fermentation

MDPI

Review

Winemaking: "With One Stone, Two Birds"? A Holistic Review of the Bio-Functional Compounds, Applications and Health Benefits of Wine and Wineries' By-Products

Alexandros Tsoupras [1,*], Victoria Ling Jun Ni [2], Éimhín O'Mahony [2] and Maria Karali [3]

1 Department of Chemistry, International Hellenic University, St. Loukas, GR65404 Kavala, Greece
2 Department of Biological Sciences, University of limerick, V94 T9PX Limerick, Ireland; victoria.ljn.work@gmail.com (V.L.J.N.); eimhinomahony99@gmail.com (É.O.)
3 Secondary Education, Ministry of Education and Religious Affairs, GR15180 Athens, Greece; marokarali@hotmail.com
* Correspondence: atsoupras@gmail.com or atsoupras@chem.ihu.gr

Abstract: The plethora of bio-functional compounds present in fermented alcoholic beverages like wine, as well as the valorisation of bioactives from wineries'/breweries' by-products like grape pomace and grape seed, has gained significant interest in the functional foods sector. This functional beverage, wine, has always accompanied humanity, for religion or for health, especially in the Mediterranean, while the benefits of its moderate consumption were documented even by the Greek physician Hippocrates of Kos (460–370 BC). After a big gap, an outbreak of research on wine benefits has surfaced only since the 1990s, when the term "French paradox" was introduced to the US public during a CBS show, while recent evidence has outlined that the beneficial effects of wine consumption are derived by the synergisms of its bio-functional compounds and their digestion-derived metabolites. Within this article, the proposed health benefits of moderate wine consumption, as a functional component of a balanced diet (i.e., the Mediterranean diet) against inflammation-related chronic disorders, is thoroughly reviewed. The various bio-functional compounds of both wine and wineries' by-products, such as their bioactive phenolics, unsaturated fatty acids, polar lipids and dietary fibres, and their functional antioxidant, anti-inflammatory and antithrombotic health-promoting properties, are also thoroughly evaluated. The mechanisms of action and synergism, by which the health benefits are elicited, are also explored. Functional properties of non-alcoholic wine products are also introduced. Emphasis is also given to applications of wineries' by-products bioactives, as ingredients of bio-functional foods, supplements and nutraceuticals. Limitations and future perspectives for this popular functional alcoholic beverage (wine) and its rich in bioactives by-products are also addressed.

Keywords: wine; grape pomace; grape seed; by-products; bioactives; phenolics; polar lipids; anti-inflammatory; antioxidant; Mediterranean diet

check for updates

Citation: Tsoupras, A.; Ni, V.L.J.; O'Mahony, É.; Karali, M. Winemaking: "With One Stone, Two Birds"? A Holistic Review of the Bio-Functional Compounds, Applications and Health Benefits of Wine and Wineries' By-Products. *Fermentation* **2023**, *9*, 838. https://doi.org/10.3390/fermentation9090838

Academic Editors: Federica Tonolo and Maria Pia Rigobello

Received: 13 June 2023
Revised: 8 September 2023
Accepted: 11 September 2023
Published: 13 September 2023

1. Introduction

The making of wine is one of the most well-established fermentation processes in human history. The vinification process was/is one of the most important traditions passed from one generation to the next one, which usually pertained to festivities or cultural events, especially in the Mediterranean during the Greek–Roman period. After industrialisation, the making of wine has become an industrial process for several types of this alcoholic beverage all around the globe. Most wines contain roughly 12–14% *v*/*v* ethanol, while non-alcoholic wine products have also become part of the wine market. The production of wine is achieved through the vinification process, which is based on the alcoholic fermentation of the juice from crushed ripe grapes in the presence of yeasts. The methods applied during the process differ depending on the grape varieties and the types of wines that are produced [1].

Wine contains a large quantity of several phenolic compounds and this distinguishes it from other alcoholic beverages [1], while several microbiota metabolites that are formed after wine consumption by digestion of all wine polyphenols (except stilbenes), further increase the diversity of bioactive phenolic compounds [2]. Wine's polyphenolic composition varies depending on several factors, including the variety of grape, geographical location, soil, weather conditions and maceration, an additional process applied for making red wine. The presence of phenolic compounds is important in relation to both the sensory properties and health benefits of wine [1]. The abundant group of bioactive compounds known as polyphenols, including resveratrol, phenolic acids, anthocyanins, several flavonoids and their microbiota-derived metabolites, possess potent antioxidant and anti-inflammatory activities, as well as antiplatelet aggregation and antiatherogenic properties [1,3–6]. Wine's bioactive phenolics can also inhibit the activities and reduce the synthesis and the levels of potent inflammatory mediators, such as those of the platelet-activating factor (PAF), which result in the inhibition of the PAF and/or thrombin-related thrombo-inflammatory signaling and their associated inflammatory manifestations, with proposed benefits against inflammation-related pathologies and chronic disorders [5–7].

Apart from the abundant phenolics, grapes, must, wine and winery by-products also contain lipid bioactive compounds, such as bioactive polar lipids and unsaturated fatty acids (UFA), with strong anti-inflammatory and antithrombotic properties, which contribute to the bio-functional activities and protective effects of grape products like wine and its by-products [1,8–23]. In particular, some polar lipids (glycolipids and phospholipids) rich in UFA (i.e., oleic, linoleic and linolenic acids) are the most effective lipid bioactives against specific thrombo-inflammatory pathways, including those associated with PAF and thrombin [8–11]. Such bioactive lipid compounds pre-exist both in grapes and in yeasts, on which fermentation is based, and subsequently they are also found in both the remaining winery by-products [16,17,22,23] and in the final fermented wine product, while favourable modifications also occur during fermentation [8–11].

Inflammation involves the innate response of the immune system to combat any causative agent that can cause homeostasis disruption, infection and/or tissue damage [6,7,24]. The inflammatory response aims to minimise the effects of such agents, as well as to stimulate appropriate immune response and wound healing and reinstate tissue homeostasis. However, several risk factors and pathological situations may lead to unresolved and chronic inflammation, which usually leads to further tissue dysfunction and loss of homeostasis and subsequently to the onset and development of inflammation-related chronic disorders, such as atherosclerosis, cardiovascular diseases (CVD), diabetes and cancer metastasis [6,7,24]. Therefore, the presence of bio-functional compounds in wine, such as polyphenols and lipid bioactives, with strong anti-inflammatory, antithrombotic and antioxidant properties, further supports the health benefits observed with moderate consumption of wine [1–23]. Bioactives of wine and winery by-products have the potential to reduce inflammation, therefore moderate consumption of wine and functional products based on wine and winery by-products' bioactives can ameliorate the risk of developing atherosclerosis and other inflammation-related chronic disorders [1–23].

Several epidemiological studies and targeted trials have shown that there are many proposed health benefits associated with wine consumption, but mostly when wine is consumed in moderation [1,11–14,18–20]. Moderate wine consumption (1–2 glasses/day for men and 0.5–1 glass/day for women) is closely correlated with less endothelial dysfunction and low-grade inflammation, which help prevent the manifestation of inflammation-related chronic disorders [25]. Moreover, additional health benefits have also been attributed to the probiotic potential linked to moderate red wine consumption, since red wine polyphenols can beneficially regulate the growth of select favourable gut microbiota [26].

The low to moderate consumption of wine with meals is a characteristic trait of the Mediterranean diet, while adherence to such a healthy dietary pattern is reported to contribute to health benefits such as attenuating the cardiometabolic risk factors associated with the onset of CVD [7,27,28]. More specifically, a "Mediterranean way" of a regular, moderate wine consumption is usually defined as up to 1–2 glasses/day for men and 0.5–1 glass/day for women, which should be consumed mainly with a meal/food. According to a plethora of studies, such moderate wine drinking increases longevity and reduces the risk of CVD and of other pathological conditions, including the overall risk of cancer (Supplementary Tables S1 and S2). Wine differs from other alcoholic beverages since such a moderate consumption not only does not increase the risk of chronic degenerative diseases, and it is also associated with several health benefits due to its rich content in bioactive compounds with potent anti-inflammatory, antithrombotic and antioxidant activities [1,11,14,18].

On the other hand, it should not be neglected that the association between alcohol consumption and corresponding health effects is usually represented by a J-shaped curve, suggesting that the alcohol content of wine should not be disregarded, since excessive consumption of wine can lead to detrimental health effects, such as liver cirrhosis, several types of cancer and an increased risk of CVD [29,30]. Therefore, sound clinical judgment should be applied in determining whether alcohol consumption in the form of wine is an appropriate recommendation in a personalised approach to each patient, taking into account other factors too, such as contraindications with other medications. Moreover, there is a small portion of the population that may be prone to addiction or fail to moderate consumption and therefore may present a hazard to society via acts of violence, accidents and spousal, child and elder abuse, as well as incurring detrimental effects on their own health. Thus, special effort must be made to promote behavioural education to prevent abuse, especially among young people.

Apart from wine, during winemaking several by-products are also derived, with the main ones being grape pomace and grape seed [22,23]. Significant amounts of grape pomace are generated from grapes during winemaking, which account for 20% of the original grape used. This by-product generated by the wine industry, if handled as an industrial waste, can create contamination and pollution issues, costly disposal issues and financial loss. Traditionally, this "waste" is undervalued and its usual re-use is as an animal feed or fertiliser. However, grape pomace is distinguished from other food by-products due to its high content in high-value compounds such as dietary fibre, lipid bioactives, phenolics and other natural antioxidants [22,23]. Many of these bioactive compounds have been linked to several health benefits, including anti-inflammatory, cardioprotective and antidiabetic effects [10,16,17,21–23].

Therefore, these by-products are attractive sustainable sources of such bioactive compounds beneficial to human health and subsequently their upcycling is becoming a new trend in food science. Many of these compounds are available in large quantities from wineries' sustainable re-usable sources, at very low cost, making their recovery and valorisation both economically viable and environmentally friendly, with growing attention to agricultural sustainability and consumer preference for natural over synthetic substances. Bioactive compounds are relatively inexpensive to appropriately extract and recover from winery by-products, since they can be valorised as ingredients for the development of added-value products with improved functionality, such as functional foods, food supplements and nutraceuticals and/or even for cosmeutics. There is a lot of interest in re-using winery by-products as food additives and ingredients of functional foods. Numerous studies have been conducted to understand the bioactivity of grapes and their products and by-products, with the main effort focused on antioxidant activity, which is associated with their high content of polyphenols acting as free radical scavengers [22,23].

Within this article, a holistic overview of the bioactive compounds, functional properties and associated health benefits and potential applications of the fermented alcoholic beverage, wine, is thoroughly conducted. In addition, the valorisation of such bioactives present in winery by-products is also evaluated. Emphasis is given to the composition, nutritional content value and health benefits of wine and winery by-products and especially of their important bio-functional components, such as their bioactive lipids, phenolics, dietary fibres, probiotics and other beneficial compounds with significant antioxidant, anti-inflammatory and antithrombotic properties and associated health benefits. Specific frameworks are also considered regarding the industrial valorisation of such produce, as well as the production of innovative functional foods and nutraceuticals against the risk of chronic diseases. This review provides a comprehensive picture of strengths and limitations, which can aid future studies in advancing the applications of wine and winery by-products and of their bioactives with respect to their health-promoting effects. A detailed table of contents–framework and the Supplementary Tables S1 and S2 of this article are provided in a Supplementary File.

2. Bio-Functional Compounds and Health Benefits of the Fermented Alcoholic Beverage, Wine, and of Its By-Products

2.1. Composition, Nutritional Value, Bio-Functional Components and Functional Properties

2.1.1. Composition and Nutritional Value of Wine

Wine is a traditional alcoholic beverage acquired by the processing of grapes and the alcoholic fermentation of the grape must. More specifically, following harvest, grapes enter the winery to finalise the vinification process and undergo de-stemming, crushing, pressing, maceration and alcoholic fermentation [1]. Wine comprises a vast range of constituents such as aldehydes, ketones, esters, minerals, lipids, phenolics, organic acids, soluble proteins, sugars and vitamins. The quality of wine is tightly linked to the complexity of its compounds and subsequently to the composition and variety of the grape and the fermentation process involved [1,11,18,23,30]. White wine is exclusively obtained from the fermentation of grape juice, while red wines are formed by the fermentation of musts combined with solid parts of the grape, the skins and seeds [30].

The maceration process for producing red wines requires the inclusion of skins, grape pieces and seeds with the must, which allows higher extraction of polyphenols from these sources, increasing the phenolic composition of red wine and subsequently substantially affecting wine's colour and flavour [1]. Thus, red wine is distinct as it usually contains much more phenolic compounds than white wine. Maceration also facilitates the production of metabolites such as acetaldehyde from yeasts, which react with phenolic compounds, while the absorption of anthocyanins by yeast cells also alters wine's colour and phenolic composition [1]. Following maceration, the separation of wine from the skins and seeds is conducted, in combination with the pressure of mash, while both these processes further significantly increase the phenolic content in wines and thus their antioxidant properties [31].

Maturation of red wine takes place in barrels and its main purpose is to soften the astringent and bitter taste due to the high phenolic content. Red wines require a more lengthened maturation process as a result of their high phenolic content to enhance quality, character and flavour [31]. By extending the maturation time, wine's alcohol levels are usually increased and this can result in the over-extraction of components from the solid element of grapes, particularly the seeds, which subsequently increases the phenolic and flavonoid content, in addition to the trans- and cis-resveratrol concentration and lipid composition [31]. Regardless of the alterations to red wine during maturation, the level of antioxidant capacity might remain consistent throughout the process [31]. The most studied bioactivity of wine is its antioxidant properties and the proposed associated health benefits, which are strongly correlated with the total phenolic content of wine. The antioxidant capacity of red wine is not defined by one single compound, as several wine components exert a synergistic effect through several mechanisms of the antioxidant activity of wine [32].

Significant interest has recently been given to several wine constituents that have also shown strong anti-inflammatory and antithrombotic bio-functional properties and protective effects, such as specific phenolic compounds [1–14,18–20,25,30–32] and lipid bioactives of wine [1,5–14,16–22]. The functionality of red wine is strongly associated with its high polyphenolic content that exerts anti-inflammatory and antioxidant effects, while some of wine's lipid bioactives, such as its unsaturated fatty acids (UFA) and bio-functional polar lipids, which are usually present in lower but substantial levels in wine, also contribute to the antithrombotic and anti-inflammatory bioactivities of wine [1–14,18–20,25,30–32].

Not only red wine but other types of wine have also exhibited potent antioxidant activities and anti-inflammatory protective effects against atherosclerosis and platelet aggregation. For example, significant antioxidant capacity and anti-inflammatory potential have been found in several white wines, even though they possess a lower concentration of phenolic compounds than that observed in red wine (Table 1) by being produced in the absence of grape skins, seeds and stems [9–12]. If the maceration process of white wines is extended in the presence of grape pomace it can result in an increase in the phenolic content and thus in the development of unique organoleptic characteristics (an orange-amber colour and a distinct tannic flavour) and increased antioxidant capacity [1]. Moreover, consumption of white wine (i.e., Robola), along with a meal, in a Mediterranean diet concept, resulted in a postprandially decreased platelet aggregation, induced by the inflammatory mediator, PAF, and maintained low triacylglycerol levels during postprandial elevation, in a comparable potency to similar beneficial effects observed in studies based in the intake of a red Cabernet Sauvignon variety, along with the same meal. It seems that the presence of PAF inhibitors in both white and red wine seems to equally influence wine's anti-inflammatory beneficial effects [9–12]. Subsequently, the incorporation of moderate consumption of either red or white wine in the diet may contribute to preventing the clinical manifestations involved in the development of inflammation-related chronic disorders.

2.1.2. Wineries' By-Products—Composition and Nutritional Value

Grape pomace is the main by-product of wineries and accounts for 20% of processed grape weight, generated through the pressing of grapes for production of must. For every 6 L of wine, 1 kg of grape pomace is produced, though this may depend on the type of press used and the grape variety. The composition of grapes and their subsequent pomace vary according to intrinsic factors, such as variety and maturity, and extrinsic factors, such as soil conditions and agricultural practices [22,23]. This affects not only the sensory properties of the wine product but also other applications of fresh pomace. Furthermore, red wine pomace and white wine pomace are inherently different due to the different winemaking processes for producing these two different wines. The incorporation of grape skin and pulps in the fermentation process for making red wine, before being filtered out, leads to red wine pomace containing a higher concentration of polyphenols. During white winemaking, the juice is pressed out and the pomace is discarded early in the process, which results in white wine pomace retaining the fermentable sugars.

The weight of the grapes is made up of 2–5% seeds and 38–52% solid waste matter created during the winemaking process. The seeds include around 40% fibre, 10% protein, 10–20% lipids and another 30–40% carbohydrates, complex phenolics, vitamins and minerals. Grape pomace contains phenolic compounds, with approximately 0.3–9% total phenolic content, as well as 17–89% total dietary fibre, 16–64% insoluble fibre, 4–14% proteins, 1–14% lipids, 12–40% carbohydrates and another 2–9% ash (Table 2) [16,22,23,33–42].

Ultimately, wineries' by-products pose a difficult waste disposal challenge for the wine industry. Though much of the grape pomace is composted and re-introduced into the vineyards to complete the carbon cycle, the utilisation of grape pomace has been largely inefficient. The pomaces are often converted to cattle feed or used as materials for biofuel digesters, and in some environmentally detrimental cases, for landfill disposal or incineration. Following the growing sustainability concerns, as well as consumer demand for natural products, there is immense potential in bioconversion of these by-products and of their bioactives into functional foods, supplements or additives. With the integration of in vitro techniques and high-end bioprocess engineering technologies, the continuous production of nutritionally improved wine pomace-derived metabolites could be achieved. Another valuable by-product is grape seed oil, which is rich in both unsaturated lipid bioactives and lipophilic/amphiphilic phenolics and thus can also promote lower production costs, being more competitive than others, and represent a new functional food source for human consumption in the food industry [22,23].

Table 1. Proximate composition of nutritional components, total phenolic content and major phenolic compounds and the antioxidant capacity of red and white wines *.

Nutritional Components [1]	Red Wine	White Wine
Glycerol	1–1.2	1–1.2
Acids	0.5–0.7	0.6–0.8
Amino acids	0.2–0.3	0.2–0.3
Phenols	0.1–0.3	0–0.02
Sugars	0.01–0.1	0.01–0.1
Lipids	0.01–0.03	0–0.02
Vitamins	0–0.02	0–0.02
Phenolic Compounds [2]	**Red Wine**	**White Wine**
Gallic acid	0–126	0–7
Protocatechuic acid	0–10	0–13
Syringic acid	0–23	0–2
Caffeic acid	0–77	0–7
Coumaric acid	0–40	0–6
Hydroxybenzaldehydes	0–46	2–6
Resveratrol	0–62	0–3
Resveratrol 3-O-glucoside	0–88	0–13
Catechin	14–390	0–46
Epigallocatechin	0–165	0–60
Quercetin	12–110	1–21
Cyanidin	0–12	-
Malvidin	12–541	0–4
Proanthocyanidins	100–560	0–2
Tyrosols	6–54	3–6
Total phenolic content	983–3624	89–434
Antioxidant Capacity [3]	**Red Wine**	**White Wine [2]**
TAAc	7.5–16.6	
FRAP	6.9–15.2	
DPPH	0.2–1.6	0.6–5.8

* Data are a combination of the ones presented in [1,30,36,43]; [1] estimates of typical gross composition (percentage weight) %; [2] expressed in mg of gallic acid equivalent (GAE) per litre (mg GAE/L); [3] expressed as Trolox equivalent (TE) antioxidant capacity (TEAC) in mmol of Trolox per L (mmol/L); TAAc: total antioxidant activity; DPPH: 2,2-diphenyl-1-picrylhydrazyl; FRAP: ferric-reducing antioxidant power assay; Trolox: 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid.

Table 2. Proximate composition, phenolic content, antioxidant activity (TAAc, ABTS and DPPH) and reducing power (FRAP) of extracts of grape pomace, based on dry weight (DW).

Nutritional Compounds	Quantity (g/100 g DW) *	Phenolic Compounds	Quantity (mg/100 g DW) *
Ash	1.7–9.1	Flavonoids	1121.3–1723.4
Protein	3.6–14.2	Anthocyanins	490.7–2983.5
Lipids	1.1–13.9	Tannins	350.0–625.2
Total dietary fibre	17.3–88.7	Procyanidin	1545.2–2582.8
Insoluble fibre	16.4–63.7	Catechin	78.8–195.0
Carbohydrates	12.2–40.5	Epicatechin	18.1–150.0
		Gallic acid	4.6–18.7
		Quercetin	157.7–1518.0
		Resveratrol	0.3–383.1

Table 2. *Cont.*

Nutritional Compounds	Quantity (g/100 g DW) *	Phenolic Compounds	Quantity (mg/100 g DW) *
Total polyphenolic content	0.28–16.2 *	-	18.5–77.0 **
Antioxidant activity		TAAc ABTS DPPH FRAP	14.6–75.1 ** 191.2–85.1 *** 185.6–510.1 *** 116.5–250.4 ***

* Expressed as mg of compound the specific phenolic group per 100 g of DW (mg/100 g DW); ** expressed as mg of gallic acid equivalent (GAE) per g of DW; *** expressed as Trolox equivalent antioxidant capacity (TEAC) in μMol of Trolox equivalent (TE) per gram of DW (μMol/g); TAAc: total antioxidant activity; ABTS: 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulphonate); DPPH: 2,2-diphenyl-1-picrylhydrazyl; Trolox: 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid; FRAP: ferric-reducing antioxidant power assay; data are a combination of the ones presented in [16,22,23,33–42].

2.2. Bio-Functional Components and Associated Health Benefits

2.2.1. Wine and Winery By-Products' Phenolic Bioactives with Antioxidant, Anti-Inflammatory and Antithrombotic Health-Promoting Effects

Phenolic Bioactives and Antioxidant Health-Promoting Bioactivities

Phenolic compounds are the most abundant bioactive components in wine [1–4,32,43,44] and are primarily present in the seeds and skins of grapes, except for hydroxycinnamic acids which are found in lesser amounts in the flesh [1,22,23,36,37,42]. The high number of factors influencing phytochemical composition and content leads to a very wide range of phenolic contents in wine (Table 1). In general, red grape varieties have more phenolic compounds than white grape varieties, and vineyard interventions similarly have a significant impact on grape phenolic compositions and subsequently on wine's phenolic content. The vinification process, maceration and several other processes like wine maturation that are applied for red wine production further induce higher phenolics' extraction and increased phenolic content in the final wine product.

The estimated overall polyphenolic composition in red wines usually ranges from 1531 to 3192 mg of gallic acid equivalents (GAE) per litre (mg GAE/L), with some specific types of red wine containing lower total phenolic content, such as some red wines produced in Spain from grape varieties like Monastrell [1]. White wine exhibits a lower phenolic composition, which usually ranges between 210 and 402 GAE/L, with some white wines exhibiting higher total phenolic content, such as white wines produced from *Malvazija istarska* grape varieties, by applying a standard vinification process but with increased bottle maturation or by incorporating some kind of a maceration process [1]. The remaining wineries' by-products like the grape pomace also contain valuable amounts of phenolic compounds (Table 2) [16,22,23,33–42].

The phenolic compounds found in both the wine product and the winery by-products can be divided into two main groups, flavonoids and non-flavonoids (Figure 1) [36,42–45]. Flavonoids comprise 85% of the phenolic constituents in red wine and are primarily present in the skins of grapes, as well as in both wine and its main by-products (grape pomace). They mainly comprise flavan-3-ols, anthocyanins and flavonols (Figure 1). Flavan-3-ols include monomers like catechin, epicatechin and polymers (polyphenols) like proanthocyanidins [1–4,36,37,42–44]. Flavanols, catechins and epicatechins are the most complicated subclass of flavonoids that contribute to the different sensory qualities and structure of wines, by interacting with proline-rich proteins in the mouth to produce an astringent sensation and bitter taste [30]. In the non-flavonoid group of phenolic compounds, several phenolic acids (cinnamic/hydroxycinnamic acids and benzoic/hydroxybenzoic acids), phenolic aldehydes, volatile simple phenolics, stilbenes, tannins and coumarins are classified (Figure 1) [36,37,42–46].

