites. PLoS ONE, 5(9).

[102] Carocho, M., and Ferreira, I. C. F. R. (2013) A review on antioxidants, prooxidants and related controversy: Natural and synthetic compounds, screening and analysis methodologies and future perspectives. Food and Chemical Toxicology, 51, pp. 15–25.

[103] Dos Santos Freitas, L., Jacques, R. A., Richter, M. F., Silva, A. L. da, Caramão, E. B. (2008) Pressurized liquid extraction of vitamin E from Brazilian grape seed oil. Journal of Chromatography. A, 1200(1), pp. 80–83.

[104] Aburjai, T., and Natsheh, F. M. (2003) Plants used in cosmetics. Phytotherapy research: PTR, 17(9), pp. 987–1000.

[105] Maffei Facino, R., Carini, M., Aldini, G., Bombardelli, E., Morazzoni, P., Morelli, R. (1994) Free radicals scavenging action and anti-enzyme activities of procyanidines from Vitis vinifera. A mechanism for their capillary protective action. Arzneimittel-Forschung, 44(5), pp. 592–601.

[106] Li, Y.-R., Li, S., Lin, C.-C. (2018) Effect of resveratrol and pterostilbene on aging and longevity. BioFactors, 44(1), pp. 69–82.

[107] Catalgol, B., Batirel, S., Taga, Y., Ozer, N. K. (2012) Resveratrol: French Paradox Revisited. Frontiers in Pharmacology, 3.

[108] Bruder, J. L., Hsieh, T., Lerea, K. M., Olson, S. C., Wu, J. M. (2001) Induced cytoskeletal changes in bovine pulmonary artery endothelial cells by resveratrol and the accompanying modified responses to arterial shear stress. BMC cell biology, 2, 1.

[109] Huang, S. S., Tsai, M. C., Chih, C. L., Hung, L. M., Tsai, S. K. (2001) Resveratrol reduction of infarct size in Long-Evans rats subjected to focal cerebral ischemia. Life Sciences, 69(9), pp. 1057–1065.

[110] Hou, X., Rooklin, D., Fang, H., Zhang, Y. (2016) Resveratrol serves as a protein-substrate interaction stabilizer in human SIRT1 activation. Scientific Reports, 6, 38186.

[111] Baydar, N. G., Sagdic, O., Ozkan, G., Cetin, S. (2006) Determination of antibacterial effects and total phenolic contents of grape (Vitis vinifera L.) seed extracts. International Journal of Food Science & Technology, 41(7), pp. 799–804.

[112] Rodriguez-Vaquero, M. J., Aredes Fernández, P.,A., Manca de Nadra, M. C., Strasser de Saad, A. M. (2013) Effect of Phenolic Compounds from Argentinean Red Wines on Pathogenic Bacteria in a Meat Model System. Journal of Food Biochemistry, 37(4), pp. 425–431.

[113] Figueiredo, A. R., Campos, F., de Freitas, V., Hogg, T., Couto, J. A. (2008) Effect of phenolic aldehydes and flavonoids on growth and inactivation of Oenococcus oeni and Lactobacillus hilgardii. Food Microbiology, 25(1), pp. 105–112.

[114] Sivarooban, T., Hettiarachchy, N. S., Johnson, M. G. (2007) Inhibition of Listeria monocytogenes using nisin with grape seed extract on turkey frankfurters stored at 4 and 10 degrees C. Journal of Food Protection, 70(4), pp. 1017–1020.

[115] Thimothe, J., Bonsi, I. A., Padilla-Zakour, O. I., Koo, H. (2007) Chemical characterization of red wine grape (Vitis vinifera and Vitis interspecific hybrids) and pomace phenolic extracts and their biological activity against Streptococcus mutans. Journal of Agricultural and Food Chemistry, 55(25), pp. 10200–10207.

[116] Katalinić, V., Možina, S. S., Skroza, D., Generalić, I., Abramovič, H., Miloš, M., … Boban, M. (2010) Polyphenolic profile, antioxidant properties and antimicrobial activity of grape skin extracts of 14 Vitis vinifera varieties grown in Dalmatia (Croatia). Food Chemistry, 119(2), pp. 715–723.

[117] Afonso, J., Passos, C. P., Coimbra, M. A., Silva, C. M., Soares-da-Silva, P. (2013) Inhibitory effect of phenolic compounds from grape seeds (Vitis vinifera L.) on the activity of angiotensin I converting enzyme. LWT - Food Science and Technology, 54(1), pp. 265–270.

[118] Khazri, O., Charradi, K., Limam, F., El May, M. V., & Aouani, E. (2016) Grape seed and skin extract protects against bleomycin-induced oxidative stress in rat lung. Biomedicine & Pharmacotherapy = Biomedecine & Pharmacotherapie, 81, pp. 242–249.

[119] Grases, F., Prieto, R. M., Fernandez-Cabot, R. A., Costa-Bauzá, A., Tur, F., Torres, J. J. (2015) Effects of Polyphenols from Grape Seeds on Renal Lithiasis. Oxidative Medicine and Cellular Longevity, 2015, 813737.