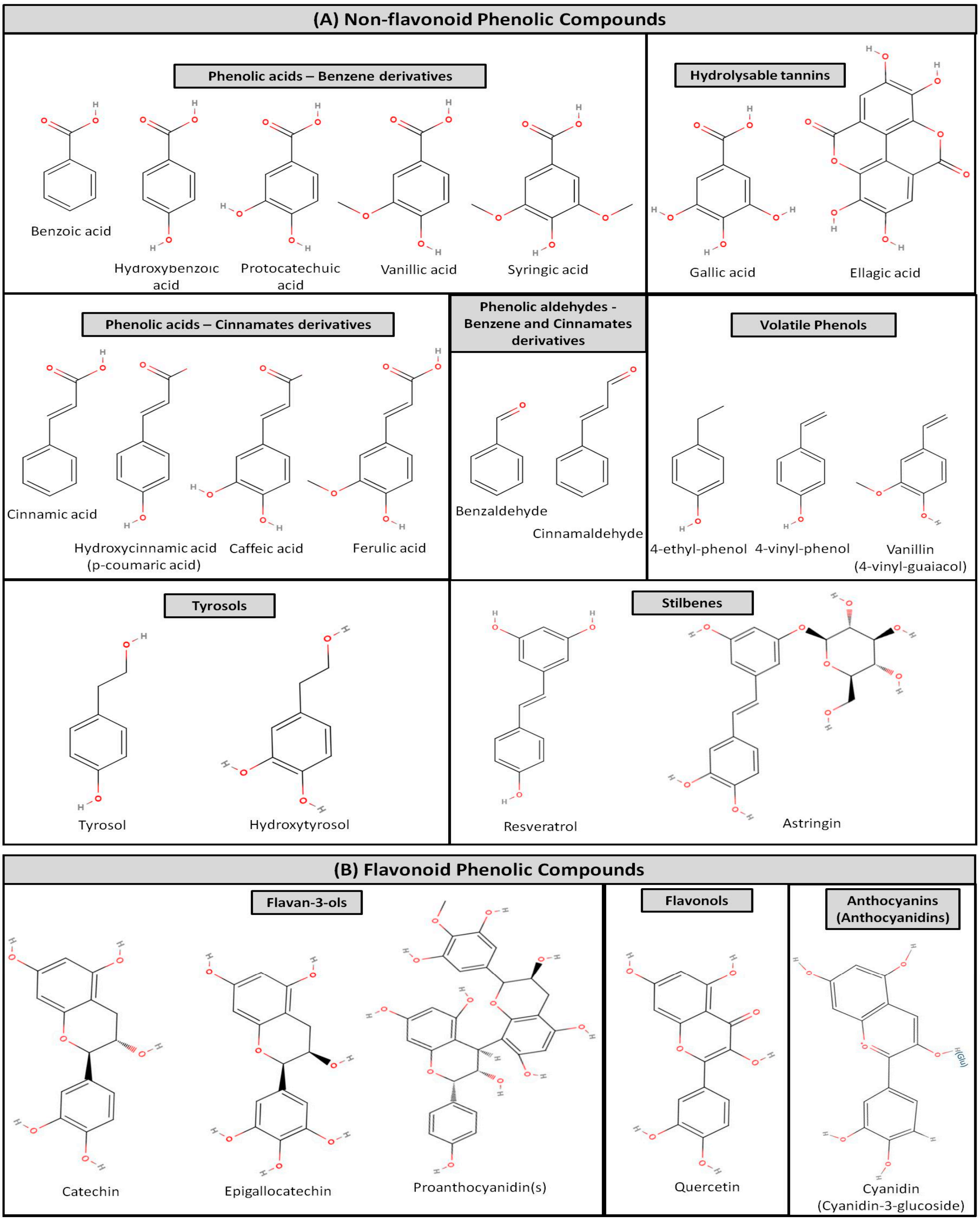

Figure 1. The structures of the most characteristic non-flavonoid (**A**) and flavonoid (**B**) phenolic compounds present in wine and/or grape pomace. Structures were obtained from https://molview.org/ (accessed on 24 April 2023).

Apart from their role on the organoleptic characteristics of wine, phenolic compounds have exhibited potent antioxidant, anti-inflammatory and antithrombotic bioactivities. Thus, they seem to contribute to the health benefits associated with moderate consumption of wine, as well as to the potential re-use of wineries' by-products as a sustainable source of functional ingredients. The most bioactive phenolics are the flavonols, flavanols and anthocyanins from the flavonoids, as well as resveratrol from the non-flavonoids [1–6,22,23,25,30,32–53].

Research on such phenolics was initially focused to their strong antioxidant capacity [1,4,20,21,32,36–41,43,51–55], within the concept of "the greater the polyphenolic content, the greater the antioxidant activity" for a wine product or its by-products [1,22]. Wine's stilbenes, flavonoids and flavan-3-ols have been proposed to protect membranes from oxidative stress, while by crossing cell membranes they can reduce reactive oxygen species (ROS) in membranes and within cells too [54]. Thus, the antioxidant activity of wine flavonoids is linked to their ability to scavenge free radicals. This can reduce the vulnerability of low-density lipoprotein (LDL) to oxidation and may prevent the manifestation of endothelial dysfunction and atherosclerosis [51,53–57]. The presence of polyphenols strongly influences the antioxidant effects of moderate wine consumption with a meal, and subsequently it can significantly enhance plasma total antioxidant capacity (TAC) and counteract oxidative lipid damage and the activation of nuclear factor kappa B (NF-κB) signaling [55].

Even though phenolics of wine and wineries' by-products are not essential nutrients, they can contribute to health through several pleiotropic effects, and subsequently they also do not fit in the classic and rigorous pharmacological definitions, as they can be modified by organisms before they interact with targets, can have different targets depending on their concentration and do not have a univocal pharmacological mechanism of action [42,43,46]. Therefore, a reductionist approach or studying mainly one mechanism of action (i.e., antioxidant activities of wine phenolics) should not be followed, because this can limit their classification to them being only free radical scavengers and antioxidants, while wine phenolics also possess manifold mechanisms of pleiotropic actions, including potent anti-inflammatory properties [43].

Pleiotropic Health-Promoting Effects of Phenolic Bioactives

Oxidative stress, inflammation and thrombosis are usually intertwined processes, while their un-regulation can further promote a vicious thrombo-inflammatory and oxidative stress cycle, which usually results in the onset and development of several chronic disorders, including atherosclerosis, CVD, insulin resistance, hypertension and cancer [6,7,9,24,43,56]. Wine phenolics are not only linked with an increase in antioxidant capacity but also with potent anti-inflammatory beneficial effects and a reduction in pro-inflammatory markers. The incorporation of phenolic bioactives of wine and wineries' by-products in functional foods and/or in the diet can promote not only antioxidant effects but also a plethora of anti-inflammatory health benefits too [4,22,25,42,43,50,56–61]. Subsequently, red wine and its polyphenolic content play an essential role in preventing inflammation-related disorders and especially CVD through their pleiotropic antioxidant, antithrombotic, anti-inflammatory and antiatherogenic properties [1–4,30,43,48–51].

The mode of action by which polyphenols of wine and winery by-products exert their beneficial properties appears to involve the interplay between molecular signaling pathways and regulators of cellular actions involved in inflammation [2,4–6,18,30,42,43,48–50,59]. The interlinked anti-inflammatory and antioxidant actions of the polyphenolic content of wine and wineries' by-products contribute to greater antioxidant serum activity, increased resistance of LDL peroxidation and subsequent inhibition of LDL oxidation, stimulation of high-density lipoprotein (HDL) levels, the promotion of vasorelaxation and endothelial protection, the inhibition of platelet aggregation and lowering of platelet sensitisation and adhesiveness, as well as the inhibition of the activities and synthesis of inflammatory mediators like PAF and cytokines. All these activities can result in a plethora of anti-inflammatory effects on several inflammatory genes, mediators, receptors, adhesive molecules, signaling pathways, thrombo-inflammatory manifestations and associated disorders [4,22,42,43,48–50,56].

Both flavonoids and non-flavonoids have exhibited such benefits, with differential effects of each compound in both groups also being reported [2,3,30,43]. The different interactions of wine flavonoids with key biological targets are linked to their unique structure. Such structure–activity relationships are crucial for the anti-inflammatory health-protective properties of both wine and of functional products derived from winery by-products against several diseases like CVD, cancer, obesity, neurodegenerative diseases, diabetes, allergies and osteoporosis [2,4,18,22,23,30,43,44,48–50,59]. Pleiotropic anti-inflammatory benefits on vascular health have been observed in trials based on monomeric or polymeric flavonoids [62]. Consumption of polymeric flavonoids like procyanidins (polyphenols that are polymers of catechin and/or epicatechin units) within a diet is correlated to the reduced risk of developing type 2 diabetes (T2D) and CVD [63].

Apart from flavan-3-ols and flavonols, grapes and grape products and by-products also contain high concentrations of anthocyanins, some of the most important water-soluble flavonoid pigments in nature [22,23,42]. Anthocyanins are found in high contents in red wine, especially in red wine's grape pomace wastes, and in lesser amounts in white wines and their grape pomaces [22,23,30,42]. Pharmacokinetics-based studies showed that anthocyanins are rapidly absorbed into the bloodstream shortly after consumption, with a positive implication and essential role in the prevention of a variety of diseases, including cancer, neurodegenerative disorders and CVD, due to both their antioxidant activities and anti-inflammatory effects [4,30,42,48,49].

Among the non-flavonoid group of phenolic compounds in grapes, wine and grape pomace, a plethora of studies have highlighted the antioxidant and anti-inflammatory health benefits and preventative–therapeutic properties of resveratrol [1–3,5–7,18,42–44,50,64–67]. The benefits of resveratrol, as the main bioactive component of wine, have been documented since the 1990s, when Drs. Michel de Lorgeril and Serge Renaud talked about the "French paradox", the observation of an unusually low rate of heart disease among southern French people who drink a lot of red wine, despite a high-saturated-fat diet, and the theoretically inhibitory effects of wine consumption against lipid peroxidation, on the "60 Minutes" CBS show [43,64,66]. At the time, the "free radical/antioxidant hypothesis" was in full swing and it was commonplace to believe that eating and drinking (poly)phenols would scavenge free radicals and prevent their detrimental effects, for example, by inhibiting LDL oxidation [43,64].

This granted red wine (poly)phenols, mostly resveratrol, immediate popularity as a possible explanation for the "French paradox" and triggered a vast amount of well-funded research [43,64,66], highlighting resveratrol as a pan-interfering compound in a wide range of signaling pathways and a highly pleiotropic molecule that modulates numerous targets and molecular functions [65–74]. Subsequently, resveratrol's usage as a nutraceutical and as a strong candidate for a natural-origin drug-designed therapeutics against several disorders has been extensively investigated in in vitro, ex vivo and in vivo studies, including preclinical and clinical trials.

Resveratrol is believed to decrease oxidative stress, lipid peroxidation and circulating LDL-cholesterol levels, as well as to reduce platelet aggregation and thus CVD risk [65–74]. Resveratrol's ability to protect against both inflammation and oxidative stress can also occur via affecting the nuclear erythroid 2-related factor 2 (Nrf2) signaling pathway [75]. Moreover, the cardioprotective anti-inflammatory effects of resveratrol have been demonstrated at nutritionally relevant concentrations, by decreasing the over-expression of intercellular and vascular cell adhesion molecules, as it inhibits the inflammatory cytokines-induced activation of coronary arterial endothelial cells. This activity includes the inhibition of tumour necrosis factor alpha (TNF-α)-induced NF-κB activation of these cells and the subsequent expression of inflammatory genes [68,76,77]. Resveratrol supplementation may partially protect against CVD, especially during the early atherosclerotic phase, by its anti-inflammatory effects and by reducing circulating levels of important chemotactic chemokines, such as the monocyte chemoattractant protein-1 (MCP-1/CCL2) and macrophage inflammatory protein-1 alpha (MIP-1α/CCL3) that regulate migration and infiltration of monocytes/macrophages and are induced and involved in various diseases [68,76].

Resveratrol beneficially affects both the actions and levels of inflammatory cytokines associated with not only CVD but also with cancer, such as interleukin (IL)-1 and TNF-α [78,79]. For example, resveratrol has improved the TNF-α-induced endothelial dysfunction during the interaction of Caco-2 tumour cells and endothelium [78]. The anticancer potential of resveratrol was also demonstrated by the induced autophagic cell death and reduction in cell viability found in oral cancer cells but absent from normal cells [80]. Very recent studies in 2023 have also indicated the antitumour effects of resveratrol and other wine phenolics through their (pro)apoptotic and immune-regulatory effects [6,50,80–87]. Resveratrol has also been reported to suppress tumour metastasis by its effects on platelets and by inhibiting platelet-mediated angiogenic responses, proposing resveratrol as a potential therapeutic drug for the prevention of tumour metastasis due to interrupting the platelet–tumour cell amplification loop [87].

The beneficial effects of wine and grape pomace phenolics and especially of resveratrol on several platelet functions, through various mechanisms, further support their health-promoting properties [22,68,70,74,87–91]. For example, resveratrol and wine and grape pomace phenolics in general have shown strong cardioprotective properties and anti-inflammatory protection and antithrombotic protection against inflammation and thrombosis-related chronic disorders by strongly inhibiting platelet aggregation and the activation and sensitisation of platelets induced by the activities and release of thrombotic and inflammatory mediators, such as PAF, thrombin, collagen, fibrinogen, arachidonic acid (AA), thromboxane A2 (TxA2), TxB2 and ADP [1,22,30,43,68,70,74,87–91].

Resveratrol-induced inhibition of platelet metabolism and TxA2 release may lead to a reduction of platelet function and thrombus formation in patients with type 2 diabetes, and thus resveratrol may be beneficial to prevent vascular complications as a future complementary treatment in aspirin-resistant diabetic patients [88]. More specifically, resveratrol reduced collagen-induced thrombi by over 50% in both the blood of healthy and diabetic patients, TxA2 release by 38% in healthy platelets and by 79% in diabetic platelets. Resveratrol also reduced the activities of enzymes responsible for glycolysis and oxidative metabolism in the platelets of both groups [88]. Such effects of resveratrol on platelets appear to be mediated through cyclooxygenase-1 (COX-1) repression, which results in decreased TxA2 production and thus inhibition of platelet aggregation, rather than through cyclooxygenase-2 (COX-2) that synthesises prostacyclins as antiplatelet factors in vascular endothelium [69]. Resveratrol can reduce platelet aggregation by forming stable complexes in platelet COX-1 channels, as well as by inhibiting the arachidonate-dependent synthesis of inflammatory agents, such as TxB2, hydroxyheptadecatrienoate and 12-hydroxyeicosatetraenoate [69,89].

Moreover, resveratrol inhibits thrombin-induced platelet aggregation through decreasing Ca^{2+} release from its stores and inhibiting store-operated Ca^{2+} influx into platelets [91], while it has also been proposed that resveratrol may inhibit platelet aggregation induced by epinephrine and other mediators by increasing NO production [70]. In addition, the antiplatelet effects of resveratrol and subsequently its antithrombotic and anti-inflammatory benefits, both in vitro and in vivo, have also been attributed to its potential to modulate gene/protein expression of tissue factor (TF) and its functions, since TF, which can be produced by several cells and especially under inflammatory cytokines' induction, is a well-known thromboplastin, which activates thrombosis through binding to and further stimulation of coagulation factor VII as a principal initiator of extrinsic coagulation cascade [69].

Wine and grape pomace phenolics and resveratrol seem to act beneficially on the functions of several other cells and tissues, where similar signaling and associated mechanisms also take place. Recent studies have outlined that resveratrol can target and activate AMP-activated protein kinase (AMPK), having an important role in reducing fat accumulation, cholesterol synthesis and inflammatory cytokines. Resveratrol seems to protect against disorders, such as improper metabolic regulation, inflammation and cell cycle abnormalities, by activating/stimulating the mammalian versions of the sirtuin family of proteins (SIRT1) and thus all the pathways regulated by these regulatory proteins [66–68]; SIRT1 proteins are implicated in deacetylation of histones and non-histone proteins, such as transcription factors, and thus they affect important processes like metabolism, stress resistance, cell survival, cellular senescence, inflammation, immune reaction, endothelial functions and circadian rhythms. Stimulation of SIRT1 and AMPK also boosts the eNOS activity in human coronary arterial endothelial cells and increases NO production and mitochondrial biogenesis, which triggers vasodilation and decreases atherosclerosis [68].

Interestingly, resveratrol-induced activation of SIRT1 also downregulates the expression of the receptor of PAF (PAFR) on platelets via proteosomal and lysosomal pathways, which also inhibits platelet aggregation, in vitro, and pulmonary thrombus formation, in vivo [88]. It has also been proposed that resveratrol might improve cardiovascular health by affecting the gene expression for producing PAFs [69]. Resveratrol has also been found to reduce the levels of PAF by inhibiting its synthesis and thus reducing the inflammatory status [5–7,92]. For example, resveratrol has inhibited PAF synthesis in human mesangial cells [5], as well as in U-937 macrophages under inflammatory conditions [92], suggesting a potential anti-PAF protective effect of resveratrol against cancer and tumour metastatic procedures [6], as well as several other anti-PAF protective effects against PAF-associated inflammatory and thrombotic chronic diseases [7].

Resveratrol presents low bioavailability and is rapidly excreted, while consumption of pure resveratrol at doses higher than those present in wines results in a low content of this compound in plasma. These findings may challenge the common idea that resveratrol is the main phenolic compound associated with cardioprotective effects. Consequently, other stilbenes and/or other wine phenolic compounds like wine flavonoids have also been proposed to provide several benefits [70]. Astringin is another stilbene for which early reports have cited promising antioxidant activity and a free radical-scavenging ability more potent than that of resveratrol, while other natural and synthetic analogues/derivatives of resveratrol have also been extensively studied for enhanced beneficial effects against inflammation, thrombosis and associated disorders [66–69,71,72,93–95].

Limitations and Future Perspectives of Phenolic Compounds as Bioactive Ingredients with Health-Promoting Properties

The majority of the reviewed phenolic phytochemicals in wine and grape pomace require relatively high doses to be active on several cells and tissues in vitro and these doses may further increase when plasma is present, for instance, in the case of resveratrol. As Professor Visioli et al. (2020) have highlighted, animal studies often employ very high doses of grape/wine (poly)phenols, such as resveratrol, with results that cannot be readily transferred to humans, who would need to ingest several grams of extracts to replicate such effects [43]. Discrepancies between animal and human effects and potential toxicity of high doses of resveratrol should also be considered [43]. High dosing of such compounds is one of the drawbacks for their testing in interventions as putative therapeutic agents [4,43,74].

Other limitations are the often-unclear bioavailability and metabolic absorption of the phytochemicals and of their metabolites, the pharmacokinetic profile in blood and non-platelet effects, which for the cardiovascular system may be positive or negative [4,43,74]. Several phenolic compounds are very weak (if at all effective) direct antioxidants in vivo, while for kinetic reasons they do not scavenge free radicals and their bioavailability is generally so low that they contribute very little to the integrated cellular antioxidant machinery, which is mostly composed of enzymes [43]. Subsequently, a gap still exists between the knowledge of wine flavonoids' bioavailability and their health-promoting effects. The beneficial effects of dietary phenolic compounds are affected by their low intestinal absorption as well as their differential bioavailability and interactions with plasma and gut microbiota that generate broad shifts in the plasma metabolome and gut microbiota composition [4,26,43,74,96–101]. It is estimated that the small intestine only absorbs 5–10% of consumed dietary polyphenols following enzymatic glycosylation. The remaining dietary polyphenols enter the colon intact and undergo degradation by the gut microbiota, yielding simple phenolic acids that are absorbed into the bloodstream [96]. Thus, it is apparent that the gut microbiota facilitates the bioaccumulation of polyphenols and their associated metabolites.

Hence, the molecular forms of phenolic compounds that contribute to health benefits are not limited to those ingested but also include their associated metabolites created in vivo by the intestinal microbiota. Lately, plenty of researchers have correctly used (poly)phenols' metabolites in their in vitro studies, while the relatively recent discovery of microbiota-synthesised metabolites amplifies the list of potential biologically active molecules produced by the body after the ingestion of (poly)phenol-rich foods [43]. Attention has been given to low-molecular-weight polyphenol-related components consisting of free anthocyanins, free proanthocyanins, pyranoanthocyanins as well as smaller amounts of phenolic acids and resveratrol, although with difficulty in synthesising such metabolites, which are often produced by the body in different forms.

Moreover, it is also necessary to better understand how biological interactions (with microbiota and cells, enzymes or general biological systems) could interfere with phenolics' bioavailability. Therefore, more in vivo results as well as studies focused on phenolic metabolites are still required. Nevertheless, the moderate consumption of red wine is positively correlated with the beneficial modulation of gut microbiota [100]. For example, resveratrol plays a significant role in the regulation of the gut microbiome, protection of the intestinal barrier and in the inhibition of intestinal inflammation [96–101]. The ability of red wine consumption to balance the growth of select gut microbiota in humans indicates the potential probiotic benefits linked to the incorporation of red wine polyphenols into the diet.

In addition, the acquired knowledge on effects of certain phytochemicals, as platelet-inhibiting and anti-inflammatory compounds, can be employed for the further selection and chemical modification of these in the design of effective antiplatelet and anti-inflammatory drugs. In other words, those phytochemical compounds with a proven effect on platelets, thrombus formation and inflammation can trigger new ways for drug discovery. This could develop into new antiplatelet and anti-inflammatory drugs and also potentiate the action of current antiplatelet drugs, as several of the phytochemicals seem to have priming effects on platelets. Interestingly, combinations of wine and grape pomace phytochemicals with other bioactives that are present can have synergistic effects on platelets and inflammatory signaling, which will further enhance the priming.

2.2.2. Bioactive Lipid Compounds of Wine and Wineries' By-Products

Wine and wineries' by-products also contain several functional lipid bioactives. The lipids present in grapes/yeast undergo modifications during fermentation with the most bioactive lipids being in the final wine product and in the remaining winery by-products. Even though wine contains lower amounts of lipids compared to grapes and grape pomace, for the last 20 years Prof. C.A. Demopoulos and colleagues (Prof. Antonopoulou SA, Dr. Fragopoulou E, Dr. Nomikos T, Dr. Tsoupras A, et al.) have highlighted that the amphiphilic polar lipids present in wine and grape pomace, such as several phospholipids and especially glycolipids (Figure 2), originating from the grapes, yeasts and wine must, as well as due to the fermentation process, are highly bioactive and have exhibited strong anti-inflammatory, antithrombotic and antiatherogenic cardioprotection [7–14,16–20,22].

Such bioactive polar lipids usually contain bio-functional UFA, such as the monounsaturated fatty acid (MUFA) oleic acid (OA; 18:1 omega-9) and the long-chain polyunsaturated fatty acids (PUFA) linoleic acid (LA: 18:2 omega-6), gamma linoleic acid (GLA; 18:3 omega-6) and alpha linolenic acid (ALA; 18:3 omega-3), in a combination that usually favours an anti-inflammatory potential [16] (Figure 2A). UFA possess on their own strong anti-inflammatory and antithrombotic properties against several inflammatory and thrombotic mediators, including PAF, thus promoting an anti-inflammatory potential and health benefits against several inflammation-related disorders [7,102–107]. UFA in general control cell fluidity, the attachment of certain enzymes to cell membranes and the transmission of signals and other metabolic activities. Specific UFA are involved in the manufacture of eicosanoids, leukotrienes, prostaglandins and resolvins, some of which possess anti-inflammatory, antiarrhythmic and antiaggregatory properties [102]. Such UFAs promote cardiovascular health, with some inducing an increase in visual function and cognition in newborns and adults [102].

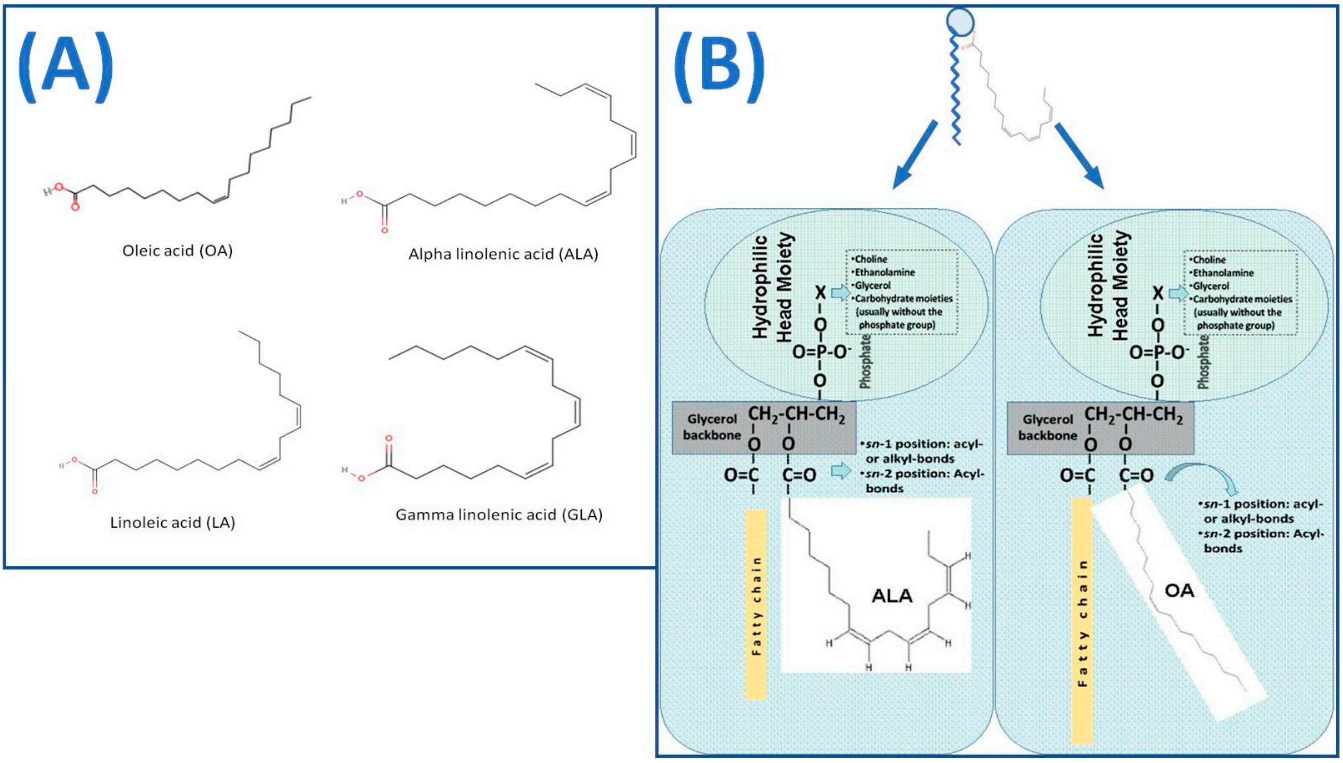

Figure 2. Structures of bioactive UFA (**A**) and biofunctional PL with UFA at the *sn*2 position of their glycerol backbone (**B**), with anti-inflammatory and antithrombotic properties and health benefits found in wine and grape pomace; ALA = alpha linolenic acid (C18:3 omega-3); OA = oleic acid (C18:1 omega-9).

Not only grape pomace but grape seeds are also high-value by-products for the extraction of lipid bioactives, such as biofunctional grape seed oils, which are rich in UFA [108,109]. In contrast to wine and grape pomace, grape seed oils have a low content of hydrophilic polyphenols, but they contain some amphiphilic/lipophilic phenolics and/or phenol-lipids [110]. The most abundant grape seed oil UFA is the omega-6 LA, which, however, has a complex nutritional role, with important functions in regulating inflammatory cellular processes. The omega-3 UFA like ALA, which is also present in high concentrations in both grape pomace and grape seed oils, possess well-known anti-inflammatory bioactivities and cardioprotective effects by reducing the synthesis and inhibiting the activities of thromboxane and PAF, as well as by demonstrating immense potential in inhibiting pro-inflammatory cytokines' synthesis [7,102,106,107]. Despite the suggestions of the possible health benefits of ALA, the anti-inflammatory effect of grape seed oil with regard to its high UFA and LA content remains to be seen [111].

Apart from UFA, recent research has focused on the bio-functionalitites of polar lipid bioactives present in wine and grape pomace [7–22]. Polar lipids are amphiphilic biomolecules and important structural elements for all cells, with a plethora of diverse bioactivities. Polar lipids generally contain two fatty acids, usually esterified or rarely etherified to a glycerol- or a sphingosine-based backbone, as well as a phosphorus-based or a sugar-based functional head group for phospholipids and glycolipids, respectively (Figure 2B). Functional polar lipids with bioactive UFAs like OA and/or ALA in their structures (usually at the *sn*2 position of their glycerol/sphingosine backbone) (Figure 2B) possess higher bioavailability of their UFA throughout the body, due to their amphiphilic properties, which allows them to easily travel in aqueous environments and be incorporated into cell membranes and/or intracellular domains, where they can release their anti-inflammatory UFA at specific sites through associated mechanisms.

Some bioactive polar lipids themselves possess strong anti-inflammatory and antithrombotic properties against several inflammatory mediators and signaling by a variety of mechanisms of actions (Figure 3). The strong anti-inflammatory and antithrombotic potential of such polar lipid bioactives of wine and winery by-products has been proposed to provide promising health benefits against atherosclerosis and CVD, cancer and metastatic procedures, renal and neurodegenerative disorders, persistent infections and associated inflammatory manifestations, allergic reactions and asthma, sepsis, etc. [6,7,11,14,18,22,102].

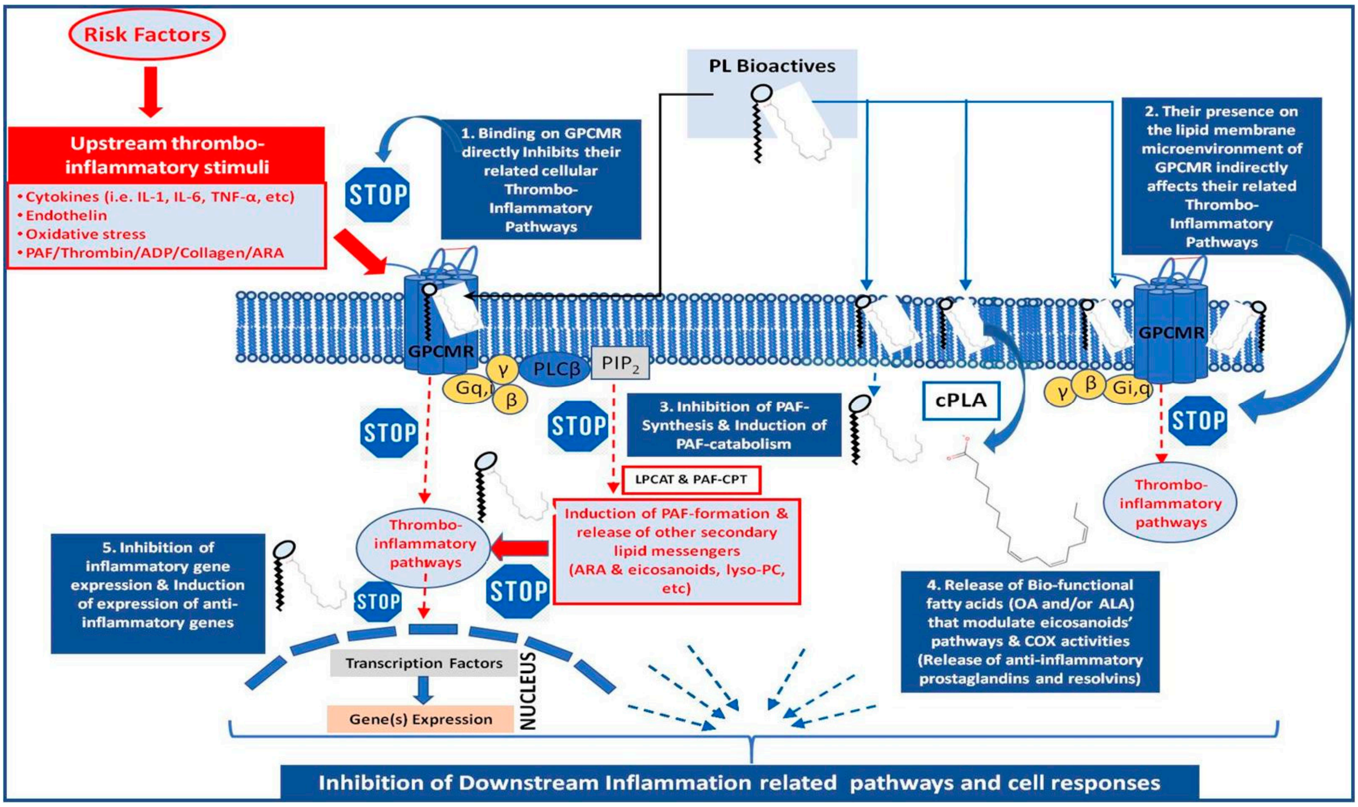

Figure 3. Modes of beneficial actions of the bioactive polar lipids (in blue) against the thrombo-inflammatory-related pathways and cell responses (red). PL = polar lipids; PAF = platelet-activating factor; ADP = adenosine 5′ diphosphate; GPCMR = G-protein coupled membrane receptors; cPLA2 = cytoplasmic phospholipase A2; LPCAT & PAF-CPT = basic regulatory biosynthetic enzymes of PAF; ARA = arachidonic acid; COX = cycloxygenases.

For example, such bioactive polar lipids have reduced the formation of atherosclerotic plaques by inhibiting the activities and modulating the metabolism of PAF towards reducing the levels of this inflammatory and thrombotic mediator and thus its atherogenic effects [7]. Since the thrombotic and inflammatory pathways of PAF are implicated in several chronic disorders, including cancer, atherosclerosis and CVD [6,7,24], the inhibition of PAF activities and the reduction of its levels by wine and grape pomace polar lipid bioactives further suggest their strong antiatherogenic, cardioprotective and antitumour potential [6–22]. Such bioactive polar lipids from wine, wine must, yeasts and grape pomace have also inhibited the inflammatory and thrombotic pathways of both PAF and thrombin in platelets, while they have reduced platelet sensitivity, activation and aggregation induced by other well-established platelet agonists like collagen and ADP too [7–22,112]. In sum, the anti-inflammatory and antithrombotic anti-PAF properties of these polar lipid bioactives occur by beneficially affecting PAF metabolism towards reduction of PAF levels to homeostatic ones, as well as by inhibiting the binding of PAF on its receptor and thus inhibiting

PAF-related inflammatory and thrombotic pathways and activities (Figure 3). Either or both of these bioactivities of polar lipids from wine and winery by-products' can reduce the risk for PAF-associated inflammatory chronic disorders, including atherosclerosis, CVD and cancer [6,7,11,14,18,22,102].

Apart from the strong anti-inflammatory and antithrombotic properties of the whole structures of such bioactive polar lipids, it has also been proposed that once the polar lipids rich in UFA have passed the intestine barrier, they bind to plasma lipoproteins by which they are transferred to membranes of all cells, where specific enzymatic machinery, such as the cytoplasmic phospholipase A2 (PLA2), releases the UFA content from these membrane-bound polar lipids towards intracellular domains. UFA released in this way further interact with inflammatory signaling, such as the eicosanoids' pathways (COX enzymes and related genes), towards reducing/resolving inflammation and the inflammatory cell response (Figure 3) [6,7,102].

Based on the above, several trials have recently been conducted in order to evaluate the effects of wine or of grape pomace extracts rich in phenolics and bioactive polar lipids against thrombo-inflammatory mediators like PAF, inflammatory cytokines' release and metabolic and oxidative stress responses [12,13,15,19–21].

The benefits of wine consumption and of grape pomace extracts are not only attributed to their rich phenolic content but also to other micro-constituents, such as their bioactive lipid compounds, and especially their glycolipids, phospholipids and UFA, as well as the synergism of all these bioactives. Although bioavailable amounts of the antioxidant wine and grape pomace polyphenols have little to do with a proposed in vivo protection against oxidative stress, they still play a crucial role as primary antioxidants against oxidation of bio-functional lipids, including polar lipids and UFA, in several natural sources, foods, beverages, cosmetics and lipid extracts, including wine and winery by-products [113]. In such extracts that contain both bioactive phenolics and lipid compounds, a very substantial improvement in oxidative stability, bioavailability and preservation of the bioactivities of phenolics, UFA and polar lipid compounds can be achieved by a co-presence and synergism of all these polar compounds. Subsequently, the presence of phenolic compounds in extracts rich in polar lipids and UFA, from any type of wine and/or winery by-product, seems to facilitate the preservation of the bioactivities of the protected lipid bioactive compounds.

Thus, the synergism of such wine and grape pomace bioactive compounds, which can ameliorate the oxidative stress response and inhibit the activities and/or reduce the levels of thrombo-inflammatory mediators like PAF and thrombin, seems to explain the potential of an extract rich in such polar organic bioactives, rather than of just one molecule like resveratrol, for the prevention/reduction of risk of several inflammation- and thrombosis-associated chronic disorders [6,7,10,11,14,18,22].

2.2.3. Bio-Functional Dietary Fibres from Wineries' By-Products

Dietary fibres are usually defined as "carbohydrate polymers that contain ten or more monomeric units, which are not hydrolysed by the endogenous enzymes in the small intestine of humans". The main proposed benefits from their inclusion in the diet are associated with prevention of CVD, cancer and diabetes, due to glucose absorption attenuation, improvement of food transit through the digestive system, blood cholesterol decrease and constipation and obesity prevention [108]. Dietary fibre has also exhibited antioxidant capacity, since products that are composed of more than 50% dietary fibre, on a dry matter basis, present a natural antioxidant capacity equivalent to at least 50 mg of vitamin E (when measured by the DPPH method) [108]. Recommendation guidelines for daily intake of dietary fibre (25–30 g/day) are not easily achieved and a need for alternative sources to cereals, vegetables and fruits has promoted the development of commercial fibre-rich products and supplements. These include by-products obtained from fruit processing, including grape pomace, as a potential sustainable source of dietary fibres, with a higher soluble dietary fibre content, better insoluble/soluble fibre ratio, low caloric content and better functional properties than those obtained from cereal processing [108].

The winemaking industry by-products have those characteristics, since grape skin is a complex lignocellulosic material containing large amounts of hemi-cellulosic sugars that, after hydrolysis, produce solutions containing a wide variety of xylose and glucose monomers [108]. The major component of dried wine pomace is dietary fibre, with concentrations as high as 85% depending on grape variety, with a major fraction of these dietary fibres being insoluble fibres such as lignin, cellulose and hemi-celluloses [33,108]. Apart from the general cardioprotective, antitumour and antidiabetic health benefits attributed to the intake of the appropriate composition of dietary fibres, grape pomace dietary fibres have also been shown to exhibit beneficial effects on the gastrointestinal tract due to the fibres' high porosity and low density but also due to being a major energy source for gut microbiota, having a significant impact on the microfloral diversity and indirectly on the innate immune response of the gut mucosa [33]. The grape pomace dietary fibres also have a complex formation with the ability to establish a linkage with polyphenols, increasing the capacity for phenolic compounds [33]. Overall, the aforementioned health benefits suggest that dietary fibres of grape pomace have potential to be used as functional ingredients in different food products, such as bakery products, beverages and meat products, as well as in cosmeceutical and nutraceutical–pharmaceutical applications and industries [33,108].

3. Health Benefits of Moderate Wine Consumption and Detrimental Effects of Alcohol Abuse: A Coin with Two Sides

3.1. Health-Promoting Effects of Incorporating Moderate Wine Consumption in Diet

The life expectancy in developing countries is continuously increasing, however, there is a resulting rise in the burden of chronic diseases related to age and lifestyle, such as diabetes mellitus, cancer, atherosclerosis and CVD, neurodegenerative disorders and amyloid diseases, notably Parkinson's and Alzheimer's diseases, among others. Numerous studies support that adherence to Mediterranean diet, or to other healthy dietary patterns, can protect against such disorders [6,7]. In recent years, extensive epidemiological studies, for instance, the Health Professionals Study, the Nurses' Health Study (NHS) and the European Prospective Investigation into Cancer and Nutrition (EPIC) study, as well as their follow-ups, have highlighted the health benefits associated with adherence to healthy diets and the detrimental effects linked to unhealthy dietary habits.

The light to moderate consumption of red wine has been characterised as one of the main characteristics of the Mediterranean diet and is proven to provide protective effects against CVD. Since the Lyon Diet Heart Study, the health benefits of wine consumption, mostly red wine, were initially attributed to the antioxidant protection of lipoproteins and cell membranes due to wine's rich content in phenolics, as presented by the main PIs of the study, Drs. Michel de Lorgeril and Serge Renaud, on the "60 Min" CBS show in the 1990s. During this show, they also talked about the "French paradox", the observation of an unusually low rate of heart disease among southern French people who drink a lot of red wine, despite a high-saturated-fat diet, and the theoretically inhibitory effects of wine consumption against lipid peroxidation [43,64,66]. Subsequently, the focus on the benefits of wine consumption was mainly given to its antioxidant potency and cardiovascular protection [18,43,48–50,56,64]. Nevertheless, as outlined in the Lyon Diet Heart Study, the components of food and alcoholic beverages included in the Mediterranean diet not only exhibit beneficial properties against lipid peroxidation but they also have an inhibitory effect against platelets' activation and aggregation [64], which was unfortunately not emphasised during that show and thus was initially neglected by many.

Since inflammation and thrombo-inflammation have been characterised as the main causes of the onset and development of CVD, as well as of several other inflammation-related chronic disorders [6,7,24], it is now well established that, apart from the antioxidant protection, the effects of moderate wine consumption that promote health benefits include mainly 1. beneficial moderation of lipid metabolism, 2. protection against oxidative stress, inflammation, platelet activation–aggregation and thrombo-inflammation, 3. improvement of endothelial function and 4. the modulatory effect on the gut microbiota.

The beneficial effects of moderate wine consumption have been extensively researched, mainly in several epidemiological studies. Recently, several interventions in animal models and humans, including randomised clinical trials, have evidenced that moderate wine consumption with meals based on a Mediterranean diet setting, or as part of other healthy diets, has exhibited health benefits against not only atherosclerosis and CVD (Supplementary Table S1) [12,13,19,20,25,53,55,60,62,64,99,114–125] but also against several other pathologies and all-cause mortality (Supplementary Table S2) [3,26,126–155].

More specifically, in Supplementary Table S1, several characteristic studies, interventions and clinical trials are outlined with respect to the benefits of moderate consumption of wine and its bio-functional compounds against inflammation, thrombosis, vascular inflammatory activation and adhesion of leukocytes, endothelial dysfunction, atherosclerosis and CVD [12,13,19,20,25,53,55,60,62,64,99,114–125]. Moreover, in Supplementary Table S2, other characteristic studies, interventions and clinical trials with respect to the benefits of moderate consumption of wine and its biofunctional compounds against other inflammatory and thrombotic manifestations and inflammation-related chronic disorders, including cancer, metabolic syndrome and diabetes mellitus, gastrointestinal disorders, pulmonary diseases, stroke, neurodegenerative diseases and depression, as well as all-cause mortality, are also presented.

As shown in all these studies presented in both Supplementary Tables, there is vast evidence demonstrating the anti-inflammatory protective effects and health benefits of moderate wine consumption. The most recent epidemiological studies are partly in agreement with the reported outcomes of the benefits of wine consumption, firstly presented in the Lyon Diet Heart study, while numerous clinical studies have now outlined the beneficial effects of wine consumption on inflammatory factors and endothelial function, which are paramount in the manifestation of chronic disorders.

A range of clinical studies have exhibited that the chemical composition of wine, with respect to its bio-functional components and their potential synergism(s), is the main contributor to the health benefits associated with moderate wine consumption. More specifically, the potent anti-inflammatory and antioxidant effects of wine and its bioactive components are major contributors to beneficial health outcomes. Moderate red wine consumption has exhibited anti-inflammatory properties by reducing markers of inflammation and, thus, preventing the likelihood of chronic inflammation. Such benefits are also provided by the positive interactions of wine and its compounds with gut microbiota.

In addition to the anti-inflammatory and antioxidant effects associated with wine and its bio-functional components, the moderate intake of wine can also provide protective effects against the pathogenesis of a range of chronic disorders. The most prominent mechanisms mediating the beneficial effects of moderate wine consumption are the induced enhancement of endothelial function and the counterbalance of inflammation by the synergistic activities of wine bioactives and/or their metabolites against inflammatory biomarkers, mediators and associated thrombo-inflammatory signaling pathways. This includes the reduction of the activities and levels of PAF and of other inflammatory chemokines and cytokines, as well as the down-regulation of monocyte adhesion to endothelial cells and the reduced expression of adhesion molecules. Once these mechanistic pathways are improved by the presence of wine bioactives and/or their metabolites during or just after moderate wine consumption, then all the other mechanisms are also beneficially affected with an overall health benefit against the risk for atherosclerosis, CVD and other inflammation-related chronic disorders (Supplementary Tables S1 and S2).

There are also studies like the Hoorn Study, in which the anti-inflammatory and endothelial protective health benefits of red wine consumption were emphasised in comparison to the other components of the Mediterranean diet. It was suggested that red wine consumption, but not fruit, vegetables, fish or dairy products, was the component that mainly protected against factors involved in the pathogenesis of CVD and other diseases, as it was associated with less endothelial dysfunction and less low-grade inflammation [23].

3.2. Alcohol-Containing Wine, Quantity Consumed and Detrimental/Beneficial Effects on Health: Is It Really a Debate or Is It a Matter of Re-Definitions and Re-Education?

With respect to the associations of wine consumption and several detrimental effects on health, including cancer, an intense scientific debate exists. Huge epidemiological studies like the Health Professionals Study, the Nurses' Health Study (NHS) and the European Prospective Investigation into Cancer and Nutrition (EPIC) study and their follow-ups have outlined that alcohol intake is associated with the presence and development of several types of cancers in both women and men, such as cutaneous basal cell carcinoma and colorectal, skin, pancreatic and, mainly, breast cancer [156–161]. However, whether an increase in the incidence of cancer is also observed in association with moderate consumption levels has not yet been definitively ascertained.

Based on the findings of such studies that alcohol is a leading risk factor for cancer, it has been observed in other studies that awareness about an alcohol–cancer link is low. Awareness may be influenced by perceptions of potential health benefits of alcohol consumption or certain alcoholic beverage types. A study based on data from the 2020 Health Information National Trends Survey, a nationally representative survey of US adults, estimated awareness of the alcohol–cancer link by beverage type and examined the relationship between this awareness and concomitant beliefs about alcohol and heart disease risk [162]. It was observed that low levels of accurate awareness exist on the cancer harms associated with alcohol use, including wine, beer and liquor consumption. Awareness of the alcohol–cancer link was higher among those recognising that alcohol use increased heart disease risk.

Based on these observations, it has been proposed that the "health halo" surrounding consumption of wine and other forms of alcohol as reducing heart disease risk has lead the public to overgeneralise alcohol's health benefits to other diseases, including cancer, and this increases the need to address high levels of perceived risk uncertainty to help the public distinguish between the impact of alcohol on heart disease versus cancer and to overcome other barriers to including alcohol use reduction as a cancer prevention strategy [163]. Given recent increases in US population drinking rates, as well as morbidity and mortality associated with alcohol use, it was also proposed that there is a need to educate US adults about the alcohol–cancer link, including raising awareness that drinking all alcoholic beverage types increases cancer risk [162,163].

Although it is clearly established that the abuse of alcohol is seriously harmful to health, much epidemiological and clinical evidence seems to underline the protective role of moderate quantities of alcohol and in particular of wine in health [50]. Wine differs from other alcoholic beverages and its moderate consumption not only does not increase the risk of chronic degenerative diseases but is also associated with health benefits particularly when included in a Mediterranean diet model. Moreover, it is worth mentioning that follow-ups of such epidemiological studies [126,164–166] and several other studies and especially interventions and clinical trials have outlined that adherence to a moderate wine consumption pattern provides antitumour protection against several types of cancer (Supplementary Table S2).

For example, only heavy (but not light or moderate) consumption of alcohol at baseline is associated with intestinal-type non-cardia gastric cancer risk in men from the EPIC cohort, while such a positive association was not observed specifically for wine consumption [164]. In addition, in a follow-up of the Health Professionals Study on the effects of alcohol consumption on prostate cancer, it was observed that cancer-free men who consumed alcohol had a slightly lower risk of lethal prostate cancer compared with abstainers, and, especially among men with prostate cancer, red wine was associated with a lower risk of progression to lethal disease. It was proposed that these observed associations seem to provide assurance that moderate alcohol consumption is safe for patients with prostate cancer [126]. Moreover, in another follow-up of the Nurses' Health Study, Nurses' Health Study II and Health Professionals Follow-Up Study, it was also proposed that in these three prospective cohorts, alcohol consumption was associated with reduced risk of pituitary adenoma, compared to almost no consumption of alcohol [165]. In another very recent follow-up study of the Nurses' Health Study and the Health Professionals Follow-Up Study, it was also proposed that encouraging an increased intake of specific flavonoid-rich foods and beverages, including tea and red wine, even in middle age, may lower early mortality risk [166]

However, all these effects seem primarily to be associated with the amount of alcohol consumed, while the role of the different alcoholic beverages and of their minor components in this regard is in fact not clearly defined. It seems that the effect of alcohol consumption on cancer and health in general is far more complex, while the type of alcoholic beverage, the quantity consumed and the frequency of consumption (Supplementary Tables S1 and S2), as well as the type of cancer and the overall personalised health status and genetic profile of each individual, seem to also play a significant role in these contradictory associations.

It should be mentioned, however, that wine and wine-derived compounds are promising chemoprotective and chemotherapeutic agents for cancer, as they have been shown to participate in several mechanisms against cancers, including deoxyribonucleic acid damage, oxidative stress, cell proliferation, cell cycle arrest, cell apoptosis, autophagy, inflammation-related cell invasion and metastasis, immunity and metabolism, as well as regulation of multiple signaling molecules and gene expression [6,167].

Due to the presence of such beneficial for health bioactives in wine, it has been proposed that the light to moderate consumption of alcohol in the form of wine (≤1 drink/day for women and 1 to 2 drinks/day for men) is associated with a lower risk of inflammation-related disorders, such as atherosclerosis and CVD, stroke, cancer and type 2 diabetes mellitus and all-cause mortality (Supplementary Tables S1 and S2) [1,6,7,11,14,19,25,43,49,50,53,55,56,60,61,64,70,114–154,164–166,168–171]. Conversely, heavy drinking (>4 drinks/day) is closely correlated with detrimental effects on health and associated with an increased risk of developing cancer, CVD and stroke (both ischaemic and haemorrhagic), among others [156–166,168–170]. Among males aged 15 to 59 years, alcohol abuse is perhaps the leading cause of premature death. Excessive alcohol intake trails behind only smoking and obesity and they are the three leading causes of premature death in westernised societies. As such, the risk-to-benefit ratio of drinking is less favourable in younger individuals.