[120] Rodríguez Montealegre, R., Romero Peces, R., Chacón Vozmediano, J. L., Martínez Gascueña, J., García Romero, E. (2006) Phenolic compounds in skins and seeds of ten grape Vitis vinifera varieties grown in a warm climate. Journal of Food Composition and Analysis, 19(6), pp. 687–693.

[121] Ricardo-da-Silva, J. M., Cheynier, V., Souquet, J.-M., Moutounet, M., Cabanis, J.-C., Bourzeix, M. (1991) Interaction of grape seed procyanidins with various proteins in relation to wine fining. Journal of the Science of Food and Agriculture, 57(1), pp. 111–125.

[122] Ky, I., Lorrain, B., Kolbas, N., Crozier, A., Teissedre, P.-L. (2014) Wine by-products: phenolic characterization and antioxidant activity evaluation of grapes and grape pomaces from six different French grape varieties. Molecules, 19(1), pp. 482–506.

[123] Shi, J., Yu, J., Pohorly, J. E., Kakuda, Y. (2003) Polyphenolics in grape seeds-biochemistry and functionality. Journal of Medicinal Food, 6(4), pp. 291–299.

[124] Zou, H., Kilmartin, P. A., Inglis, M. J., Frost, A. (2002) Extraction of phenolic compounds during vinification of Pinot Noir wine examined by HPLC and cyclic voltammetry. Australian Journal of Grape and Wine Research, 8(3), pp. 163–174.

[125] Rombaut, N., Savoire, R., Thomasset, B., Castello, J., Van Hecke, E., Lanoisellé, J.-L. (2015) Optimization of oil yield and oil total phenolic content during grape seed cold screw pressing. Industrial Crops and Products, 63, pp. 26–33.

[126] Sabir, A., Unver, A., Kara, Z. (2012) The fatty acid and tocopherol constituents of the seed oil extracted from 21 grape varieties (Vitis spp.). Journal of the Science of Food and Agriculture, 92(9), pp. 1982–1987.

[127] Granzotto, A., and Zatta, P. (2014) Resveratrol and Alzheimer's disease: message in a bottle on red wine and cognition. Frontiers in Aging Neuroscience, 6, 95.

[128] Youssef, P., Chami, B., Lim, J., Middleton, T., Sutherland, G. T., Witting, P. K. (2018) Evidence supporting oxidative stress in a moderately affected area of

the brain in Alzheimer's disease. Scientific Reports, 8(1), 11553.

[129] Hayden, E. Y., Yamin, G., Beroukhim, S., Chen, B., Kibalchenko, M., Jiang, L., … Teplow, D. B. (2015) Inhibiting amyloid β-protein assembly: Size-activity relationships among grape seed-derived polyphenols. Journal of Neurochemistry, 135(2), pp. 416–430.

[130] Pasinetti, G. M. (2012) Novel role of red wine-derived polyphenols in the prevention of Alzheimer's disease dementia and brain pathology: experimental approaches and clinical implications. Planta Medica, 78(15), E24.

[131] Ho, L., Ferruzzi, M. G., Janle, E. M., Wang, J., Gong, B., Chen, T.-Y., Pasinetti, G. M. (2013) Identification of brain-targeted bioactive dietary quercetin-3-O-glucuronide as a novel intervention for Alzheimer's disease. FASEB Journal 27(2), pp. 769–781.

[132] de Almeida, N. E. C., Do, T. D., LaPointe, N. E., Tro, M., Feinstein, S. C., Shea, J.-E., Bowers, M. T. (2017) 1,2,3,4,6-penta-O-galloyl-β-D-glucopyranose Binds to the N-terminal Metal Binding Region to Inhibit Amyloid β-protein Oligomer and Fibril Formation. International Journal of Mass Spectrometry, 420, pp. 24–34.

[133] Ono, K., Condron, M. M., Ho, L., Wang, J., Zhao, W., Pasinetti, G. M., Teplow, D. B. (2008) Effects of grape seed-derived polyphenols on amyloid beta-protein self-assembly and cytotoxicity. The Journal of Biological Chemistry, 283(47), pp. 32176–32187.

[134] Wang, J., Ho, L., Zhao, W., Ono, K., Rosensweig, C., Chen, L., … Pasinetti, G. M. (2008) Grape-derived polyphenolics prevent Abeta oligomerization and attenuate cognitive deterioration in a mouse model of Alzheimer's disease. The Journal of Neuroscience, 28(25), pp. 6388–6392.

[135] Ho, L., Yemul, S., Wang, J., Pasinetti, G. M. (2009) Grape seed polyphenolic extract as a potential novel therapeutic agent in tauopathies. Journal of Alzheimer's disease: JAD, 16(2), pp. 433–439.

[136] Guéroux, M., Pinaud-Szlosek, M., Fouquet, E., De Freitas, V., Laguerre, M., Pianet, I. (2015). How wine polyphenols can fight Alzheimer disease progression: towards a molecular explanation. Tetrahedron, 71(20), pp. 3163–3170.