Because of the opposite direction of the association between alcohol consumption and cardiovascular and cancer events, the association with all-cause mortality is complex and J-shaped [168–170], with a consumption window theoretically associated with a reduction in all-cause mortality of up to 25 g alcohol per day. The J-shaped curve indicates that light to moderate alcohol consumption leads to lesser risk of chronic disorders than for abstainers and heavy consumers of alcohol, with the latter being at the most risk in terms of health. Most of the studies on alcohol and health are observational, and correlation does not prove causation [156–166], while the recent increase in interventions and trials conducted on wine consumption have provided more robust evidence for the health benefits of wine consumption in moderation (Supplementary Tables S1 and S2). A daily habit of light to moderate drinking is ideal for those who choose to consume alcohol regularly. Red wine before or during the evening meal is linked with the best long-term health outcomes. Subsequently, health care professionals need to advise non-drinkers to begin drinking with caution because of the paucity of randomised outcome data coupled with the potential for alcohol abuse even among seemingly low-risk individuals and the possible interaction(s) of wine bioactives with specific drugs and therapies of elderly people. Moreover, every effort must be made to promote behavioural education to prevent abuse, especially among young people. Additional research is required to evaluate and clarify the doubts that still exist.

For example, in all type of studies, including epidemiological studies, interventions and trials, the abuse of alcoholic beverages has been associated with an increased risk of chronic–degenerative diseases, including diabetes mellitus, so there is a general diffidence towards the low/moderate consumption of wine by individuals with type 2 diabetes or those at risk of developing it. Whether wine/grape derivatives must be excluded or if their low/moderate consumption could be part of the daily diet of individuals with type 2 diabetes is still being studied. Although further intervention studies on the consumption of alcoholic beverages and the development or control of type 2 diabetes are needed, the burden of evidence suggests that, especially for wine, low/moderate consumption seems to provide beneficial effects (Supplementary Table S2). It has also been proposed that for older adult drinkers, registered dietitians and physicians may find benefit in inquiring about the specific alcohol types consumed, as opposed to inquiring merely about holistic alcohol intake, as part of patient consultations or routine visits, while they should also encourage older adult alcohol drinkers to consume alcohol in moderation and to consume mainly red wine as part of total alcohol intake in order to help reduce the risk of weight gain, metabolic syndrome, adiposity-associated health risks and diabetes.

3.3. Concluding Remarks on the Health-Promoting Effects of Wine Consumption in Moderation: From Ancient Times (Religion, Philosophy and Scientific Approaches) to Recent Scientific Evaluation

Wine is actually a mixture of bioactives with unique properties, with a rich and unique composition in terms of polyphenols and other phenolic and non-phenolic bioactive components, such as the wine polar lipid bioactives and UFA, which may contribute to the alleged health effects and to a protective association between low to moderate wine consumption and inflammation-related chronic diseases like CVD, type 2 diabetes and neurodegenerative disorders, while it does not appreciably influence the overall risk of cancer. There is therefore strong scientific evidence from Mediterranean and non-Mediterranean countries that moderate wine consumption as part of a healthy diet can provide protection against all-cause mortality and thus increase longevity.

Bioactive components are not the only reason for the beneficial effects associated with wine consumption; social factors also matter. The Mediterranean diet is a dietary model that is considered healthy because it suggests consuming wine in moderation (up to 1–2 glasses/day for men and 0.5–1 glass/day for women) during meals, especially in the presence of company and during socialising. When consumed during meals with others, wine tends to be sipped more slowly than other alcoholic beverages and this may provide metabolic benefits. In addition, the concomitant presence of food in the stomach slows the absorption of ethanol, aiding metabolism and hepatic clearance and lowering the peak blood alcohol concentration. The concomitant presence of food may also reduce the amount of alcohol available to the oral microbiota, which has the ability to metabolise ethanol to acetaldehyde and thus reduces the produced levels of this compound that, if increased, are associated with the tumour-inducing effects of ethanol in the upper gastrointestinal tract. In addition, the presence of alcohol may improve the bioavailability of wine bioactives in the food bolus, making them more assimilable and possibly reducing glucose bioaccessibility, which is consistent with the hypoglycaemic effects observed in intervention and observational studies of moderate wine consumption [50].

Wine has always accompanied humanity, for religion or for health. For example, wine is mentioned in the Bible, where it is written that Jesus Christ himself chose wine for his Last Supper, and subsequently Christians also use wine for the re-enactment of the "Holy Communion". The wise King-Prophet David had also emphasised in several of his psalms the benefits of food with wine and oil, with characteristic examples being the 4th (8th verse; "ἔδωκας εὐφροσύνην εἰς τὴν καρδίαν μου· ἀπὸ καρποῦ σίτου, οἴνου καὶ ἐλαίου αὐτῶν ἐπληθύνθησαν") and 103rd psalms (15th verse; "καὶ οἶνος εὐφραίνει καρδίαν ἀνθρώπου τοῦ ἱλαρῦναι πρόσωπον ἐν ἐλαίῳ, καὶ ἄρτος καρδίαν ἀνθρώπου στηρίζει"). The reason why the original Greek versions of these psalms are presented here is because, unfortunately, the most common English translations of the original Greek phrases used in such important ancient scripts like these psalms, such as "εὐφροσύνην εἰς τὴν καρδίαν μου" and "εὐφραίνει καρδίαν ανθρώπου", are usually based on simple phrases like "gladdens the heart" in this case.

However, we should not neglect that the Greek language and thus several Greek words, phrases and quotes like the aforementioned ones are conceptual and thus they usually provide a deeper meaning derived from the synthesis of their root words ("εὐ-φροσύνην" and "εὐ-φραίνει" from the origin word "εὐ-", which means "in a good way (καλώς)", and the verb "φρονώ", which means "wisely taking care"). Subsequently, the phrases mentioned in these psalms seem to have a more proper meaning like, for example, "consumption of food with wine and oil wisely takes care and gladdens men's heart".

All the above further indicate an in-depth Greek-based philosophy of the Mediterranean diet principles, which is usually characterised by the famous Greek quote "Μέτρον Ἄριστον" (simply translated as "all things in moderation", while its more in-depth translation indicates that "using all things in moderation is the best and just way to deal with anything"), first mentioned by the Greek poet Cleobulus of Lindos in the 6th century BC. It has been engulfed since then by all Mediterranean civilizations as a way of life. Moving from religion and philosophy towards a more scientific way of studying such effects, it should also not be neglected that the Greek physician Hippocrates, who incorporated scientific approaches for therapy and thus is now usually characterised as the "father of modern medicine", had also highlighted that, in one of his quotes, "Wine is a thing wonderfully appropriate to man if, in health as in disease, it is administered with appropriate and just measure according to the individual constitution" [171]. Within the same quote, apart from an appropriate and wise measure of wine administration, Hippocrates also insightfully introduced us to recommendations in a personalised approach to each patient, taking into account other factors too, such as individual constitution and contraindications with other medications.

Since then, and as science moved on, apart from industrialising the winemaking process, only recently has a lot of research been carried out to study wine and its bioactives in order to solve the mystery of its benefits, making wine responsible for the lot of ink that has been spilled to explain the French and/or the Crete paradox. Beyond its cardiovascular effects, there are also beneficial effects of wine on longevity, metabolism, cancer prevention and neuroprotection, when it is consumed in moderation, and the list goes on. Wine acts mostly as an alcoholic solution and is a reserve of antioxidants and anti-inflammatory compounds, especially for the winter, when there usually are no grapes available. Even though several epidemiological studies have suggested an association of alcohol, including alcoholic wine, with cancer and other diseases [156–166], such studies only bring up associations but not evidence. There are also studies proposing health benefits from alcohol-free wines [155], while the plethora of recent interventions and trials have provided more robust evidence for the health benefits of wine consumption in moderation (Supplementary Tables S1 and S2), making researchers suggest that a wine without alcohol is not really wine, rather a "pure heresy" [171].

Wine is the elixir that by design, over millennia, has acted as a pharmacopoeia that has enabled man to heal and prosper on the planet [171]. From Hippocrates to Michel de Lorgeril and Serge Renaud, nutrition has now been considered the key to health and longevity and, whether considering the Cretan, Ikarian or Okinawa diets of the Blue Zones, it seems that small doses of alcohol (either in wine or sake) as a part of such healthy diets allow the appropriate beneficial interaction(s) of the other wine components with gut microbiota and the bioavailability of their bioactive compounds and bio-functional metabolites. Moderate drinking provides protection against diseases and the potential of longevity. In conclusion, as Prof. Poli has suggested, let us drink fewer, but drink better, to live older [171].

4. Recovery and Valorisation of Bioactive Compounds from Wineries' By-Products as Ingredients for Developing Health-Promoting Functional Foods, Supplements and Nutraceuticals

4.1. The Importance of Wineries' By-Products and Their Bioactives in the Functional Foods Sector

Almost a hundred million tons of grapes are globally produced annually, with the majority of them (approx. 55–65%) being used for wine production. The winemaking process generates large amounts of grape pomace, the main winery by-product that presents an economic and environmental problem. It is estimated that every 100 kg of grapes used for winemaking yields a quarter of this amount (20–25 kg) of grape pomace, with an annually estimate of grape pomace production ranging from approximately 10 to 15 million tons worldwide [46,70]. Grape pomace is constituted mainly by grape skin, seeds, stems and the remaining pulp. Moreover, in grape seeds, the majority of the polyphenolic content of grapes is stored, which if valorised efficiently exhibit rich bioactivities, with promising application prospects in the food industry, while they can also produce grape seed oil, another valuable by-product from wineries [46,108]. The harvesting and winemaking processes are short, and a large quantity of grape pomace and/or grape seed is generated in a very short time [46,108]. Even though grape pomace and grape seed can be used for animal feeding and compost, only a small amount is re-used and disposal raises environmental concerns while representing a high cost to the industry [33,46,70,108].

After the fermentation–maceration process of winemaking, not all the valuable compounds of grapes are transferred to wine, and thus grape pomace and grape seed are usually rich in bioactive phenolic compounds, UFA, polar lipids and functional dietary fibres [22,33,39,42,44,46,70,108,172–174]. These bio-functional compounds present in grape pomace and in grape seed and its oil exhibit a variety of bioactivities, such as antioxidant, anti-inflammatory and anticancer effects, while they are also beneficial in alleviating metabolic syndrome and regulating intestinal flora [22,33,39,42,44,46,70,108,172–174]. In this sense, research has now become focused on the potential health properties of the bioactives from such wineries' by-products for the prevention of disorders associated with oxidative stress, inflammation and thrombosis, such as endothelial dysfunction, atherosclerosis and CVD, hypertension, hyperglycaemia, metabolic syndrome, diabetes, obesity, cancer and neurodegenerative disorders, among others [10,16,17,21,22,33,39,42,44,46,70,108,172–175]. The mechanisms involved in such beneficial effects of the bioactive compounds of wineries' by-products are mainly associated with modulation of antioxidant/pro-oxidant activity, the improvement of nitric oxide bioavailability, inhibition of platelet aggregation, reduction of pro-inflammatory cytokines and modulation of antioxidant/inflammatory signal pathways, as well as beneficial interactions with gut microbiota.

Grape pomace extracts can be applied in food, pharmaceuticals, cosmetics and other products in the form of liquid extracts, concentrate or powder/flour (Figure 4) [46,108]. In addition, grape seed extract has been generally recognised as safe (GRAS) by the Food and Drug Administration (FDA) and is commercially sold as a dietary additive listed in "Everything Added to Food in the United States" (EAFUS) to improve the overall quality of products and extend their shelf life [46,173].

Nowadays, several commercialised cosmetic products, such as day or night cream, face serum and mattifying, antiwrinkle and protective fluid, declare the use of polyphenols and other compounds from grape pomace and/or grape seed. In the food supplementation field, there are a few brands claiming to use grape polyphenols, mainly resveratrol. Such products confirm the commercial potential of bioactive compounds extracted from grape or grape by-products. Nevertheless, despite the potential health benefits of resveratrol and of other phenolics from wineries' by-products, their employment as nutraceutical ingredients within the food industry has specific limitations, mainly due to their poor water solubility, chemical instability and limited bioavailability. For these reasons, several delivery systems in the form of emulsions have been employed as promising encapsulation approaches, since encapsulation of such amphiphilic/lipophilic bioactive ingredients inside the hydrophobic core of the lipid droplets can protect them from degradation during storage and liberate them only after ingestion.

Moreover, discrepancies have been observed with extracts from wineries' by-products against several disorders, mainly because the bioactives of the extracts have not been well quantified and characterised for each subclass of functional molecules that target specific molecular, cellular and biological processes. Moreover, some studies used enzymatic extraction while other used different solvents such as methanol, ethanol or acetone, and the different methods applied provided different contents and biofunctional outcomes. For this reason, several investigations have focused on the appropriate extraction methods and recovery of bioactive compounds from wineries' by-products [108,176–180], as well as on their potential use as antioxidant and functional agents in the food, cosmetic and pharmaceutical industries [22,33,70,108]. Recovery and clarification of bioactive compound profiles of wineries' by-products, their bioavailability and the action mechanisms for maintaining the redox cell balance and anti-inflammatory index involved in health benefits are of great importance for their potential use as good and inexpensive functional ingredients of supplements and nutraceuticals for the prevention of inflammation-related chronic disorders [22].

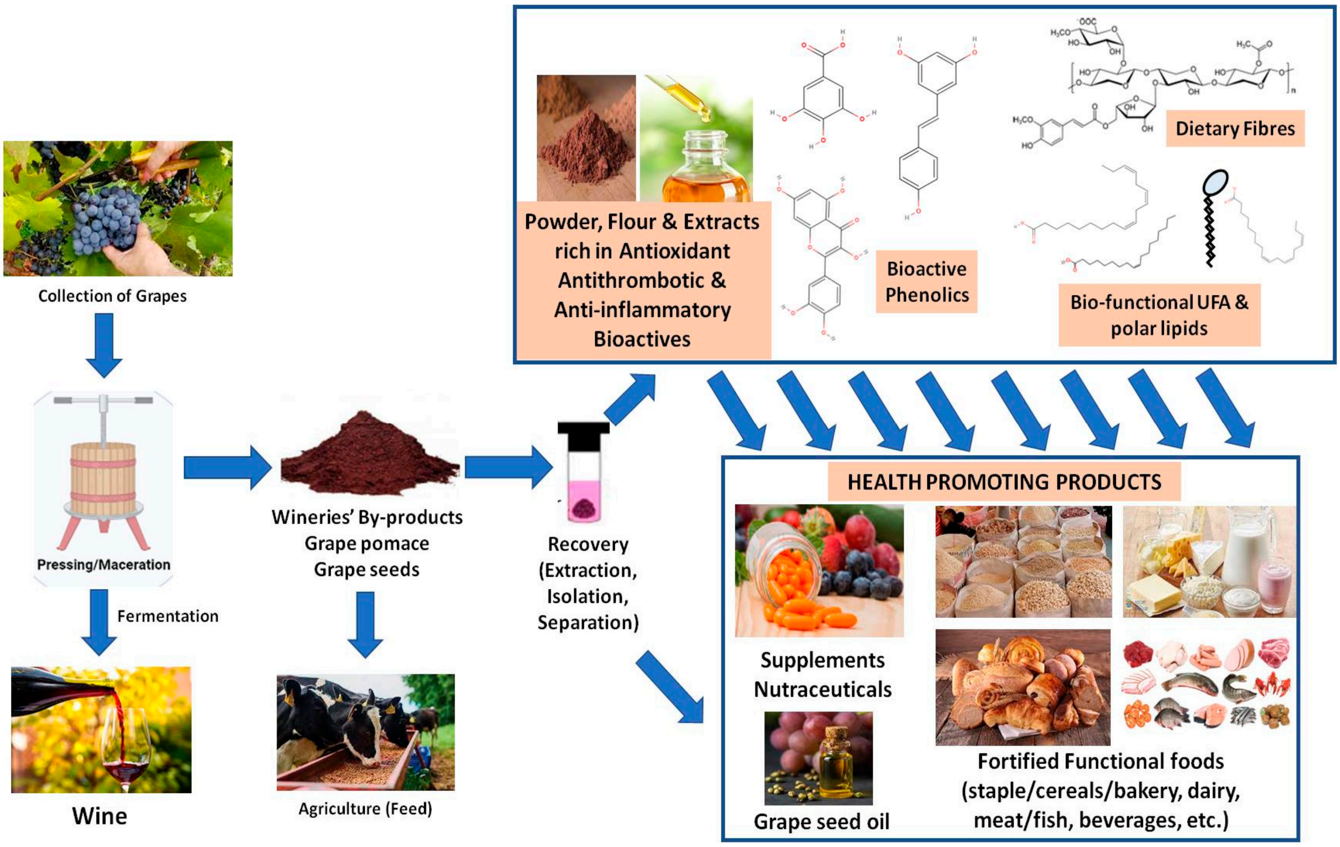

Figure 4. Applications of wineries' by-products and their bioactives in the food industry, as ingredient(s) for the fortification/production of existing/novel functional food products, supplements and nutraceuticals with increased antioxidant protection, shelf life and antithrombotic and anti-inflammatory health-promoting properties against chronic disorders.

4.2. Characteristic Extraction Methods for the Recovery of Bioactive Compounds of Wineries' By-Products

In order to carry out suitable applications of the vast amounts of winery by-products and their bioactives for the food and health sectors, a number of aspects must be addressed, and especially the extraction method and its efficiency [108,176–180]. Pomace collection should also be preceded by preliminary careful selection to determine the best pomace for the manufacturing of food-grade components based on functional constituent composition. In typical extraction processes, the medicinally active sections of plant or animal tissue are separated from the inactive or inert components using selected solvents [176].

Soxhlet extraction, maceration and reflux extraction are some of the traditional procedures that have been employed for a long time [108,176]. As these procedures need a substantial volume of solvents, which are also usually associated with toxicity issues, they are not suitable for commercial use. Furthermore, the high heat required for these methods leads to the loss/oxidation of phenolics, UFA and UFA-containing lipid compounds, while these approaches also consume high amounts of energy and are costly. Traditional mechanical techniques damage cell walls and also release polyphenols, but they also speed up the release of enzymes like polyphenoloxidase and peroxidase, which might speed up polyphenol oxidation and destruction. A similar methodology is also used for the production of grape seed oil, but the use of cold temperatures and alternative pressing approaches may optimise the yield and quality [109]. Nevertheless, due to the drawbacks, non-conventional green and sustainable extraction methods had to be developed/used for extracting grape pomace bioactives in such a way that they remain unaffected by the process, with the highest possible yield and low energy cost [176].

For example, solid–liquid extraction through mechanical agitation and Soxhlet extraction with ethanolic or methanolic solutions as solvent are the most often utilised extraction methods for value-added by-products from grape pomace [108,178,179]. The extraction method is an extensively used unit operation to recover many important food components, including phenolics, lipids and dietary fibres [108]. Alterations to the extraction process of grape pomace under various different experimental conditions, such as solvent type (ethanol, methanol, water, etc.), temperature and time, usually produce different yields of extracted compounds and antiradical activities of extracts, depending on the desirable extracted content of grape pomace. For example, a significant amount of anthocyanins or phenolics in general can be extracted by specific methods [108,176,180], while dietary fibres or grape seed oil will need a similar or much different methodology for a higher yield [108]. Especially for the extraction of all phenolics, there are a few available standardised procedures on solid–liquid extraction, but more understanding and systematic research for a high yield of unaffected extracted compounds are required [108,176,181].

Due to an increasing need for "natural" methods that do not introduce any leftover organic compounds, several "green" methodologies like the use of nanofiltration membranes or supercritical fluid extraction have emerged as appealing separation approaches for the extraction of valuable compounds from food wastes [176], including grape pomace, to be used in the food and pharmaceutical sectors [108]. The basic premise of supercritical fluid extraction involves a fluid in its supercritical state where discrete liquid and gas phases do not exist, which occurs at temperatures and pressures over its critical point [176]. Supercritical carbon dioxide's unusual solvent qualities, as well as its low cost, have made it a popular choice for extracting antioxidants, pigments and fatty acids from plant and animal sources, including grape seed oil that is rich in such lipid bioactives [182]. When modified with ethanol, it drastically increases polyphenol extraction, while reducing extraction times, especially when compared to other methods such as Soxhlet extraction or solid–liquid extraction [176,183,184]. In another study, modification of ethanol use (60%) extracted more polyphenols and anthocyanins from pomace, increasing the extract's antioxidant, antiproliferation and anti-inflammation activities. Furthermore, the functional activities of wine were increased when the crushed seeds in the fruit extract were included [185]. A similar assessment with supercritical fluid extraction compared the yield of resveratrol with carbon dioxide and the ethanol combination, with the latter extracting significantly more [186].

The extraction of bioactives from food by-products like grape pomace through microwave-assisted extraction has also been thoroughly investigated [176,187,188], revealing its many advantages in natural compound valorisation. With the use of microwave techniques, extractions from grape pomace had a higher polyphenol content compared to traditional methods [176,189].

Ultrasound has also been utilised for extracting valuable compounds from food by-products, including grape pomace, with high product yield whilst maintaining low solvent consumption and a shorter processing time [47,108]. Thus, when carried out with ultrasound-assisted techniques, the extraction of oil from grape seeds was very efficient compared to Soxhlet methods, while taking less time [190,191].

The recovery of valuable chemicals from food wastes and by-products like grape pomace using pulsed electric field treatment is also another promising technology. Pulsed electric field processing is a non-thermal food-processing technology that uses brief, high-voltage pulses that result in cell disintegration and microbial inactivation [192]. The pulsed electric field process is instantaneous, targeted and minimises heat, and the procedure is energy efficient whilst resulting in high-quality products [193]. A pulsed electric field allows for the recovery of polyphenols without addition of liquids, even in cases of fermented grape pomace, which has low relative humidity [194]. The shelf life of the product is also significantly extended due to the inactivation of microorganisms from the electromechanical instability [195]. When a pulsed electric field was used, total anthocyanin contents of up to 45% were extracted from grape by-products [196,197].

Overall, even though the traditional methods are still the most used for the extraction of compounds of interest from grape pomace, alternative technologies are emerging to recover bioactive compounds from this winemaking by-product, in order to promote faster and "greener" technologies [108,176–180].

4.3. Applications of Wineries' By-Products and Their Bioactives in the Food Industry as Ingredient(s) for the Fortification/Production of Existing/Novel Functional Food Products

The utilisation of wineries' by-products and their bioactive compounds as a source of functional ingredients is a promising field in the food and health sectors [22,33,42,46,70,108,110,111,172,182]. The recovery and valorisation of bioactive compounds, dietary fibres and functional lipids/oil from wineries' by-products as ingredients to fortify foods and/or to develop novel nutraceutical, pharmaceutical and cosmeceutical products are interesting alternatives for environmental and economic approaches in the agro-food and pharmaceutical sector.

Recently, the exploitation and application of wineries' by-products as important candidates and sustainable sources of bioactive ingredients in the production of fortified foods have gained increasing scientific and industrial interest (Figure 4). The addition of bioactive compounds of wineries' by-products to a wide range of food products, such as plant-origin food, meat, fish and dairy products, could improve the nutritional composition of the final fortified products and increase their nutritional value, quality and oxidative stability, mainly due to higher contents in polyphenols, lipid bioactives and dietary fibres (Figure 4) [22,33,42,46,70,108,172,182]. Nevertheless, changes in colour and undesirable changes in texture and sensory properties of the final products are the most commonly observed adverse effects of the fortification of foods with wineries' by-products [46]. If such adverse effects can be overcome, bioactive compounds of wineries' by-products may undoubtedly be used as functional components in foods and beverages, providing health advantages in addition to nutritional value and other desirable physiochemical characteristics, with a wide range of applications in both the food and pharmaceutical sectors [22,33,42,46,70,108,172,182]. Additional in vitro and in vivo studies, including pre-clinical and clinical ones, are needed to examine the health efficacy and safety of such products.

4.3.1. Applications of Wineries' By-Products and Their Bioactive Ingredients for the Fortification/Production of Functional Flour/Cereal-Based Foods

The fortification of flour/cereal-based staple foods such as bread and pasta with grape pomace extracts/flour has been investigated in an effort to improve the nutritional value of such foods. Grape pomace flour has been studied regarding the fortification of different staple foods, due to its high antioxidant capacity and delaying lipid oxidation properties [108]. Thus, research has also evaluated the use of grape pomace and seed flours in different flour/cereal-based pastry products and snacks too (i.e., popsicles, cereal bars, biscuits and cookies, extruded snacks and muffins), obtaining novel products rich in fibre with potent antioxidant capacity and good acceptance by consumers [46,108]. The incorporation of grape pomace flour in different baked products enhanced their antioxidant properties and increased their total dietary fibre content [198]. The antioxidant capacity was also improved when such products were enriched with phenols like anthocyanins [199]. Nevertheless, biscuits were shown to be less brittle, reporting reduced hardness after incorporation of grape pomace phenols and dietary fibre [200]. In cookies, the consumer acceptance was highest only at additions of 5%, while further additions of grape pomace flour caused textural property changes [201].

Similar approaches have been carried out on bread through replacement or enrichment of wheat flour with grape pomace flour and extracts. In these studies, the extract greatly increased the antioxidant activity of the final product despite some losses of phenolic compounds due to thermal treatment [202–204]. However, in some cases grape pomace powder negatively influenced the shelf life of bread-based products like breadsticks, and thus showed an increase in oxidation rates [205]. This was attributed to the grape pomace powder used with 9 g/100 g dry matter of fat, of which 50% was UFA that are prone to oxidation [206]. Although the increase in phenolic compounds and nutrients is valuable, all the studies carried out on bread reported negative impacts on textural properties of the product, with reports of noticeable astringency and acidity that could affect consumer acceptance. Hardness and porosity of the bread have also been observed, likely due to the reduction of yeast activity, which lowered the gassing power of yeast, as phenolics can limit endogenous amylase activity in dough, resulting in insufficient maltose release for yeast activity during proving [207,208].

Fortification of pasta with winemaking by-products has shown promising results too. Substitution of flour or semolina with grape pomace powder at different rates has shown a significant increase in dietary fibres. However, the studies showed different proportions of anthocyanins retained after the cooking process [209], with one showing no detection of anthocyanin after the cooking process, while other phenols and condensed tannin content in the pasta were not affected, which could be due to the highly bound phenol–fibre matrix [210]. The loss of phenolic content and antioxidant activity could also be attributed to the loss of the gluten protein network from grape pomace fibre interference [211]. Due to the same effect, cooking time was also reduced, which also affected the final products [212].

An easily overlooked aspect of grape pomace is its mineral composition, as it has been undervalued and there are no applications yet that focus on utilising the mineral content, which is likely due to the intense focus on polyphenols and dietary fibre. However, incorporation of grape pomace flour has led to observations of improved mineral content that brings product stability. The calcium concentration obtained from grape seed flour aided in the stabilisation of enzymes such as proteases and α-amylases, improving the quality of bread and cereal products [213,214].

Overall, new applications of grape pomace in this area of functional flour/cereal-based products may arise in the coming years, especially in plant-based foods and dietary patterns.

4.3.2. Applications of Wineries' By-Products and Their Bioactive Ingredients for the Fortification/Production of Functional Dairy-Based Foods

Improved physicochemical parameters, sensory properties and biological activities have also been observed in dairy products that were fortified with grape pomace ingredients [215]. For example, fortification of phenolics in dairy products, aside from the enhanced nutritional benefits, has also demonstrated increased stability in physicochemical properties, as well as antimicrobial and anticancer effects [215–217].

More specifically, the incorporation of phenolic compounds in yogurt showed beneficial modifications in its sensory properties and antioxidant capacity [216]. The incorporation of grape pomace powder into yogurt improved total phenolic content, which was further increased as the grape pomace powder ratio increased [218]. Grape fibre can be used as an alternative source of antioxidants and the addition of such dietary fibre in yogurt and salad dressings not only increases their fibre and phenolic content but also delays lipid oxidation during storage, thus extending the shelf life of these products [219]. The addition of grape pomace powder to yogurt (1, 3–5%) significantly improved the yogurt's colour, even at the end of the storage period [218]. A greater perception of sweetness and grape aroma in probiotic goat milk yogurts was also achieved, which assisted in facilitating the consumption of these products by consumers unfamiliar with goat milk products by decreasing the perception of acidity and goat milk aroma [220]. Nevertheless, when grape pomace powder was added into semi-hard and hard cheeses, aside from increasing the total phenolic content and radical-scavenging activity, it produced a significant pH decrease due to the presence of organic acids from the grape pomace powder [221], which was also observed in grape pomace powder-fortified yogurt that showed a relatively higher acidity too [218]

Fortification of buffalo stirred-type yogurt with 0.5% grape seed extract significantly increased the inhibition of free radicals, in comparison to control, indicating that the high phytochemical content found in grape seed extract was most likely responsible for increasing the antiradical ability of the yogurt fortified with grape seed extract [222]. Fortified cheeses with grape pomace displayed increased antioxidant activity too, without affecting starter development and acid generation that is crucial in their production [223]. Stirred-type yogurt supplemented with grape seed extract also showed antibacterial properties against several pathogens, such as *E. coli* and *S. aureus* [222]. This effect was significantly increased by increasing the concentration of grape seed extract in yogurt, suggesting that besides the endogenous presence of milk bioactive peptides, grape seed extract provided antibacterial components in the yogurt product [222].

With fortification of both full-fat and non-fat yoghurts with grape pomace, the commercial shelf life was extended without affecting product stability or *lactobacilli* count [224]. The total phenol content, antioxidant activity and lactic acid bacteria trend were also retained throughout the shelf life [225,226]. It was also proposed that the production of functional yogurts supplemented with grape seed antioxidants is feasible, given that the supplementation is carried out in the fermented product and not in milk prior to fermentation [224]. Moreover, yogurt containing 0.5% grape seed extract significantly increased cytotoxicity activity, achieving 62.47 and 70.36% cell death against MCF-7 and HCT-116 cancer cell lines, respectively, with the grape-seed-extract-derived phenolic substances, found in the fortified yogurt, playing an important role in the observed increased anticancer activity, in comparison to the anticancer activity of the control yogurt of 0% grape seed extract [222].

4.3.3. Applications of Wineries' By-Products and Their Bioactive Ingredients for the Fortification/Production of Functional Meat/Fish-Based Foods

Meat, fish and their products are the most prominent dietary categories in which wineries' by-products have been used to prevent mostly lipid oxidation and thus prolong storage or shelf life [33,46,108]. Several studies have used grape pomace extracts as food protectors due to their antibacterial capacity against different bacteria, while seedless grape pomace products also showed bactericidal effects against total aerobic mesophilic bacteria, lactic acid bacteria and *Enterobacteriacea* [108]. Thus, research on the influence of grape pomace fortification in meat and fish products was primarily conducted to determine the effects on shelf life and storage stability as well as antioxidative capacities [46]. These fortifications were carried out largely through addition of grape pomace powder or extract or marination in grape-pomace-derived solutions.

Grape pomace dietary fibres and grape seed oil rich in UFA have also been utilised in meat products [108]. For example, the addition of grape seed extract to western-style smoked sausage improved its colour and extended its shelf life due to the strong antioxidant properties of grape seed extract [46,227]. In particular, grape seed extract could significantly substitute and thus decrease residual nitrite, which may inhibit the formation of harmful and carcinogenic substances, such as N-nitrosamine [46,227]. Such modifications in the formulation of meat products have been made in order to address an increased interest from consumers in healthier and functional animal-based foods, such as the reduction of some compounds such as fat and saturated fatty acids, as well as the addition to such food products of healthier ingredients, such as fibre, UFA and antioxidants, by fortifying them with grape pomace, grape seed oil and/or their functional ingredients [108].

For example, there is an increasing consumer demand to limit the utilisation of nitrite and other preservatives and synthetic antioxidants in processed meat products due to associated carcinogenic activities, therefore incentivising researchers to use natural antioxidants as a substitute in processed meats to achieve similar shelf stability and antimicrobial qualities. In several studies incorporating grape pomace into preserved meat products, the antioxidant capacity scaled accordingly with different concentrations, with most inhibiting lipid oxidation [228–230]. A low microbial count was also achieved [231], likely due to the bacteriostatic or bactericidal effects exhibited at low or high phenolic concentrations, respectively. This result showed similar effects to the usage of nitrite in preserved meats, suggesting that grape pomace could be used as an alternative additive for preservation.

Phenolic extracts from grape pomace have also effectively been used in meat products as natural antioxidant preservatives to replace synthetic antioxidants usually added for the preservation of meat, such as the use of red grape pomace in pork burgers [232]. With the addition of grape seed extract to raw pork at 1% *w*/*w*, oxidative stability was achieved without negatively affecting sensory qualities of the meat [233]. Grape seed extract also effectively reduced lipid oxidation and improved the shelf life of stored lamb meat, equally to similar effects observed by the addition of vitamin E [234]. Grape pomace extract has also been effectively used to improve shelf life of both raw and cooked chicken meat [235,236], in which fortification resulted in strong antioxidant activity during storage time, comparable to the common antioxidant food additive butyl hydroxy toluene (BHT). However, negative changes in sensory properties were observed following fortification of chicken meat.

Grape antioxidant dietary fibre added to chicken breast hamburger and fish muscle showed an improvement in the oxidative stability and the radical-scavenging activity of both products [237,238]. When grape seed flour was used at different concentrations in sausages, similar decreased levels of oxidation were also observed, followed by enhanced protein and increased total dietary fibre [239]. However, water-holding capacity was also increased, likely due to the increase in fibre–matrix complexes, which could increase the water activity of the product and thereby increase susceptibility to microbial growth. Of these studies, most saw alterations in colour with other sensory properties such as texture and taste unaffected.

Pre-emulsified grape seed oil has also been used to replace pork back fat in frankfurter sausages, resulting in fatty acid composition being beneficially affected and an overall reduction of the fat content, which was closer to the target value of 20% (fat content) [240]. Consumers' acceptability was similar for such reduced-fat frankfurters compared to regular-fat frankfurters, while an increase in gumminess and chewiness was also observed that improved textural properties [240]. Similar results were obtained when different concentrations of grape seed oil were used to replace animal fat in frankfurter sausages, which, even though the decrease in the lipid oxidation was not significant, were well accepted by panelists [239].

Whole grape pomace was also successfully used in minced fish frozen for lipid oxidation prevention [108,241], which was also observed in the fortification of fish products with grape pomace at concentrations of 1% [239] and 2% [242]. Other studies also used grape pomace extracts as food protectors, based on their antioxidant ability to prevent lipid oxidation in fish-based products [243]. Similar observations were also made regarding oxidation inhibition, storage stability and increase in dietary fibres after the addition of grape pomace flour to salmon patties [242]. The addition of grape seed extract to minced fish muscle demonstrated inhibition of lipid oxidation throughout cold storage too, but similarly to what was observed in fortified meat products, a deeper colour of the finished enriched product was noticed, leading to lower consumer acceptance. The application of fibre from grape pomace has also been performed in fish products, such as codfish and seafood, where the addition of these compounds is a promising tool for minimising flavour changes, colour, texture and lipid oxidation during freezing storage [238,244,245].

In the application of wine pomace in preserved meat products, the mineral content allowed the product to have a lower level of sodium and higher levels of calcium and potassium, whilst maintaining product shelf stability [228], which may help to lower blood pressure, minimise the risk of stroke and prevent CVD, particularly in hypertensive people. Finally, the use of grape pomace flour for coating has also improved the nutritional value of meat or fish. For example, daily consumption of beef burgers prepared with wine grape pomace flour for one month in 27 male volunteers with metabolic syndrome improved their blood biochemical parameters, such as fasting glucose and insulin resistance, plasma antioxidant levels and oxidative stress biomarkers, in comparison to the other periods of the intervention, during which they either did not consume burgers (second month) or they consumed daily one control burger (third month) [246].

Therefore, it seems that such grape pomace and grape seed oil functional ingredients have the potential to be successfully valorised as dietary supplements and/or fortifying agents in both meat-based and fish-based foods to beneficially manage chronic disease risk in humans, without affecting the overall nutritional and sensory properties of such fortified animal-based foods.

4.3.4. Applications of Wineries' By-Products and Their Bioactive Ingredients for the Fortification/Production of Other Plant-Based Functional Foods and Beverages

Wineries' by-products and their bioactive ingredients have also been effectively used for the fortification/production of several other plant-based functional foods and beverages. For example, even though no significant impact on polyphenol concentrations was observed in tomato puree that was supplemented with grape skin powder with varied particle sizes at a concentration of 3.2%, the antioxidant potential of the fortified tomato puree was greater due to the introduction of grape pomace anthocyanins, while the reduced particle size of grape skin powder resulted in higher values in sensory studies too [247]. Moreover, tomato lycopene and grape pomace anthocyanins seem to work synergistically in vitro, since when combined they demonstrated not only antioxidant improvement but also strong anti-inflammatory potential through a significant increase in inhibition of cytokine IL-8 [248]. In a similar evaluation, walnut paste was encapsulated and emulsified with grape skin extract to evaluate the oxidative stability and phenolic retention. However, results showed that though the antioxidant capacity of the walnut paste was enhanced, further thermal stress did not bring significant benefits, and most antioxidant properties were traced back to tocopherols that were originally present in the walnuts [249]. Therefore, the combined synergistic abilities of different antioxidant bioactives require further investigation.

Aside from antioxidant capacity, the possibility of inhibiting acrylamide formation through grape pomace addition was also studied. Acrylamide is a molecule produced during the formation of browning in Maillard reactions, and it has been found to exhibit carcinogenicity and neurotoxicity in several human and animal studies [250]. Through incorporation of grape pomace extract into potato chips, a significant reduction of 90% less acrylamide was observed in the final product [251]. This was also reflected in another study, where the decrease in acrylamides was observed not only by the free radical-scavenging effects but also by reactions with carbonyl species [252].

Apart from the traditional application of grape pomace in the food industry as a substrate for the production of some spirits by distillation [46], grape pomace and its extracts can also be used as functional supplement(s) in food production, to enrich beverages or even as the ingredient(s) of an osmotic solution for obtaining dehydrated fruit with increased phenolic content [253]. Due to its ability to absorb tannin, a study suggested that grape fibre in red wine production would be able to remove up to 38% of tannins generated during the process [254]. Grape ingredients have also been successfully used to address the unpleasant taste and flavour of fermented products made from plant-based dairy alternatives. Thus, supplementing such plant-based yogurt-like fermented products with some natural functional ingredients, including grape bioactives, can overcome the alleged unpleasant or poor taste in this kind of plant-based products [215].

4.4. Health Benefits and Applications of Wineries' By-Products and Their Bioactives as Ingredients of Bio-Functional Food Products, Supplements and Nutraceuticals

The application of wineries' byproducts, such as grape pomace and grape seed, has shown promising outcomes, with progress reported regarding their valorisation and/or the incorporation of their bioactive ingredients in producing bio-functional foods, supplements and nutraceuticals with several promising observed benefits and health-promoting effects (Figure 4) [22,33,42,46,70,108,110,111,172,182,255]. The bioactive ingredients of these by-products, such as their phenolics, UFA, polar lipids and dietary fibres, or even several forms of the by-products themselves or extracts of these by-products containing several of these bioactives, which usually act synergistically, have been assessed for health benefits by either improving fortified bio-functional foods or in the form of supplements or nutraceuticals. For example, several products derived from these by-products have been developed, such as supplements containing grape pomace extracts or grape seed extract capsules, while grape seed oil on its own has been characterised and sold as a supplement product of high nutritional value with observed health benefits (Figure 4) [46,108,110,111,182,255].

The most characteristic bioactive ingredients of the wineries' by-products used in such applications are several of their phenolic-rich extracts and/or the specific phenolic ingredient(s) recovered from them, with specific metabolic and bio-functional properties and health-promoting effects [16,22,33,38–42,46,47,70,108,110,172,174,176,182]. Apart from vitamins and minerals, phenolic compounds may be some of the most popular dietary supplements. Wineries' by-products like grape pomace and grape seeds seem to be sustainable sources of phenolic bioactives like resveratrol for developing bio-functional food products and promoting health supplements and nutraceuticals, while such by-products also contain other bioactive ingredients like UFA, polar lipid bioactives and dietary fibres, which have also shown several health benefits (Figure 4) [22,33,42,46,70,108,110,172–174].

However, it is still necessary to implement more in vivo studies, including targeted clinical trials, in order to be able to draw safer conclusions on the possible valorisation of winery by-products and their bioactives, either as single isolated compounds with a known concentration or as a validated standardised mixture, with increased bioavailability, for the production of protective and/or therapeutic bio-functional products, supplements and nutraceuticals, and with antioxidant, antithrombotic and anti-inflammatory health-promoting effects.

4.4.1. Antioxidant, Anti-Inflammatory and Antithrombotic Health-Promoting Effects of Grape Pomace and of Its Bioactives, Extracts and Relevant Bio-Functional Products

Grape pomace is an important source of phenolic compounds, with many beneficial effects on health, such as free radical-scavenging activity, antiplatelet and anti-inflammatory properties and anticancer and cardioprotective activities [22,33,42,46,70,108,172,174,176]. Several phenolic molecules and classes of polyphenols found in grape pomace, like flavonoids, stilbenes, lignans and phenolic acids, have been investigated as important alternative natural substances that could be used in the management of oxidative stress, platelet activation, inflammation and many other pathological manifestations [22,42,70,108,172,256,257].

Extensive in vitro and in vivo studies have exhibited the beneficial antioxidant and anti-inflammatory actions of grape pomace and its bioactive ingredients. The in vitro antioxidant effects include the observed decrease in ROS, MDA and TBARS levels, as well as an increase in GSH levels, while the observed in vivo antioxidant benefits usually include an increase in CAT, SOD and GPx4 levels, a stimulation of endothelial eNOS gene expression, as well as a beneficial modification of uric acid (UA), protein carbonyls (PCs) and TBARS levels [21,38–42,108,172,257–259].

The in vitro anti-inflammatory actions of grape pomace and its bioactive ingredients, and especially those of the grape pomace phenolics, usually include the inhibition of NF-κB and PGE2-associated inflammatory pathways, as well as the decrease in some inflammatory markers such as IL-8 [42,108]. In addition, the inhibition of platelet activation and aggregation induced by several inflammatory and thrombotic mediators, like PAF, thrombin, collagen and ADP, by grape pomace and/or grape seed extracts rich in bioactive phenolics, UFA and polar lipids further support their protective effects against several thrombotic and inflammatory manifestations and associated disorders [6,7,10,16,17,22,42,70,74,90–92,108,260–265]. The in vivo anti-inflammatory properties of grape pomace and its bioactive ingredients also include the inhibition of the release of several inflammatory markers, such as IL-1α, IL-1β, IL-6, IFN-γ, TNF-α and CRP [42], as well as the protection against thrombo-inflammatory activation of platelets [15].

For example, grape pomace extract rich in phenolic compounds like quercetin, catechin, epicatechin and gallic acid have shown better inhibition of platelet aggregation induced by ADP, compared with wine's effect on platelets. Nevertheless, such phenomena could be explained by the higher concentration of phenolic compounds present in the pomace extract [261]. Extracts of both red grape pomace and white grape pomace have also been found to inhibit platelet aggregation activity using ADP as an agonist [265].

Strong antiplatelet effects of red grape pomace extracts were also observed against the thrombo-inflammatory signaling of either PAF or thrombin and subsequently against their associated platelet aggregatory induction [16,17]. Such extracts were rich in bioactive phenolics but they were also found to contain considerable amounts of biofunctional polar lipids and UFA, which further support their strong anti-inflammatory and antithrombotic potency [16]. In a randomised trial in healthy individuals that was based on the consumption of a supplement containing several plant extracts, including grape pomace extract, a strong protective effect against PAF-associated thrombo-inflammatory signaling was observed, due to reducing both the activities (reduced PAF-induced platelet aggregation) and levels (increased PAF catabolism) of the inflammatory mediator PAF [15].

Several human studies have shown that consumption of grape pomace products significantly reduces the risk for atherosclerosis-, hypertension- and diabetes-related conditions [70,108]. For example, grape pomace extract presented protective vascular and antioxidant properties [258], since such extracts induced a relaxation or inhibition in the contraction of aortic rings in a dose-dependent manner, mainly due to antioxidant activity of the extract's phenolic compounds and the induced activation of eNOS through a NO-dependent mechanism. Supplementation with red grape pomace flour in SR-B1 KO/ApoER61$^{h/h}$ mice fed an atherogenic diet (an animal model of lethal ischaemic heart disease) increased plasma antioxidant activity, changed TNF-α and IL-10 levels, decreased atheromatous aortic and brachiocephalic plaque sizes, attenuated myocardial infarction and dysfunction and thus reduced premature death [266].

Grape pomace extracts and products have also exhibited antioxidant and anti-postprandial hyperglycaemic protective activities in vitro and in vivo, suggesting their use as a functional ingredient against hypertensive and diabetic manifestations too [21,267]. For example, an intervention study showed that consumption of wine grape pomace flour, as a dietary supplement, improved the blood pressure of patients, as well as enhanced insulin sensitivity and antioxidant protection [268]. More specifically, the consumption of grape pomace flour rich in fibre and polyphenol antioxidants, either as a food supplement in a regular diet or as an ingredient of functional foods fortified with this winery by-product, improved fasting glucose levels, glycaemia and postprandial insulin, systolic and diastolic blood pressure and plasma antioxidant levels (i.e., increased levels of plasma γ-tocopherol and δ-tocopherol, which further provide antioxidant protection and decrease oxidative protein damage) in males with at least one component of metabolic syndrome. Such beneficial outcomes indicate an attenuation of oxidative stress and subsequent protection against all these parameters of metabolic syndrome in humans [246,268].

In another double-blind placebo-controlled study, blood pressure was significantly lowered when polyphenol-rich grape extracts were administered [269]. A double-blind randomised placebo-controlled trial also showed that foods fortified with wine pomace, or with its bioactive flavanols, can attenuate hyperglycaemia-induced endothelial dysfunction and oxidative damage in endothelial cells and thus can significantly improve vascular function [270,271]. The antioxidant activity demonstrated in the various applications of wine grape pomace and fortification in different functional foods seems to be beneficial, as it was also shown in another trial in healthy normal and overweight/obese women, based on the consumption of a grape pomace extract, which resulted in postprandial metabolic benefits and protection against oxidative stress responses [21]. Moreover, treatment of intestinal cells with grape pomace extract provided antioxidant protection, as it neutralised the production of reactive oxygen induced by tert-butyl hydroperoxide [272].

The presence of high concentrations of grape pomace phenolics (polyphenols, tannins, flavonoids and anthocyanins) can also provide plasma-lipid-lowering protective effects, since polyphenolic grape pomace extract reduced cholesterol levels by lowering the enzymatic activities of enzymes involved in intracellular cholesterol production [38]. Moreover, in a triple-blind, randomised controlled trial, grape extract consumption reduced atherogenic markers and exhibited additional cardioprotective effects, including decreased levels of LDL and apolipoprotein-B [273].

Even though glucose, total cholesterol, HDL-cholesterol and LDL-cholesterol levels were not affected in vivo in male Wistar rats treated with a grape pomace extract rich in phenolics (malvidin, quercetin, gallic acid and procyanidin dimer type B were the main compounds identified), other biomarkers of CVD, such as VLDL-cholesterol and triacylglycerols levels, were decreased with grape pomace extract treatment [274]. On the other hand, in another randomised crossover clinical trial based on consumption of a grape seed extract by hyperlipidaemia patients (21–64 years old), a decrease in total cholesterol, LDL-cholesterol and Ox-LDL-cholesterol levels was observed, while triacyclglycerols, HDL-cholesterol and VLDL-cholesterol levels were not modified [275]. The observed differences between these two studies may be explained either by the different winery by-product sources used for obtaining the extracts rich in phenolics or by the organisms of the trials and/or by the amount of extract supplemented, because higher dosages were given to the rats compared with those given to the hyperlipidaemia patients.

Most studies have presented the effects of specific concentrations of single grape pomace polyphenols, such as resveratrol, quercetin and gallic acid, against oxidative and inflammatory damage, but recent experimental data have shown that grape pomace extracts are more effective than a single bioactive ingredient, possibly because of their synergistic action that interferes with more than one pathophysiological mechanism [15–17,21,22,42,46,70,108,172]. All these studies have presented grape pomace as a whole extract, but different individual bioactive ingredients contained in grape pomace can also modulate the endogenous pathway responsible for reducing oxidative stress and chronic inflammation [22], indicating that they may be successfully utilised as valuable therapeutic candidates able to reduce the thrombo-inflammatory and oxidative-stress-associated pathological processes. Although further research is needed, the bioactive molecules from wineries' by-products show promise for use as antioxidant supplements [21,38–42,108,172,257–259]. The ethanolic extracts of grape pomace have been proposed as candidates for food supplements and nutraceuticals with antioxidant protection and antiplatelet benefits as well [15,21].

4.4.2. Antioxidant, Anti-Inflammatory and Antithrombotic Health-Promoting Effects of Grape Seeds and of Their Bioactives, Extracts and Relevant Bio-Functional Products

Considerable interest has also been shown in the use of grape seed and its extracts as raw material to develop products with nutritional value and health benefits [46,108,173,262–264,275–283], with considerable popularisation and application prospects [46,108,173]. For example, grape seed extract capsules have been developed and sold by some companies as dietary nutritional supplement products to protect humans from oxidative damage and to maintain health. Moreover, due to its solubility in water and ethanol, grape seed extract has considerable potential as a beverage to produce products with health benefits that could satisfy the taste standards of consumers [46,276,277].

Grape seed products and extracts have shown potent antioxidant and anti-inflammatory vascular protection, lipid-lowering effects and subsequent cardiovascular benefits [46,108,173,262–264,275–283]. For example, administration of grape seed extract to hamsters for 12 weeks resulted in a substantial reduction of plasma cholesterol [256]. Moreover, grape seeds hold a large amount of proanthocyanidins, also known as condensed tannins [277], while the pharmacokinetics and biological metabolism of these grape seed bioactives have shown that they possess significant antioxidant and anti-inflammatory capacities, demonstrated by the suppression of IL-3 activity, inhibition of inflammatory mediators and lipoxygenase, as well as by reduced LDL oxidation [283–285]. In in vivo studies, grape seed powder and proanthocyanidin consumption have been shown to exert antioxidative, anti-inflammatory and cardioprotective effects [282,285].