[137] García-Morales, G., Huerta-Reyes, M., González-Cortazar, M., Zamilpa, A., Jiménez-Ferrer, E., Silva-García, R., … Aguilar-Rojas, A. (2015) Anti-inflammatory, antioxidant and anti-acetylcholinesterase activities of Bouvardia ternifolia: potential implications in Alzheimer's disease. Archives of Pharmacal Research, 38(7), pp. 1369–1379.

[138] Pejchal, V., Štěpánková, Š., Pejchalová, M., Královec, K., Havelek, R., Růžičková, Z., … Lepšík, M. (2016) Synthesis, structural characterization, docking, lipophilicity and cytotoxicity of 1-[(1R)-1-(6-fluoro-1,3-benzothiazol-2-yl)ethyl]-3-alkyl carbamates, novel acetylcholinesterase and butyrylcholinesterase pseudo-irreversible inhibitors. Bioorganic & Medicinal Chemistry, 24(7), pp. 1560–1572.

[139] Wang, X., Cao, J., Wu, Y., Wang, Q., Xiao, J. (2016) Flavonoids, Antioxidant Potential, and Acetylcholinesterase Inhibition Activity of the Extracts from the Gametophyte and Archegoniophore of Marchantia polymorpha L. Molecules, 21(3), 360.

[140] Fang, J., Wu, P., Yang, R., Gao, L., Li, C., Wang, D., Du, G.-H. (2014) Inhibition of acetylcholinesterase by two genistein derivatives: kinetic analysis, molecular docking and molecular dynamics simulation. Acta Pharmaceutica Sinica B, 4(6), pp. 430–437.

[141] Moniruzzaman, M., Asaduzzaman, M., Hossain, M. S., Sarker, J., Rahman, S. M. A., Rashid, M., Rahman, M. M. (2015) In vitro antioxidant and cholinesterase inhibitory activities of methanolic fruit extract of Phyllanthus acidus. BMC complementary and alternative medicine, 15, 403.

[142] Grisaru, D., Sternfeld, M., Eldor, A., Glick, D., Soreq, H. (1999) Structural roles of acetylcholinesterase variants in biology and pathology. European journal of biochemistry / FEBS, 264(3), pp. 672–686.

[143] Salazar, P. B., de Athayde Moncorvo Collado, A., Canal-Martínez, V., Minahk, C. J. (2017). Differential inhibition of human erythrocyte acetylcholinesterase by polyphenols epigallocatechin-3-gallate and resveratrol. Relevance of the membrane-bound form. BioFactors, 43(1), pp. 73–81.

[144] Moussaud, S., Jones, D. R., Moussaud-Lamodière, E. L., Delenclos, M., Ross, O. A., McLean, P. J. (2014) Alpha-synuclein and tau: teammates in neurodegeneration? Molecular Neurodegeneration, 9(1), 43.

[145] Albani, D., Polito, L., Batelli, S., De Mauro, S., Fracasso, C., Martelli, G., … Forloni, G. (2009) The SIRT1 activator resveratrol protects SK-N-BE cells from oxidative stress and against toxicity caused by alpha-synuclein or amyloid-beta (1-42) peptide. Journal of Neurochemistry, 110(5), pp. 1445–1456.

[146] Wu, Y., Li, X., Zhu, J. X., Xie, W., Le, W., Fan, Z., Pan, T. (2011) Resveratrol-activated AMPK/SIRT1/autophagy in cellular models of Parkinson's disease. Neuro-Signals, 19(3), pp. 163–174.

[147] Caruana, M., Högen, T., Levin, J., Hillmer, A., Giese, A., & Vassallo, N. (2011) Inhibition and disaggregation of α-synuclein oligomers by natural polyphenolic compounds. FEBS letters, 585(8), pp. 1113–1120.

[148] Ehrnhoefer, D. E., Bieschke, J., Boeddrich, A., Herbst, M., Masino, L., Lurz, R., Wanker, E. E. (2008) EGCG redirects amyloidogenic polypeptides into unstructured, off-pathway oligomers. Nature Structural & Molecular Biology, 15(6), pp. 558–566.

[149] Lorenzen, N., Nielsen, S. B., Yoshimura, Y., Vad, B. S., Andersen, C. B., Betzer, C., Otzen, D. E. (2014) How epigallocatechin gallate can inhibit α-synuclein oligomer toxicity in vitro. The Journal of Biological Chemistry, 289(31), pp. 21299–21310.

[150] Liu, Y., Carver, J. A., Calabrese, A. N., & Pukala, T. L. (2014) Gallic acid interacts with α-synuclein to prevent the structural collapse necessary for its aggregation. BBA Proteins & Proteomics, 1844(9), pp. 1481–1485.

[151] Ardah, M. T., Paleologou, K. E., Lv, G., Abul Khair, S. B., Kazim, A. S., Minhas, S. T., El-Agnaf, O. M. A. (2014) Structure activity relationship of phenolic acid inhibitors of α-synuclein fibril formation and toxicity. Frontiers in Aging Neuroscience, 6, 197.