Grape seed extracts have also shown potent antiplatelet cardioprotective effects [70,108,262–264]. For example, grape seed extracts (containing a mixture of polyphenols including gallic acid, falvan-3-ols and proanthocyanins) inhibited the platelet activation induced by proteolytic (thrombin-induced) and non-proteolytic (thrombin receptor activation peptide-induced) signaling more potently than resveratrol, while platelet microparticle (PMP) generation was also reduced [262]. It seems that the presence of a variety of phenolic bioactives in grape seed extracts provides the ability of this wineries' by-product to interact with several pathways in platelet activation, leading to decreased degranulation and PMP shedding, thus contributing to its higher inhibition in comparison to pure resveratrol. The specific method by which such phenolic compounds limit platelet activity has yet to be determined, however, it appears that these phytochemicals alter the fluidity of membranes, the affinity of the ligand receptor and the signaling pathways inside cells. These effects might be mediated by antioxidant processes, as well as the control of pathways linked to nitric oxide generation and release, which alleviate the oxidative stress-induced platelet activation and PMP shedding by scavenging free radicals. Similarly, flavan-3-ol-rich extracts from grape seed were shown to have a platelet-inhibiting effect under flow in response to collagen or ADP [263]. Interestingly, grape seed and grape skin extracts elicit a greater antiplatelet effect against collagen-induced platelet aggregation when used in combination than when used individually in both dogs and humans [264].

As aforementioned, wineries' by-products and their products and extracts, as well as several of their fortified functional foods, have also exhibited potent antidiabetic benefits [108]. For example, the incorporation of extracts from grape pomace, grape seed or grape skin in yogurt resulted in a significant increase in total phenolic content and antioxidant and antidiabetic properties compared to the controls. The functional yogurt fortified with grape skin extracts exhibited the highest phenolic content and antioxidant capacity, as well as the highest inhibition of the activity of α-glucosidase [286], an enzyme that is associated with the digestion of carbohydrates as well as with the elevation of postprandial glucose levels in diabetic patients. Furthermore, another study also showed that resveratrol-rich grape skin extracts inhibited fat accumulation and fatty acid synthesis, as well as modulated insulin sensitivity, all of which led to risk reduction in obesity rates [287]. With respect to grape seed, an extract of this winery by-product has inhibited intestinal α-glucosidases and α-pancreatic amylase in vitro that may delay carbohydrate digestion and absorption, resulting in the suppression of postprandial glycaemia, while in vivo this extract has reduced postprandial plasma glucose in healthy participants receiving a high-carbohydrate meal in an acute, randomised, controlled crossover study [278]. Moreover, oligomers of grape seed procyanidin extract were able to enhance insulin-mediated glucose uptake by their interaction in the GLUT4-mediated glucose uptake process [279], which further supports the antidiabetic protective properties of grape seed bioactive phenolics.

Several studies have also shown the potential use of grape seed extracts rich in bioactive phenolics as therapeutics against several neurodegenerative disorders. For example, a commercially available grape seed polyphenolic extract significantly attenuated Alzheimer's disease-type cognitive deterioration and reduced cerebral amyloid deposition [281].

Grape seed is also a valuable source of bio-functional oils [46,108,110,111,182,255]. Grape seed oil also contains phenolics, but it is also rich in UFA (especially LA) and lipid-soluble vitamins (A, D and E), granting grape seed oil with various health-promoting activities [18–111,182,255]. Recently, some lipid-embedded substances in grape seed oil, such as tocopherols, phytosterols and lipophilic phenols, have attracted increasing attention from researchers because of their diverse biological activities, such as antioxidant and anti-inflammatory activities [108,110,111,182]. Beneficial hepatoprotective, neuroprotective and liver cholesterol-reducing effects of grape seed oil have also been reported [108,288–290]. The potent antioxidant, anti-inflammatory, antiapoptotic and lipid-lowering activities of grape seed oil exhibited a protective effect on acute liver injury, while similar protective mechanisms of grape seed oil against oxidative damage and inflammatory cascades in the brain provided strong neuroprotection too [288–290]. Such neuroprotective effects include the ability to scavenge free radicals, improved activity of antioxidant enzymes, down-regulated gene expression levels of xanthine oxidase and inducible nitric oxide synthase and suppressed inflammatory responses in the brain.

In this respect, the recovery of bio-functional lipids and oil from grape seeds is of considerable significance with respect to the exploitation and utilisation of grape seed oil as a functional food and supplement on its own or as the ingredient(s) of other fortified products [108,110,111]. Some grape seed oil products have been sold by companies and are consumed as part of the daily diet.

4.4.3. Anticancer Protective Effects of Wineries' By-Products and of Their Bioactives, Extracts and Relevant Bio-Functional Products

Extracts and products derived from winery by-products, containing several of their phenolic bioactive compounds, and especially anthocyanins and/or resveratrol, have also exhibited antitumour properties against several types of cancers [22,33,46,58,65–67, 72,81–87,108,172,280,291–298]. For example, grape seed extracts have exhibited anticancer actions against different cancer types (skin, prostate, breast) [280]. In addition, a daily dose of 80 g resveratrol-containing freeze-dried grape powder for 14 days in eight colon cancer patients resulted in a significant inhibition of the Wnt signaling pathway, which is one of the key cascades regulating development and stemness and has also been tightly associated with cancer [291]. The chemopreventive mechanisms of resveratrol-containing extracts of winery by-products have also been attributed to resveratrol's capacity to control inflammation, remove reactive oxygen species and deactivate pro-carcinogens [6,81–87,291].

Anthocyanins similarly exhibit anti-carcinogenic activity against cancer cells, in vitro and in vivo [293]. In vitro, the observed chemopreventive properties of anthocyanins include radical-scavenging actions, decreased cell proliferation, decreased inflammation, as well as induction of apoptosis. Dietary anthocyanins have also inhibited in vivo gastrointestinal cancers. More specifically, anthocyanin-rich extracts from grapes, and several pure anthocyanins and anthocyanidins, seem to exhibit pro-apoptotic effects in multiple cancer cell types in vitro, through both intrinsic (mitochondrial) and extrinsic (FAS type I transmembrane protein of the TNF-α superfamily) pathways. In the intrinsic pathway, anthocyanin treatment of cancer cells results in an increase in mitochondrial membrane potential, cytochrome c release and modulation of caspase-dependent anti- and pro-apoptotic proteins. In the extrinsic pathway, anthocyanins modulate the expression of FAS and the FAS ligand pathway in cancer cells, resulting in apoptosis. In addition, treatment of cancer cells, but not normal cells, with anthocyanins leads to an accumulation of ROS and subsequent apoptosis, suggesting that the ROS-mediated mitochondrial caspase-independent pathway is important for anthocyanin-induced apoptosis too.

For example, administration of an anthocyanin-rich extract from bilberry, chokeberry and grape (containing 3.85 g anthocyanins per kg diet) in rats with colon cancer induced by azoxumethane (AOM) significantly reduced the formation of the AOM-induced colonic aberrant crypt foci (the earliest identifiable intermediate precancerous lesions during colon carcinogenesis). This reduction was associated with decreased cell proliferation and COX-2 gene expression, however, the levels of urinary 8-OHdG were similar among rats fed the different diets [294]. Administration of grape pomace in female mice with AOM/dextran sulphate sodium (DSS)-induced colorectal cancer showed protective effects against colitis-associated carcinogenesis, since it ameliorated the disease activity index (DAI) score, reduced tumour number, tumour size and pathological scores, as well as suppressed cell proliferation and inflammation (suppression of colonic expression of inflammatory cytokines, IL-1β and TNF-α, inhibition of NF-κB inflammatory signaling, as well as a simultaneous increase in anti-inflammatory cytokine TGF-β mRNA expression were observed) and it alleviated DNA methylation of the promoter region of the Cdx2 gene and hypermethylation of CpG island methylator phenotype (CIMP), which commonly occurs during CRC carcinogenesis [295].

Recently, two phenolic-rich extracts from biotransformed grape pomace, which was derived by a 15-day solid-state fermentation with the white-rot fungi *Phanerochaete chrysosporium* and *Trametes gibbosa*, respectively, have exhibited potent antioxidant and antiproliferative potentials against colorectal cancer in vitro, in both Caco-2 and SW620 colorectal cancer cell lines [296]. In addition, an anthocyanin-rich grape extract and a grape anthocyanin component have shown breast cancer chemopreventive potential, in part due to their capacity to block carcinogen–DNA adduct formation, to modulate activities of carcinogen-metabolising enzymes and to suppress ROS in non-cancerous human breast cells [297]. Fractions of a grape pomace derived from the muscadine "Noble" variety, which contained a mixture of anthocyanidins and ellagic acids, exhibited the strongest antioxidative activity, as determined at both low and high concentrations in 2,2-diphenyl-1-picrylhydrazyl (DPPH) and ferric-reducing antioxidant power (FRAP) assays, while they were also able to potently induce cell cycle arrest and apoptosis in MDA-MB-231 breast cancer cells, via caspase activation and by downregulating cyclin A and upregulating p21 [298].

4.4.4. Antimicrobial Protective Effects of Wineries' By-Products and of Their Bioactives, Extracts and Relevant Bio-Functional Products

Natural products as sources of potential antimicrobials, and especially those derived from valorising food wastes like wineries' by-products that are rich in phenolics (pomace, skins, stalks, leaves and especially seeds), seem to provide an alternative sustainable way to counteract bacterial infections. Some phenolics like resveratrol are bacteriostatic/bactericidal against several pathogenic bacteria and may have a synergistic action towards antibiotics, mitigating or reverting bacterial resistance to these drugs. Complex phenolic mixtures, such as those present in these winemaking residues, are even more effective as chemotherapeutic antibacterial agents and could be used in combined therapy, thereby contributing to management of the antibiotic resistance crisis [299], while they can also be successfully used to replace artificial preservatives.

For example, grape seed extracts were efficient in their antibacterial activities after inoculation into cheese and demonstrated bactericidal effects against Escherichia coli [300]. The antibacterial impact was shown at greater concentrations than in in vitro experiments, suggesting that the antimicrobial effect was reduced when the items were introduced to meals. The reduced impact is most likely due to polyphenols' limited solubility in specific meals and their interaction with other dietary components [301]. In a study, resveratrol showed significant antibacterial activity against Gram-positive bacteria through disruption of the phospholipid bilayer and causing significant cell membrane damage when tested against Listeria monocytogenes [302]. This observation was reflected similarly in other studies against Gram-positive bacteria [299,303].

4.4.5. Biodelivery Systems to Improve the Bioavailability and Bio-Functionality of Wineries' By-Products and of Their Bioactives, Extracts and Relevant Bio-Functional Products

Delivery of phenolic bioactives of winery by-products and of their bioactives into the body system is limited due to their poor water solubility, bioavailability and chemical stability [303,304]. With the use of different encapsulation techniques as an approach, the delivery for such bioactives may be achieved. Emulsion-based delivery methods, in particular, are potential encapsulation methods. Lipophilic bioactive substances can be contained inside the hydrophobic core of lipid droplets, protecting them from destruction while allowing them to be released after consumption [305]. The value of an encapsulation technique for stabilising bioactive chemicals derived from winemaking by-products was also shown in a study where crude extract polyphenols were observed to degrade faster than encapsulated ones [304].

For example, formulation of cosmetic emulsions with grape seed oil and diluted wine in the aqueous phase presented advantages, such as direct inclusion of natural antioxidants, aroma and colour compounds, which enhanced their organoleptic characteristics [306]. In another cosmetic application of grape pomace, inactivation of proteolytic enzymes related to skin aging, such as collagenase and elastase, was observed, due to the higher availability of hydrophilic polyphenols, such as low-molecular-weight phenolic acids, especially gallic acid [307]. An antioxidant therapeutic nanoplatform consisting of nano-sized functionalised liposomes loaded with selected polyphenol-rich extracts from grape seeds and skins, with high blood–brain-barrier-crossing capabilities, successfully reduced oxidative stress (decreased ROS levels), prevented the aggregation of α-synuclein fibrils and restored cell viability in a relevant in vitro model of Parkinson's disease [308].

In another nanoemulsion, grape seed oil and grape skin extract were combined to encapsulate resveratrol and thus created a stable delivery system for resveratrol, with minimal damage to the UV-light induced isomerisation and degradation, which reduced oxidation damage [309]. In another study, the synergistic effect between a sunscreen system containing UV filters and grape pomace extract on improving the antioxidant activity and UVB protection of this winery by-product has also been observed [310]. More specifically, both samples (control formulation containing UV filters and sample formulation containing UV filters + grape pomace extract at 10.0% w/w) were considered safe, while a sample formulation containing UV filters + grape pomace extract was more efficient in protecting skin against UVB radiation, with it taking more time for UVB to induce erythema compared to the extract-free control.

Dietary fibres of wineries' by-products seem to be another popular grape-derived product with significant antioxidant effects, which can also be used as a natural system that increases the biodelivery of bioactives of wineries' by-products [108,175,311,312]. The antioxidant activity of dietary fibre of wineries' by-products may differ significantly depending on the extraction method used [108,175,313–316].

For example, the overall antioxidant activity of generated fibres was increased through a method of hot aqueous extraction of white grape pomace followed by membrane concentration [313]. Fibre components in grape pomace have been shown to form chemical bonds with phenolic substances through a complex matrix, thus increasing the phenols' ability to scavenge free radicals as they form an antioxidant dietary fibre compound and thus enhancing the nutraceutical properties of the fortified bio-functional food product [200,311,312]. Furthermore, enhanced bio-functionality, nutritional value and storability of yogurt and salad dressing were observed when these food products were fortified with grape pomace fibres [219], while when grape pomace was used as a dietary fibre supplement for use in prebiotics and bio-preservatives, an increase in probiotic population was observed [317].

In human studies, even though the dietary fibre delayed the absorption of phenolics, the intake of grape pomace dietary fibre resulted in increased plasma antioxidant capacity, which further suggests that the combination makes it partially bioavailable to humans [312]. Such outcomes make dietary fibres from wineries' by-products a promising source to be further studied for the development of nutraceuticals with the goal of long-term enhanced biodelivery of their bioactives.

4.5. Limitations in the Applications of Wineries' By-Products and Their Bioactive Ingredients

The first impediment to widespread industrial utilisation of grape pomace is its limited chemical stability largely due to its high water content, which is likely to also cause microbial and enzymatic degradation. As discussed regarding the extraction processes, the low thermal stability of the bioactive compounds in the pomace makes them susceptible to degradation and oxidation under high heat. Due to these reasons, dehydration of wet grape pomace has been proposed as an essential procedure prior to any subsequent application. Many conventional process techniques have been suggested, such as infrared drying, freeze drying and gamma irradiation [318–320]. Furthermore, non-conventional extraction methods such as ultrasound, supercritical fluid extraction and pulsed electric fields have also been brought up, only to be limited by high initial costs and integrations. Therefore, traditional drying procedures are still the most popular ways of treating wine pomace due to costs. A study has revealed that drying grape pomace, instead of seeds and skins individually, in a vacuum drier at 70 °C exhibited the quickest drying time and energy savings. The process also showed high polyphenol stability despite their volatility when heated, when compared to conventional drying methods [321]. Further processing with surfactants could also increase polyphenol stability. In a demonstration to decrease anthocyanin colour change and degradation rate, both polysorbate 20 and sorbic acid were used as surfactants to process phenolic compounds with promising success [322].

Overall, numerous studies have demonstrated the successful incorporation of grape pomace and its bioactive compounds into many plant-derived and animal-derived foodstuffs for the purpose of fortification of foods with functional ingredients and/or for developing supplements, nutraceuticals or even cosmeutics. The result of such a fortification includes increased overall polyphenolic concentration and, as a result, oxidative stability, leading to longer and more stable shelf life in most products. However, phenols exhibit sensory properties that include bitterness, acidity and astringency and are likely not well accepted by consumers, especially when presented in meat derivatives. Discolouration of meat products has generally led to lowered consumer acceptance. Of course, the amount of discolouration generated by grape pomace extract may vary depending on the grape variety, and antioxidants with lower anthocyanin contents may be more suitable in these conditions. However, textural differences have also been described with the addition of grape pomace, especially in baked products, showing decreased chewiness or hardness, demonstrating a commercial challenge if incorporation of grape pomace were to be included in large-scale production. Textural issues were also shown in pasta products, as the addition of grape pomace increased water-binding capacity and water retention rates were higher in products containing grape pomace. In cheese products, the fortified samples displayed a marbling effect, as well as negative sensory properties such as increased granularity and saltiness [323].

In addition to sensory issues, polyphenol interaction with other compounds plays a critical part in the formulation of successful functional food products. The most extensively studied are wine- and grape-derived tannins, also found in high amounts in wineries' by-products, which demonstrate the ability to bind to residual proteins and polysaccharides. The astringency of such products is decreased during an increase in polysaccharides, rather than a reduction in tannin content [324]. However, the addition of the sweetener aspartame had no effect on the perceived astringency [325]. Similarly, a study showed that the higher the addition of grape pomace, the lower the protein digestibility in cookies, signaling a related issue [326]. These examples exhibit the requirement for extending our knowledge of polyphenol structure and binding, as they would have important implications in their applications as ingredients in novel food products.

Another issue that is worth mentioning is whether the effects of added grape pomace or isolated phenols and their subsequent health benefits are obtainable by the body. The bioavailability may depend on bioaccessibility of compounds in the food matrix [327]. As aforementioned, a solution to that may be the use of several delivery systems like emulsions, which may enhance the biodelivery and bioavailability of bioactives of winery by-products [303–310]. Another natural biodelivery system of such bioactives is winery by-product dietary fibres [108,200,219,311–317]. However, it was also observed that an increase in dietary fibre lowered polyphenol bioaccessibility in the small intestine [311]. This is extremely interesting as the same fibre complex that forms with polyphenols was also able to increase the holding capacity for phenolic compounds [175], while simultaneously decreasing digestibility of the compounds. This could potentially increase the quantity of polyphenols that could reach the lower portions of the intestines. However, more research is needed to understand the influence of dietary fibres and further beneficial activities in the colon.

Another primary concern when using a waste product such as grape pomace is the possibility of harmful residues such as pesticides or heavy metals. Fortunately, vinification processes such as pressing and separation and post processes such as the drying process drastically reduce pesticide and fungicide residue ([328,329]. However, usage of grape skin powders gave rise to high amounts of sodium, as well as lead and cadmium, though the latter two were well below the legal limits [330]. The source of grape pomace would have to be constantly monitored for any contaminants and the extracts would have to be carefully selected to avoid any harmful residues.

5. Conclusions

Within this article, a holistic review was conducted on wine's bioactives, their mode of action and the associated health benefits of this bio-functional beverage when consumed in moderation, as well as on the valorisation of the bioactive compounds of wineries' by-products in several health-promoting applications and as functional ingredients for fortification of foods and the development of supplements and nutraceuticals.

With respect to the health benefits of moderate wine consumption, as part of a healthy, balanced diet, apart from observed associations mentioned in a plethora of epidemiological studies, a broad range of in vitro and in vivo studies, including randomised control clinical trials, have also outlined the various mechanisms and synergistic actions by which wine's bioactives (phenolics, UFA and polar lipids, as well as their metabolites after digestion) mediate their antioxidant, antithrombotic and anti-inflammatory effects against several biomolecular, biochemical and biological inflammatory manifestations and cell/tissue/body responses, which further support the bio-functional health-promoting effects of wine consumption in moderation against inflammation-related chronic disorders. On the other hand, excessive consumption of this alcoholic beverage is not recommended, as it may lead to several negative implications on health, observed in other alcoholic drinks too. Attention has also been given to the putative benefits of de-alcoholised wines, but more targeted research is needed to fully evidence them.

The wine industry is responsible for a considerable number of environmental issues, as it disposes of large amounts of residues that are rich in polyphenols and fibres, such as grape pomace and seeds. On the other hand, the rich content of such wine industry by-products in several of these compounds has made them promising sustainable sources of natural anti-inflammatory bioactives and antioxidants, as well as great sources of dietary fibre and plant-based bio-functional oils, which if appropriately recovered can be valorised as functional ingredients in food products and supplements/nutraceuticals or even used for improving cosmetics.

The potential of the key bioactive components of wineries' by-products, dietary fibre, polyphenols, UFA and polar lipids, as well as several of their extracts, to be employed for the fortification of existing/novel nutraceutical food products and supplements, with higher overall polyphenolic content, improved oxidative stability and shelf life and in some cases enhanced health-promoting effects, has also been outlined. These compounds can replace synthetic additives, adding multifunctional concepts by combining health benefits with technological use. The positive biochemical qualities and appropriate recovery and utilisation of these bioactive compounds and extracts from wineries' by-products have been connected to a number of health benefits, including inflammatory pathway suppression, oxidative stress reduction and lipid-lowering effects, protection against tumours, neurodegenerative disorders and several pathogens and an overall protection against several chronic diseases.

The large number of applications mentioned in this review demonstrate the tremendous untapped potential for the food sector to re-evaluate and promote further research on the valorisation of wineries' by-products and/or of their bioactives. Not only does this improve environmental issues and encourage sustainable use of waste products, but it could also potentially lower production costs for antioxidants and preservatives and provide new methods to diversify food production and the development of supplements.

More bioactive compounds in wine residues should be isolated and identified and their underlying mechanisms of action should be further evaluated, while their applications should be further explored in more food products and more clinical trials should also be carried out to further confirm the health benefits of thus-produced functional foods.

Notably, the undesirable effects of the extraction and isolation processes on the recovered bioactives, as well as the drawbacks of negative sensory properties, should also be considered. Traditional methods are still the most used for the extraction of compounds of interest, while alternative "greener" technologies are emerging to recover bioactive compounds from wineries' by-products. The food industry should also consider consumer response and their acceptance towards such products closely. Thus, further research is required in the optimisation and modification of recovery processes and food formulas, so that they may be used to their maximum potential, while every attempt to study and improve the usage of bioactive compounds should be made and assessed with care and considering consumers' acceptance, in order to appropriately address the demand for new, safe and improved sustainable natural products with higher efficacy and health-promoting effects.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/fermentation9090838/s1, Supplementary Tables S1 and S2; Supplementary Table of Contents–Framework. Tables S1: Characteristic studies, interventions and clinical trials on the benefits of moderate consumption of wine and its bio-functional compounds against inflammation, thrombosis, vascular inflammatory activation and adhesion of leukocytes, endothelial dysfunction, atherosclerosis and CVD; Tables S2: Characteristic studies, interventions and clinical trials on the benefits of moderate consumption of wine and its bio-functional compounds against other inflammatory and thrombotic manifestations and inflammation-related chronic disorders and all-cause mortality, including cancer, metabolic syndrome and diabetes mellitus, gastrointestinal disorders, chronic obstructive pulmonary disease, stroke, neurodegenerative diseases and depression.

Author Contributions: Conceptualisation, A.T.; methodology, A.T.; software, É.O., V.L.J.N., M.K. and A.T.; validation, A.T. and M.K.; investigation, A.T.; writing—original draft preparation, É.O., V.L.J.N., M.K. and A.T.; writing—review and editing, A.T.; visualisation, A.T.; supervision, A.T.; project administration, A.T. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Acknowledgments: We would like to thank the Department of Chemistry of the International Hellenic University (Kavala, Greece) and especially the Head of the Department, G. Kyzas, as well as the Department of Biological Sciences of the School of Science and Engineering of the University of Limerick (Limerick, Ireland) and especially its Dean, Sean Arkins, for their continuous support.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Basalekou, M.; Kallithraka, S.; Kyraleou, M. Wine bioactive compounds. In *Functional Foods and Their Implications for Health Promotion*, 1st ed.; Zabetakis, I., Tsoupras, A., Lordan, R., Ramji, D., Eds.; Academic Press: Cambridge, MA, USA, 2023; Volume 13, pp. 341–363.
2. Calabriso, N.; Scoditti, E.; Massaro, M.; Pellegrino, M.; Storelli, C.; Ingrosso, I.; Giovinazzo, G.; Carluccio, M.A. Multiple anti-inflammatory and anti-atherosclerotic properties of red wine polyphenolic extracts: Differential role of hydroxycinnamic acids, flavonols and stilbenes on endothelial inflammatory gene expression. *Eur. J. Nutr.* **2016**, *55*, 477–489. [CrossRef] [PubMed]
3. Sánchez-Fidalgo, S.; Cárdeno, A.; Villegas, I.; Talero, E.; de la Lastra, C.A. Dietary supplementation of resveratrol attenuates chronic colonic inflammation in mice. *Eur. J. Pharmac.* **2010**, *633*, 78–84. [CrossRef] [PubMed]
4. Fernandes, I.; Pérez-Gregorio, R.; Soares, S.; Mateus, N.; De Freitas, V. Wine Flavonoids in Health and Disease Prevention. *Molecules* **2017**, *22*, 292. [CrossRef] [PubMed]

5. Tsoupras, A.B.; Fragopoulou, E.; Nomikos, T.; Iatrou, C.; Antonopoulou, S.; Demopoulos, C.A. Characterization of the de novo biosynthetic enzyme of platelet activating factor, DDT-insensitive cholinephosphotransferase, of human mesangial cells. *Mediators Inflamm.* **2007**, *2007*, 27683. [CrossRef] [PubMed]
6. Tsoupras, A.B.; Iatrou, C.; Frangia, C.; Demopoulos, C.A. The implication of platelet activating factor in cancer growth and metastasis: Potent beneficial role of PAF-inhibitors and antioxidants. *Infect. Disord. Drug Targets* **2009**, *9*, 390–399. [CrossRef] [PubMed]
7. Tsoupras, A.; Lordan, R.; Zabetakis, I. Inflammation, not Cholesterol, Is a Cause of Chronic Disease. *Nutrients* **2018**, *10*, 604. [CrossRef]
8. Fragopoulou, E.; Nomikos, T.; Tsantila, N.; Mitropoulou, A.; Zabetakis, I.; Demopoulos, C.A. Biological Activity of Total Lipids from Red and White Wine/Must. *J. Agr. Food Chem.* **2001**, *49*, 5186–5193. [CrossRef]
9. Fragopoulou, E.; Antonopoulou, S.; Demopoulos, C.A. Biologically Active Lipids with Antiatherogenic Properties from White Wine and Must. *J. Agr. Food Chem.* **2002**, *50*, 2684–2694. [CrossRef]
10. Fragopoulou, E.; Antonopoulou, S.; Tsoupras, A.; Tsantila, N.; Grypioti, A.; Gribilas, G.; Gritzapi, H.; Konsta, E.; Skandalou, E.; Papadopoulou, A. Antiatherogenic properties of red/white wine, musts, grape-skins, and yeast. In Proceedings of the 45th International Conference on the Bioscience of Lipids, University of Ioannina, Ioannina, Greece, 25–29 May 2004; p. 66.
11. Fragopoulou, E.; Demopoulos, C.A.; Antonopoulou, S. Lipid Minor Constituents in Wines. A Biochemical Approach in the French Paradox. *Int. J. Wine Res.* **2009**, *1*, 131–143.
12. Xanthopoulou, M.N.; Kalathara, K.; Melachroinou, S.; Arampatzi-Menenakou, K.; Antonopoulou, S.; Yannakoulia, M.; Fragopoulou, E. Wine Consumption Reduced Postprandial Platelet Sensitivity against Platelet Activating Factor in Healthy Men. *Eur. J. Nutr.* **2017**, *56*, 1485–1492. [CrossRef]
13. Argyrou, C.; Vlachogianni, I.; Stamatakis, G.; Demopoulos, C.A.; Antonopoulou, S.; Fragopoulou, E. Postprandial Effects of Wine Consumption on Platelet Activating Factor Metabolic Enzymes. *Prostaglandins Other Lipid Mediat.* **2017**, *130*, 23–29. [CrossRef] [PubMed]
14. Fragopoulou, E.; Choleva, M.; Antonopoulou, S.; Demopoulos, C.A. Wine and its metabolic effects. A comprehensive review of clinical trials. *Metabolism* **2018**, *83*, 102–119. [CrossRef] [PubMed]
15. Gavriil, L.; Detopoulou, M.; Petsini, F.; Antonopoulou, S.; Fragopoulou, E. Consumption of plant extract supplement reduces platelet activating factor-induced platelet aggregation and increases platelet activating factor catabolism: A randomised, double-blind and placebo-controlled trial. *Br. J. Nutr.* **2019**, *121*, 982–991. [CrossRef] [PubMed]
16. Choleva, M.; Boulougouri, V.; Panara, A.; Panagopoulou, E.; Chiou, A.; Thomaidis, N.S.; Antonopoulou, S.; Fragopoulou, E. Evaluation of Anti-Platelet Activity of Grape Pomace Extracts. *Food Funct.* **2019**, *10*, 8069–8080. [CrossRef] [PubMed]
17. Choleva, M.; Tsota, M.; Boulougouri, V.; Panara, A.; Thomaidis, N.; Antonopoulou, S.; Fragopoulou, E. Anti-platelet and anti-inflammatory properties of an ethanol-water red grape pomace extract. *Proc. Nutr. Soc.* **2020**, *79*, E370. [CrossRef]
18. Fragopoulou, E.; Antonopoulou, S. The French paradox three decades later: Role of inflammation and thrombosis. *Clin. Chim. Acta* **2020**, *510*, 160–169. [CrossRef] [PubMed]
19. Fragopoulou, E.; Argyrou, C.; Detopoulou, M.; Tsitsou, S.; Seremeti, S.; Yannakoulia, M.; Antonopoulou, S.; Kolovou, G.; Kalogeropoulos, P. The Effect of Moderate Wine Consumption on Cytokine Secretion by Peripheral Blood Mononuclear Cells: A Randomized Clinical Study in Coronary Heart Disease Patients. *Cytokine* **2021**, *146*, 155629. [CrossRef]
20. Choleva, M.; Argyrou, C.; Detopoulou, M.; Donta, M.-E.; Gerogianni, A.; Moustou, E.; Papaemmanouil, A.; Skitsa, C.; Kolovou, G.; Kalogeropoulos, P.; et al. Effect of Moderate Wine Consumption on Oxidative Stress Markers in Coronary Heart Disease Patients. *Nutrients* **2022**, *14*, 1377. [CrossRef]
21. Choleva, M.; Matalliotaki, E.; Antoniou, S.; Asimomyti, E.; Drouka, A.; Stefani, M.; Yannakoulia, M.; Fragopoulou, E. Postprandial Metabolic and Oxidative Stress Responses to Grape Pomace Extract in Healthy Normal and Overweight/Obese Women: A Randomized, Double-Blind, Placebo-Controlled Crossover Study. *Nutrients* **2023**, *15*, 156. [CrossRef]
22. Karantonis, H.C.; Tsoupras, A.; Moran, D.; Zabetakis, I.; Nasopoulou, C. Olive, apple, and grape pomaces with antioxidant and anti-inflammatory bioactivities for functional foods. In *Functional Foods and Their Implications for Health Promotion*, 1st ed.; Zabetakis, I., Tsoupras, A., Lordan, R., Ramji, D., Eds.; Academic Press: Cambridge, MA, USA, 2023; Volume 5, pp. 131–159.
23. Sabra, A.; Netticadan, T.; Wijekoon, C. Grape bioactive molecules, and the potential health benefits in reducing the risk of heart diseases. *Food Chem. X* **2021**, *12*, 100149. [CrossRef]
24. Tsoupras, A.; Lordan, R.; Zabetakis, I. Inflammation and Cardiovascular Diseases. In *The Impact of Nutrition and Statins on Cardiovascular Diseases*, 1st ed.; Zabetakis, I., Lordan, R., Tsoupras, A., Eds.; Academic Press: Cambridge, MA, USA, 2019; Volume 3, pp. 53–117.
25. Van Bussel, B.C.T.; Henry, R.M.A.; Schalkwijk, C.G.; Dekker, J.M.; Nijpels, G.; Feskens, E.J.M.; Stehouwer, C.D.A. Alcohol and red wine consumption, but not fruit, vegetables, fish or dairy products, are associated with less endothelial dysfunction and less low-grade inflammation: The Hoorn Study. *Eur. J. Nutr.* **2018**, *57*, 1409–1419. [CrossRef] [PubMed]
26. Queipo-Ortuño, M.I.; Boto-Ordóñez, M.; Murri, M.; Gomez-Zumaquero, J.M.; Clemente-Postigo, M.; Estruch, R.; Cardona Diaz, F.; Andrés-Lacueva, C.; Tinahones, F.J. Influence of red wine polyphenols and ethanol on the gut microbiota ecology and biochemical biomarkers. *Am. J. Clin. Nutr.* **2012**, *95*, 1323–1334. [CrossRef] [PubMed]

27. Panagiotakos, D.B.; Pitsavos, C.; Arvaniti, F.; Stefanadis, C. Adherence to the Mediterranean Food Pattern Predicts the Prevalence of Hypertension, Hypercholesterolemia, Diabetes and Obesity, among Healthy Adults; the Accuracy of the MedDietScore. *Prev. Med.* **2007**, *44*, 335–340. [CrossRef] [PubMed]
28. Esposito, K.; Maiorino, M.I.; Bellastella, G.; Panagiotakos, D.B.; Giugliano, D. Mediterranean diet for type 2 diabetes: Cardiometabolic benefits. *Endocrine* **2017**, *56*, 27–32. [CrossRef] [PubMed]
29. Piano, M.R. Alcohol's Effects on the Cardiovascular System. *Alcohol Res.* **2017**, *38*, 219–241. [PubMed]
30. Markoski, M.M.; Garavaglia, J.; Oliveira, A.; Olivaes, J.; Marcadenti, A. Molecular Properties of Red Wine Compounds and Cardiometabolic Benefits. *Nutr. Metabol. Insights* **2016**, *9*, 51–57. [CrossRef] [PubMed]
31. Poklar Ulrih, N.; Opara, R.; Skrt, M.; Košmerl, T.; Wondra, M.; Abram, V.; Part, I. Polyphenols composition and antioxidant potential during 'Blaufränkisch' grape maceration and red wine maturation, and the effects of trans-resveratrol addition. *Food Chem. Toxicol.* **2020**, *137*, 111122. [CrossRef]
32. Xiang, L.; Xiao, L.; Wang, Y.; Li, H.; Huang, Z.; He, X. Health benefits of wine: Don't expect resveratrol too much. *Food Chem.* **2014**, *156*, 258–263. [CrossRef]
33. Antonić, B.; Jančíková, S.; Dordević, D.; Tremlová, B. Grape Pomace Valorization: A Systematic Review and Meta-Analysis. *Foods* **2020**, *9*, 1627. [CrossRef]
34. Rockenbach, I.I.; Rodrigues, E.; Gonzaga, L.V.; Caliari, V.; Genovese, M.I.; de Souza Schmidt Gonçalves, A.E.; Fett, R. Phenolic compounds content and antioxidant activity in pomace from selected red grapes (*Vitis vinifera* L. and *Vitis labrusca* L.) widely produced in Brazil. *Food Chem.* **2011**, *127*, 174–179. [CrossRef]
35. Onache, P.A.; Geana, E.-I.; Ciucure, C.T.; Florea, A.; Sumedrea, D.I.; Ionete, R.E.; Tița, O. Bioactive Phytochemical Composition of Grape Pomace Resulted from Different White and Red Grape Cultivars. *Separations* **2022**, *9*, 395. [CrossRef]
36. Lingua, M.S.; Fabani, M.P.; Wunderlin, D.A.; Baroni, M.V. From grape to wine: Changes in phenolic composition and its influence on antioxidant activity. *Food Chem.* **2016**, *208*, 228–238. [CrossRef] [PubMed]
37. Yilmaz, Y.; Göksel, Z.; Erdoğan, S.S.; Öztürk, A.; Atak, A.; Özer, C. Antioxidant Activity and Phenolic Content of Seed, Skin and Pulp Parts of 22 Grape (*Vitis vinifera* L.) Cultivars (4 Common and 18 Registered or Candidate for Registration). *J. Food Proc. Preserv.* **2015**, *39*, 1682–1691. [CrossRef]
38. Ferri, M.; Bin, S.; Vallini, V.; Fava, F.; Michelini, E.; Roda, A.; Minnucci, G.; Bucchi, G.; Tassoni, A. Recovery of polyphenols from red grape pomace and assessment of their antioxidant and anti-cholesterol activities. *New Biotechnol.* **2016**, *33*, 338–344. [CrossRef] [PubMed]
39. Iora, S.R.F.; Maciel, G.M.; Zielinski, A.A.F.; da Silva, M.V.; Pontes, P.V.d.A.; Haminiuk, C.W.I.; Granato, D. Evaluation of the bioactive compounds and the antioxidant capacity of grape pomace. *Int. J. Food Sci. Technol.* **2015**, *50*, 62–69. [CrossRef]
40. Yammine, S.; Delsart, C.; Vitrac, X.; Mietton Peuchot, M.; Ghidossi, R. Characterisation of polyphenols and antioxidant potential of red and white pomace by-product extracts using subcritical water extraction. *OENO One* **2020**, *54*, 263–278.
41. Szabó, É.; Marosvölgyi, T.; Szilágyi, G.; Kőrösi, L.; Schmidt, J.; Csepregi, K.; Márk, L.; Bóna, Á. Correlations between Total Antioxidant Capacity, Polyphenol and Fatty Acid Content of Native Grape Seed and Pomace of Four Different Grape Varieties in Hungary. *Antioxidants* **2021**, *10*, 1101. [CrossRef] [PubMed]
42. Chedea, V.S.; Macovei, Ș.O.; Bocșan, I.C.; Măgureanu, D.C.; Levai, A.M.; Buzoianu, A.D.; Pop, R.M. Grape Pomace Polyphenols as a Source of Compounds for Management of Oxidative Stress and Inflammation—A Possible Alternative for Non-Steroidal Anti-Inflammatory Drugs? *Molecules* **2022**, *27*, 6826. [CrossRef]
43. Visioli, F.; Panaite, S.A.; Tomé-Carneiro, J. Wine's Phenolic Compounds and Health: A Pythagorean View. *Molecules* **2020**, *25*, 4105. [CrossRef]
44. Kennedy, J.A.; Saucier, C.; Glories, Y. Grape and Wine Phenolics: History and Perspective. *Am. J. Enol. Vitic.* **2006**, *57*, 239–248. [CrossRef]
45. Lago-Vanzela, E.; Alves Baffi, M.; Castilhos, M.; Ribeiro-Pinto, M.; Del Bianchi, V.; Ramos, A.; Stringheta, P.; Hermosín-Gutiérrez, I.; Da Silva, R. Phenolic compounds in grapes and wines: Chemical and biochemical characteristics and technological quality. In *Grapes: Production, Phenolic Composition and Potential Biomedical Effects*, 1st ed.; Câmara, J.S., Ed.; Nova Science Publishers Inc.: Hauppauge, NY, USA, 2014; Volume 3, pp. 1–18.
46. Zhou, D.-D.; Li, J.; Xiong, R.-G.; Saimaiti, A.; Huang, S.-Y.; Wu, S.-X.; Yang, Z.-J.; Shang, A.; Zhao, C.-N.; Gan, R.-Y.; et al. Bioactive Compounds, Health Benefits and Food Applications of Grape. *Foods* **2022**, *11*, 2755. [CrossRef] [PubMed]
47. Panzella, L.; Napolitano, A. Natural Phenol Polymers: Recent Advances in Food and Health Applications. *Antioxidants* **2017**, *6*, 30. [CrossRef] [PubMed]
48. Cordova, A.C.; Sumpio, B.E. Polyphenols are medicine: Is it time to prescribe red wine for our patients? *Int. J. Angiol.* **2009**, *18*, 111–117. [CrossRef] [PubMed]
49. Snopek, L.; Mlcek, J.; Sochorova, L.; Baron, M.; Hlavacova, I.; Jurikova, T.; Kizek, R.; Sedlackova, E.; Sochor, J. Contribution of Red Wine Consumption to Human Health Protection. *Molecules* **2018**, *23*, 1684. [CrossRef] [PubMed]
50. Hrelia, S.; Di Renzo, L.; Bavaresco, L.; Bernardi, E.; Malaguti, M.; Giacosa, A. Moderate Wine Consumption and Health: A Narrative Review. *Nutrients* **2023**, *15*, 175. [CrossRef] [PubMed]
51. Aviram, M.; Fuhrman, B. Wine Flavonoids Protect against LDL Oxidation and Atherosclerosis. *Ann. N. Y. Acad. Sci.* **2002**, *957*, 146–161. [CrossRef] [PubMed]

52. Nigdikar, S.V.; Williams, N.R.; Griffin, B.A.; Howard, A.N. Consumption of red wine polyphenols reduces the susceptibility of low-density lipoproteins to oxidation in vivo. *Am. J. Clin. Nutr.* **1998**, *68*, 258–265. [CrossRef] [PubMed]
53. Apostolidou, C.; Adamopoulos, K.; Lymperaki, E.; Iliadis, S.; Papapreponis, P.; Kourtidou-Papadeli, C. Cardiovascular risk and benefits from antioxidant dietary intervention with red wine in asymptomatic hypercholesterolemics. *Clin. Nutr. ESPEN* **2015**, *10*, e224–e233. [CrossRef]
54. Stranieri, C.; Guzzo, F.; Gambini, S.; Cominacini, L.; Fratta Pasini, A.M. Intracellular Polyphenol Wine Metabolites Oppose Oxidative Stress and Upregulate Nrf2/ARE Pathway. *Antioxidants* **2022**, *11*, 2055. [CrossRef]
55. Schrieks, I.C.; van den Berg, R.; Sierksma, A.; Beulens, J.W.; Vaes, W.H.; Hendriks, H.F. Effect of red wine consumption on biomarkers of oxidative stress. *Alcohol Alcohol.* **2013**, *48*, 153–159. [CrossRef]
56. Chiva-Blanch, G.; Arranz, S.; Lamuela-Raventos, R.M.; Estruch, R. Effects of wine, alcohol and polyphenols on cardiovascular disease risk factors: Evidences from human studies. *Alcohol Alcohol.* **2013**, *48*, 270–277. [CrossRef]
57. Mangge, H.; Becker, K.; Fuchs, D.; Gostner, J.M. Antioxidants, inflammation and cardiovascular disease. *World J. Cardiol.* **2014**, *6*, 462–477. [CrossRef] [PubMed]
58. Leri, M.; Scuto, M.; Ontario, M.L.; Calabrese, V.; Calabrese, E.J.; Bucciantini, M.; Stefani, M. Healthy Effects of Plant Polyphenols: Molecular Mechanisms. *Int. J. Mol. Sci.* **2020**, *21*, 1250. [CrossRef] [PubMed]
59. Habauzit, V.; Morand, C. Evidence for a protective effect of polyphenols-containing foods on cardiovascular health: An update for clinicians. *Ther. Adv. Chronic. Dis.* **2012**, *3*, 87–106. [CrossRef] [PubMed]
60. Di Renzo, L.; Marsella, L.T.; Carraro, A.; Valente, R.; Gualtieri, P.; Gratteri, S.; Tomasi, D.; Gaiotti, F.; De Lorenzo, A. Changes in LDL Oxidative Status and Oxidative and Inflammatory Gene Expression after Red Wine Intake in Healthy People: A Randomized Trial. *Mediat. Inflamm.* **2015**, *2015*, 317348. [CrossRef] [PubMed]
61. Torres, A.; Cachofeiro, V.; Millán, J.; Lahera, V.; Nieto, M.L.; Martín, R.; Bello, E.; Alvarez-Sala, L.A. Red wine intake but not other alcoholic beverages increases total antioxidant capacity and improves pro-inflammatory profile after an oral fat diet in healthy volunteers. *Rev. Clin. Esp.* **2015**, *215*, 486–494. [CrossRef]
62. Weseler, A.R.; Ruijters, E.J.B.; Drittij-Reijnders, M.-J.; Reesink, K.D.; Haenen, G.R.M.M.; Bast, A. Pleiotropic Benefit of Monomeric and Oligomeric Flavanols on Vascular Health—A Randomized Controlled Clinical Pilot Study. *PLoS ONE* **2011**, *6*, e28460. [CrossRef]
63. Yang, H.; Xiao, L.; Yuan, Y.; Luo, X.; Jiang, M.; Ni, J.; Wang, N. Procyanidin B2 inhibits NLRP3 inflammasome activation in human vascular endothelial cells. *Biochem. Pharmacol.* **2014**, *92*, 599–606. [CrossRef]
64. De Lorgeril, M.; Salen, P.; Martin, J.L.; Monjaud, I.; Delaye, J.; Mamelle, N. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: Final report of the Lyon Diet Heart Study. *Circulation* **1999**, *99*, 779–785. [CrossRef]
65. Meng, X.; Zhou, J.; Zhao, C.N.; Gan, R.Y.; Li, H.B. Health benefits and molecular mechanisms of resveratrol: A narrative review. *Foods* **2020**, *9*, 340. [CrossRef]
66. Khattar, S.; Khan, S.A.; Zaidi, S.A.A.; Darvishikolour, M.; Farooq, U.; Naseef, P.P.; Kurunian, M.S.; Khan, M.Z.; Shamim, A.; Khan, M.M.U.; et al. Resveratrol from Dietary Supplement to a Drug Candidate: An Assessment of Potential. *Pharmaceuticals* **2022**, *15*, 957. [CrossRef] [PubMed]
67. Zhang, L.X.; Li, C.X.; Kakar, M.U.; Khan, M.S.; Wu, P.F.; Amir, R.M.; Dai, D.F.; Naveed, M.; Li, Q.Y.; Saeed, M.; et al. Resveratrol (RV): A pharmacological review and call for further research. *Biomed. Pharmacother.* **2021**, *143*, 112164. [CrossRef] [PubMed]
68. Sharifi-Rad, J.; Quispe, C.; Zam, W.; Kumar, M.; Cardoso, S.M.; Pereira, O.R.; Ademiluyi, A.O.; Adeleke, O.; Moreira, A.C.; Živković, J. Phenolic bioactives as antiplatelet aggregation factors: The pivotal ingredients in maintaining cardiovascular health. *Oxid. Med. Cell. Longev.* **2021**, *2021*, 2195902. [CrossRef] [PubMed]
69. Parsamanesh, N.; Asghari, A.; Sardari, S.; Tasbandi, A.; Jamialahmadi, T.; Xu, S.; Sahebkar, A. Resveratrol and endothelial function: A literature review. *Pharmacol. Res.* **2021**, *170*, 105725. [CrossRef] [PubMed]
70. Muñoz-Bernal, Ó.A.; Coria-Oliveros, A.J.; de la Rosa, L.A.; Rodrigo-García, J.; Del Rocío Martínez-Ruiz, N.; Sayago-Ayerdi, S.G.; Alvarez-Parrilla, E. Cardioprotective effect of red wine and grape pomace. *Food Res. Int.* **2021**, *140*, 110069. [CrossRef] [PubMed]
71. Wiciński, M.; Socha, M.; Walczak, M.; Wódkiewicz, E.; Malinowski, B.; Rewerski, S.; Górski, K.; Pawlak-Osińska, K. Beneficial Effects of Resveratrol Administration-Focus on Potential Biochemical Mechanisms in Cardiovascular Conditions. *Nutrients* **2018**, *10*, 1813. [CrossRef] [PubMed]
72. Kuršvietienė, L.; Stanevičienė, I.; Mongirdienė, A.; Bernatonienė, J. Multiplicity of effects and health benefits of resveratrol. *Medicina* **2016**, *52*, 148–155. [CrossRef]
73. Riccioni, G.; Gammone, M.A.; Tettamanti, G.; Bergante, S.; Pluchinotta, F.R.; D'Orazio, N. Resveratrol and anti-atherogenic effects. *Int. J. Food Sci. Nutr.* **2015**, *66*, 603–610. [CrossRef]
74. Tamer, F.; Tullemans, B.M.E.; Kuijpers, M.J.E.; Claushuis, T.A.M.; Heemskerk, J.W.M. Nutrition Phytochemicals Affecting Platelet Signaling and Responsiveness: Implications for Thrombosis and Hemostasis. *Thromb. Haemost.* **2022**, *122*, 879–894. [CrossRef]
75. Shahcheraghi, S.H.; Salemi, F.; Small, S.; Syed, S.; Salari, F.; Alam, W.; Cheang, W.S.; Saso, L.; Khan, H. Resveratrol regulates inflammation and improves oxidative stress via Nrf2 signaling pathway: Therapeutic and biotechnological prospects. *Phytother. Res.* **2023**, *37*, 1590–1605. [CrossRef]
76. Rius, C.; Abu-Taha, M.; Hermenegildo, C.; Piqueras, L.; Cerda-Nicolas, J.M.; Issekutz, A.C.; Estañ, L.; Cortijo, J.; Morcillo, E.J.; Orallo, F.; et al. Trans- but Not Cis-Resveratrol impairs angiotensin-II-mediated vascular inflammation through inhibition of

NF-κB activation and peroxisome proliferator-activated Receptor-γ upregulation. *J. Immunol.* **2010**, *185*, 3718–3727. [CrossRef] [PubMed]
77. Csiszar, A.; Smith, K.; Labinskyy, N.; Orosz, Z.; Rivera, A.; Ungvari, Z. Resveratrol attenuates TNF-alpha-induced activation of coronary arterial endothelial cells: Role of NF-kappaB inhibition. *Am. J. Physiol. Heart Circ. Physiol.* **2006**, *291*, H1694–H1699. [CrossRef] [PubMed]
78. Toaldo, I.M.; Van Camp, J.; Gonzales, G.B.; Kamiloglu, S.; Bordignon-Luiz, M.T.; Smagghe, G.; Raes, K.; Capanoglu, E.; Grootaert, C. Resveratrol improves TNF-α-induced endothelial dysfunction in a coculture model of a Caco-2 with an endothelial cell line. *J. Nutr. Biochem.* **2016**, *36*, 21–30. [CrossRef] [PubMed]
79. Chalons, P.; Amor, S.; Courtaut, F.; Cantos-Villar, E.; Richard, T.; Auger, C.; Chabert, P.; Schni-Kerth, V.; Aires, V.; Delmas, D. Study of potential anti-inflammatory effects of red wine extract and resveratrol through a modulation of interleukin-1-beta in macrophages. *Nutrients* **2018**, *10*, 1856. [CrossRef] [PubMed]
80. Fukuda, M.; Ogasawara, Y.; Hayashi, H.; Inoue, K.; Sakashita, H. Resveratrol Inhibits Proliferation and Induces Autophagy by Blocking SREBP1 Expression in Oral Cancer Cells. *Molecules* **2022**, *27*, 8250. [CrossRef] [PubMed]
81. Zucchi, A.; Claps, F.; Pastore, A.L.; Perotti, A.; Biagini, A.; Sallicandro, L.; Gentile, R.; Caglioti, C.; Palazzetti, F.; Fioretti, B. Focus on the Use of Resveratrol in Bladder Cancer. *Int. J. Mol. Sci.* **2023**, *24*, 4562. [CrossRef] [PubMed]
82. Buljeta, I.; Pichler, A.; Šimunović, J.; Kopjar, M. Beneficial Effects of Red Wine Polyphenols on Human Health: Comprehensive Review. *Curr. Issues Mol. Biol.* **2023**, *45*, 782–798. [CrossRef]
83. Chimento, A.; D'Amico, M.; De Luca, A.; Conforti, F.L.; Pezzi, V.; De Amicis, F. Resveratrol, Epigallocatechin Gallate and Curcumin for Cancer Therapy: Challenges from Their Pro-Apoptotic Properties. *Life* **2023**, *13*, 261. [CrossRef]
84. Lalani, A.R.; Fakhari, F.; Radgoudarzi, S.; Rastegar-Pouyani, N.; Moloudi, K.; Khodamoradi, E.; Taeb, S.; Najafi, M. Immunoregulation by resveratrol; implications for normal tissue protection and tumour suppression. *Clin. Exp. Pharmacol. Physiol.* **2023**, *50*, 353–368. [CrossRef]
85. Angellotti, G.; Di Prima, G.; Belfiore, E.; Campisi, G.; De Caro, V. Chemopreventive and Anticancer Role of Resveratrol against Oral Squamous Cell Carcinoma. *Pharmaceutics* **2023**, *15*, 275. [CrossRef]
86. Gupta, D.S.; Gadi, V.; Kaur, G.; Chintamaneni, M.; Tuli, H.; Ramniwas, S.; Sethi, G. Resveratrol and Its Role in the Management of B-Cell Malignancies-A Recent Update. *Biomedicines* **2023**, *11*, 221. [CrossRef] [PubMed]
87. He, L.; Fan, F.; Hou, X.; Gao, C.; Meng, L.; Meng, S.; Huang, S.; Wu, H. Resveratrol suppresses pulmonary tumor metastasis by inhibiting platelet-mediated angiogenic responses. *J. Surg. Res.* **2017**, *217*, 113–122. [CrossRef] [PubMed]
88. Kim, Y.H.; Bae, J.U.; Kim, I.S.; Chang, C.L.; Oh, S.O.; Kim, C.D. SIRT1 prevents pulmonary thrombus formation induced by arachidonic acid via downregulation of PAF receptor expression in platelets. *Platelets* **2016**, *27*, 735–742. [CrossRef] [PubMed]
89. Michno, A.; Grużewska, K.; Ronowska, A.; Gul-Hinc, S.; Zyśk, M.; Jankowska-Kulawy, A. Resveratrol Inhibits Metabolism and Affects Blood Platelet Function in Type 2 Diabetes. *Nutrients* **2022**, *14*, 1633. [CrossRef] [PubMed]
90. Crescente, M.; Jessen, G.; Momi, S.; Höltje, H.D.; Gresele, P.; Cerletti, C.; de Gaetano, G. Interactions of gallic acid, resveratrol, quercetin and aspirin at the platelet cyclooxygenase-1 level. Functional and modelling studies. *Thromb. Haem.* **2009**, *102*, 336–346. [CrossRef] [PubMed]
91. Marumo, M.; Ekawa, K.; Wakabayashi, I. Resveratrol inhibits Ca^{2+} signals and aggregation of platelets. *Environ. Health Prev. Med.* **2020**, *25*, 70. [CrossRef] [PubMed]
92. Vlachogianni, I.C.; Fragopoulou, E.; Stamatakis, G.M.; Kostakis, I.K.; Antonopoulou, S. Platelet Activating Factor (PAF) biosynthesis is inhibited by phenolic compounds in U-937 cells under inflammatory conditions. *Prostaglandins Other Lipid Mediat.* **2015**, *121*, 176–183. [CrossRef] [PubMed]
93. Eräsalo, H.; Hämäläinen, M.; Leppänen, T.; Mäki-Opas, I.; Laavola, M.; Haavikko, R.; Yli-Kauhaluoma, J.; Moilanen, E. Natural Stilbenoids Have Anti-Inflammatory Properties in Vivo and Down-Regulate the Production of Inflammatory Mediators NO, IL6, and MCP1 Possibly in a PI3K/Akt-Dependent Manner. *J. Nat. Prod.* **2018**, *81*, 1131–1142. [CrossRef]
94. Dutra, L.A.; Guanaes, J.F.O.; Johmann, N.; Lopes Pires, M.E.; Chin, C.M.; Marcondes, S.; Dos Santos, J.L. Synthesis, antiplatelet and antithrombotic activities of resveratrol derivatives with NO-donor properties. *Bioorg. Med. Chem. Lett.* **2017**, *27*, 2450–2453. [CrossRef]
95. Deng, Y.H.; Alex, D.; Huang, H.Q.; Wang, N.; Yu, N.; Wang, Y.T.; Leung, G.P.; Lee, S.M. Inhibition of TNF-α-mediated endothelial cell-monocyte cell adhesion and adhesion molecules expression by the resveratrol derivative, trans-3,5,4′-trimethoxystilbene. *Phytother. Res.* **2011**, *25*, 451–457. [CrossRef]
96. Nash, V.; Ranadheera, C.S.; Georgousopoulou, E.N.; Mellor, D.D.; Panagiotakos, D.B.; McKune, A.J.; Kellett, J.; Naumovski, N. The effects of grape and red wine polyphenols on gut microbiota—A systematic review. *Food Res. Int.* **2018**, *113*, 277–287. [CrossRef]
97. Dueñas, M.; Cueva, C.; Muñoz-González, I.; Jiménez-Girón, A.; Sánchez-Patán, F.; Santos-Buelga, C.; Moreno-Arribas, M.V.; Bartolomé, B. Studies on Modulation of Gut Microbiota by Wine Polyphenols: From Isolated Cultures to Omic Approaches. *Antioxidants* **2015**, *4*, 1–21. [CrossRef] [PubMed]
98. O'Callaghan, A.; van Sinderen, D. Bifidobacteria and Their Role as Members of the Human Gut Microbiota. *Front. Microbiol.* **2016**, *7*, 925. [CrossRef]
99. Haas, E.A.; Saad, M.J.A.; Santos, A.; Vitulo, N.; Lemos, W.J.F.; Martins, A.M.A.; Picossi, C.R.C.; Favarato, D.; Gaspar, R.S.; Magro, D.O.; et al. WineFlora Study. A red wine intervention does not modify plasma trimethylamine N-oxide but is associated with

broad shifts in the plasma metabolome and gut microbiota composition. *Am. J. Clin. Nutr.* **2022**, *116*, 1515–1529. [CrossRef] [PubMed]
100. Suo, H.; Shishir, M.R.I.; Xiao, J.; Wang, M.; Chen, F.; Cheng, K.-W. Red Wine High-Molecular-Weight Polyphenolic Complex: An Emerging Modulator of Human Metabolic Disease Risk and Gut Microbiota. *J. Agr. Food Chem.* **2021**, *69*, 10907–10919. [CrossRef]
101. Chen, X.; Zhang, J.; Yin, N.; Wele, P.; Li, F.; Dave, S.; Lin, J.; Xiao, H.; Wu, X. Resveratrol in disease prevention and health promotion: A role of the gut microbiome. *Crit. Rev. Food Sci. Nutr.* **2023**, 1–18. [CrossRef] [PubMed]
102. Tsoupras, A.; Brummell, C.; Kealy, C.; Vitkaitis, K.; Redfern, S.; Zabetakis, I. Cardio-Protective Properties and Health Benefits of Fish Lipid Bioactives; The Effects of Thermal Processing. *Mar. Drugs* **2022**, *20*, 187. [CrossRef]
103. Nunez, D.; Randon, J.; Gandhi, C.; Siafaka-Kapadai, A.; Olson, M.S.; Hanahan, D.J. The inibition of platelet-activating factor-induced platelet activation by oleic acid is associated with a decrease in polyphosphoinositide metabolism. *J. Biol. Chem.* **1990**, *265*, 18330–18338. [CrossRef]
104. Perdomo, L.; Beneit, N.; Otero, Y.F.; Escribano, O.; Diaz-Castroverde, S.; Gómez-Hernández, A.; Benito, M. Protective role of oleic acid against cardiovascular insulin resistance and in the early and late cellular atherosclerotic process. *Cardiovasc. Diabetol.* **2015**, *14*, 75–87. [CrossRef]
105. Delgado, G.E.; Krämer, B.K.; Lorkowski, S.; März, W.; Von Schacky, C.; Kleber, M.E. Individual omega-9 monounsaturated fatty acids and mortality—The Ludwigshafen Risk and Cardiovascular Health Study. *J. Clin. Lipidol.* **2017**, *11*, 126–135. [CrossRef]
106. Holy, E.W.; Forestier, M.; Richter, E.K.; Akhmedov, A.; Leiber, F.; Camici, G.C.; Mocharla, P.; Lüscher, T.F.; Beer, J.H.; Tanner, F.C. Dietary α-linolenic acid inhibits arterial thrombus formation, tissue factor expression, and platelet activation. *Arterioscler. Thromb. Vasc. Biol.* **2011**, *31*, 1772–1780. [CrossRef] [PubMed]
107. Bazán-Salinas, I.L.; Matías-Pérez, D.; Pérez-Campos, E.; Pérez-Campos Mayoral, L.; García-Montalvo, I.A. Reduction of platelet aggregation from ingestion of oleic and linoleic acids found in *Vitis vinifera* and Arachis hypogaea Oils. *Am. J. Ther.* **2016**, *23*, e1315–e1319. [CrossRef] [PubMed]
108. Beres, C.; Costa, G.N.S.; Cabezudo, I.; da Silva-James, N.K.; Teles, A.S.C.; Cruz, A.P.G.; Mellinger-Silva, C.; Tonon, R.V.; Cabral, L.M.C.; Freitas, S.P. Towards integral utilization of grape pomace from winemaking process: A review. *Waste Manag.* **2017**, *68*, 581–594. [CrossRef] [PubMed]
109. Rombaut, N.; Savoire, R.; Thomasset, B.; Castello, J.; Van Hecke, E.; Lanoisellé, J.-L. Optimization of oil yield and oil total phenolic content during grape seed cold screw pressing. *Ind. Crops Prod.* **2015**, *63*, 26–33. [CrossRef]
110. Garavaglia, J.; Markoski, M.M.; Oliveira, A.; Marcadenti, A. Grape Seed Oil Compounds: Biological and Chemical Actions for Health. *Nutr. Metab. Insights* **2016**, *9*, 59–64. [CrossRef] [PubMed]
111. Matthäus, B. Virgin grape seed oil: Is it really a nutritional highlight? *Eur. J. Lipid. Sci. Technol.* **2008**, *110*, 645–650. [CrossRef]
112. Moran, D.; Fleming, M.; Daly, E.; Gaughan, N.; Zabetakis, I.; Traas, C.; Tsoupras, A. Anti-Platelet Properties of Apple Must/Skin Yeasts and of Their Fermented Apple Cider Products. *Beverages* **2021**, *7*, 54. [CrossRef]
113. Tsoupras, A.; Lordan, R.; Harrington, J.; Pienaar, R.; Devaney, K.; Heaney, S.; Koidis, A.; Zabetakis, I. The Effects of Oxidation on the Antithrombotic Properties of Tea Lipids against PAF, Thrombin, Collagen, and ADP. *Foods* **2020**, *9*, 385. [CrossRef]
114. Janssen, I.; Landay, A.L.; Ruppert, K.; Powell, L.H. Moderate wine consumption is associated with lower hemostatic and inflammatory risk factors over 8 years: The study of women's health across the nation (SWAN). *Nutr. Aging* **2014**, *2*, 91–99. [CrossRef]
115. Panagiotakos, D.B.; Kouli, G.-M.; Magripis, E.; Kyrou, I.; Georgousopoulou, E.N.; Chrysohoou, C.; Tsigos, C.; Tousoulis, D.; Pitsavos, C. Beer, wine consumption, and 10-year CVD incidence: The ATTICA study. *Eur. J. Clin. Nutr.* **2019**, *73*, 1015–1023. [CrossRef]
116. Taborsky, M.; Ostadal, P.; Adam, T.; Moravec, O.; Gloger, V.; Schee, A.; Skala, T. Red or white wine consumption effect on atherosclerosis in healthy individuals (In Vino Veritas study). *Bratisl. Lekárske Listy* **2017**, *118*, 292–298. [CrossRef] [PubMed]
117. Salazar, H.M.; de Deus Mendonça, R.; Laclaustra, M.; Moreno-Franco, B.; Åkesson, A.; Guallar-Castillón, P.; Donat-Vargas, C. The intake of flavonoids, stilbenes, and tyrosols, mainly consumed through red wine and virgin olive oil, is associated with lower carotid and femoral subclinical atherosclerosis and coronary calcium. *Eur. J. Nutr.* **2022**, *61*, 2697–2709. [CrossRef] [PubMed]
118. Chiva-Blanch, G.; Urpi-Sarda, M.; Llorach, R.; Rotches-Ribalta, M.; Guillén, M.; Casas, R.; Arranz, S.; Valderas-Martinez, P.; Portoles, O.; Corella, D. Differential effects of polyphenols and alcohol of red wine on the expression of adhesion molecules and inflammatory cytokines related to atherosclerosis: A randomized clinical trial. *Am. J. Clin. Nutr.* **2011**, *95*, 326–334. [CrossRef] [PubMed]
119. Canali, R.; Comitato, R.; Ambra, R.; Virgili, F. Red wine metabolites modulate NF-κB, activator protein-1 and cAMP response element-binding proteins in human endothelial cells. *Br. J. Nutr.* **2010**, *103*, 807–814. [CrossRef] [PubMed]
120. Nallasamy, P.; Kang, Z.Y.; Sun, X.; Anandh Babu, P.V.; Liu, D.; Jia, Z. Natural compound resveratrol attenuates TNF-alpha-induced vascular dysfunction in mice and human endothelial cells: The involvement of the NF-κB signaling pathway. *Int. J. Mol. Sci.* **2021**, *22*, 12486. [CrossRef] [PubMed]
121. Kechagias, S.; Zanjani, S.; Gjellan, S.; Leinhard, O.D.; Kihlberg, J.; Smedby, O.; Johansson, L.; Kullberg, J.; Ahlström, H.; Lindström, T.; et al. Effects of moderate red wine consumption on liver fat and blood lipids: A prospective randomized study. *Ann. Med.* **2011**, *43*, 545–554. [CrossRef] [PubMed]

122. Roth, I.; Casas, R.; Medina-Remón, A.; Lamuela-Raventós, R.M.; Estruch, R. Consumption of aged white wine modulates cardiovascular risk factors via circulating endothelial progenitor cells and inflammatory biomarkers. *Clin. Nutr.* **2019**, *38*, 1036–1044. [CrossRef]
123. Huang, P.H.; Chen, Y.H.; Tsai, H.Y.; Chen, J.S.; Wu, T.C.; Lin, F.Y.; Sata, M.; Chen, J.W.; Lin, S.J. Intake of Red Wine Increases the Number and Functional Capacity of Circulating Endothelial Progenitor Cells by Enhancing Nitric Oxide Bioavailability. *Arterioscler. Thromb. Vasc. Biol.* **2010**, *30*, 869–877. [CrossRef]
124. Tomé-Carneiro, J.; Gonzálvez, M.; Larrosa, M.; Yáñez-Gascón, M.J.; García-Almagro, F.J.; Ruiz-Ros, J.A.; Tomás-Barberán, F.A.; García-Conesa, M.T.; Espín, J.C. Grape resveratrol increases serum adiponectin and downregulates inflammatory genes in peripheral blood mononuclear cells: A triple-blind, placebo-controlled, one-year clinical trial in patients with stable coronary artery disease. *Cardiovasc. Drugs Ther.* **2013**, *27*, 37–48. [CrossRef]
125. Cosmi, F.; Di Giulio, P.; Masson, S.; Finzi, A.; Marfisi, R.M.; Cosmi, D.; Scarano, M.; Tognoni, G.; Maggioni, A.P.; Porcu, M.; et al. Regular Wine Consumption in Chronic Heart Failure: Impact on Outcomes, Quality of Life, and Circulating Biomarkers. *Circ. Heart Fail.* **2015**, *8*, 428–437. [CrossRef]
126. Downer, M.K.; Kenfield, S.A.; Stampfer, M.J.; Wilson, K.M.; Dickerman, B.A.; Giovannucci, E.L.; Rimm, E.B.; Wang, M.; Mucci, L.A.; Willett, W.C.; et al. Alcohol Intake and Risk of Lethal Prostate Cancer in the Health Professionals Follow-Up Study. *J. Clin. Oncol.* **2019**, *37*, 1499–1511. [CrossRef] [PubMed]
127. Crockett, S.D.; Long, M.D.; Dellon, E.S.; Martin, C.F.; Galanko, J.A.; Sandler, R.S. Inverse relationship between moderate alcohol intake and rectal cancer: Analysis of the North Carolina Colon Cancer Study. *Dis. Colon. Rectum.* **2011**, *54*, 887–894. [CrossRef] [PubMed]
128. Liu, Z.; Song, C.; Suo, C.; Fan, H.; Zhang, T.; Jin, L.; Chen, X. Alcohol consumption and hepatocellular carcinoma: Novel insights from a prospective cohort study and nonlinear Mendelian randomization analysis. *BMC Med.* **2022**, *20*, 413. [CrossRef] [PubMed]
129. Wang, X.; Jia, M.; Mao, Y.; Jia, Z.; Liu, H.; Yang, G.; Wang, S.; Sun, B.; Zhang, H. Very-light alcohol consumption suppresses breast tumor progression in a mouse model. *Food Funct.* **2022**, *13*, 3391–3404. [CrossRef] [PubMed]
130. Schaefer, S.M.; Kaiser, A.; Behrendt, I.; Eichner, G.; Fasshauer, M. Association of alcohol types, coffee and tea intake with mortality: Prospective cohort study of UK Biobank participants. *Br. J. Nutr.* **2022**, *129*, 1–11. [CrossRef] [PubMed]
131. Turati, F.; Carioli, G.; Bravi, F.; Ferraroni, M.; Serraino, D.; Montella, M.; Giacosa, A.; Toffolutti, F.; Negri, E.; Levi, F.; et al. Mediterranean Diet and Breast Cancer Risk. *Nutrients* **2018**, *10*, 326. [CrossRef] [PubMed]
132. Shufelt, C.; Merz, C.N.; Yang, Y.; Kirschner, J.; Polk, D.; Stanczyk, F.; Paul-Labrador, M.; Braunstein, D. Red versus white wine as a nutritional aromatase inhibitor in premenopausal women: A pilot study. *J. Womens Health* **2012**, *21*, 281–284. [CrossRef] [PubMed]
133. Armstrong, M.J.; Mellinger, J.L.; Trivedi, P.J. Alcohol Consumption in Patients with Non-alcoholic Fatty Liver Disease: Convenient vs. Inconvenient Truths. *Am. J. Gastroenterol.* **2018**, *113*, 1437–1439. [CrossRef]
134. Zhu, W.; Qin, W.; Zhang, K.; Rottinghaus, G.E.; Chen, Y.C.; Kliethermes, B.; Sauter, E.R. Trans-resveratrol alters mammary promoter hypermethylation in women at increased risk for breast cancer. *Nutr. Cancer.* **2012**, *64*, 393–400. [CrossRef]
135. Tresserra-Rimbau, A.; Medina-Remón, A.; Lamuela-Raventós, R.M.; Bulló, M.; Salas-Salvadó, J.; Corella, D.; Fitó, M.; Gea, A.; Gómez-Gracia, E.; Lapetra, J.; et al. Moderate red wine consumption is associated with a lower prevalence of the metabolic syndrome in the PREDIMED population. *Br. J. Nutr.* **2015**, *113*, S121–S130. [CrossRef]
136. Larsen, B.A.; Klinedinst, B.S.; Le, S.T.; Pappas, C.; Wolf, T.; Meier, N.F.; Lim, Y.L.; Willette, A.A. Beer, wine, and spirits differentially influence body composition in older white adults-a United Kingdom Biobank study. *Obes. Sci. Pract.* **2022**, *8*, 641–656. [CrossRef] [PubMed]
137. Gepner, Y.; Golan, R.; Harman-Boehm, I.; Henkin, Y.; Schwarzfuchs, D.; Shelef, I.; Durst, R.; Kovsan, J.; Bolotin, A.; Leitersdorf, E.; et al. Effects of Initiating Moderate Alcohol Intake on Cardiometabolic Risk in Adults With Type 2 Diabetes: A 2-Year Randomized, Controlled Trial. *Ann. Intern. Med.* **2015**, *163*, 569–579. [CrossRef] [PubMed]
138. Golan, R.; Shai, I.; Gepner, Y.; Harman-Boehm, I.; Schwarzfuchs, D.; Spence, J.D.; Parraga, G.; Buchanan, D.; Witkow, S.; Friger, M.; et al. Effect of wine on carotid atherosclerosis in type 2 diabetes: A 2-year randomized controlled trial. *Eur. J. Clin. Nutr.* **2018**, *72*, 871–878. [CrossRef] [PubMed]
139. Ma, H.; Wang, X.; Li, X.; Heianza, Y.; Qi, L. Moderate alcohol drinking with meals is related to lower incidence of type 2 diabetes. *Am. J. Clin. Nutr.* **2022**, *116*, 1507–1514. [CrossRef] [PubMed]
140. Chiva-Blanch, G.; Urpi-Sarda, M.; Ros, E.; Valderas-Martinez, P.; Casas, R.; Arranz, S.; Guillén, M.; Lamuela-Raventós, R.M.; Llorach, R.; Andres-Lacueva, C.; et al. Effects of red wine polyphenols and alcohol on glucose metabolism and the lipid profile: A randomized clinical trial. *Clin. Nutr.* **2013**, *32*, 200–206. [CrossRef] [PubMed]
141. Ismail, M.; Stagling, S.; Lundberg, A.; Nystrom, F.H. A cross-over study of postprandial effects from moist snuff and red wine on metabolic rate, appetite-related hormones and glucose. *Drug Alcohol Depend.* **2022**, *236*, 109479. [CrossRef]
142. Sattarinezhad, A.; Roozbeh, J.; Shirazi Yeganeh, B.; Omrani, G.R.; Shams, M. Resveratrol reduces albuminuria in diabetic nephropathy: A randomized double-blind placebo-controlled clinical trial. *Diabetes Metab.* **2019**, *45*, 53–59. [CrossRef] [PubMed]
143. Tian, X.; Liu, Y.; Ren, G.; Yin, L.; Liang, X.; Geng, T.; Dang, H.; An, R. Resveratrol limits diabetes-associated cognitive decline in rats by preventing oxidative stress and inflammation and modulating hippocampal structural synaptic plasticity. *Brain Res.* **2016**, *1650*, 1–9. [CrossRef]

144. Fischer, K.; Melo van Lent, D.; Wolfsgruber, S.; Weinhold, L.; Kleineidam, L.; Bickel, H.; Scherer, M.; Eisele, M.; van den Bussche, H.; Wiese, B.; et al. Prospective Associations between Single Foods, Alzheimer's Dementia and Memory Decline in the Elderly. *Nutrients* **2018**, *10*, 852. [CrossRef]
145. Mendes, D.; Oliveira, M.M.; Moreira, P.I.; Coutinho, J.; Nunes, F.M.; Pereira, D.M.; Valentão, P.; Andrade, P.B.; Videira, R.A. Beneficial effects of white wine polyphenols-enriched diet on Alzheimer's disease-like pathology. *J. Nutr. Biochem.* **2018**, *55*, 165–177. [CrossRef]
146. Xu, W.; Wang, H.; Wan, Y.; Tan, C.; Li, J.; Tan, L.; Yu, J.T. Alcohol consumption and dementia risk: A dose-response meta-analysis of prospective studies. *Eur. J. Epidemiol.* **2017**, *32*, 31–42. [CrossRef] [PubMed]
147. Ho, L.; Ferruzzi, M.G.; Janle, E.M.; Wang, J.; Gong, B.; Chen, T.Y.; Lobo, J.; Cooper, B.; Wu, Q.L.; Talcott, S.T.; et al. Identification of brain-targeted bioactive dietary quercetin-3-O-glucuronide as a novel intervention for Alzheimer's disease. *FASEB J.* **2013**, *27*, 769–781. [CrossRef] [PubMed]
148. Valls-Pedret, C.; Lamuela-Raventós, R.M.; Medina-Remón, A.; Quintana, M.; Corella, D.; Pintó, X.; Martínez-González, M.Á.; Estruch, R.; Ros, E. Polyphenol-rich foods in the Mediterranean diet are associated with better cognitive function in elderly subjects at high cardiovascular risk. *J. Alzheimers Dis.* **2012**, *29*, 773–782. [CrossRef] [PubMed]
149. Smyth, A.; O'Donnell, M.; Rangarajan, S.; Hankey, G.J.; Oveisgharan, S.; Canavan, M.; McDermott, C.; Xavier, D.; Zhang, H.; Damasceno, A.; et al. INTERSTROKE Investigators. Alcohol Intake as a Risk Factor for Acute Stroke: The INTERSTROKE Study. *Neurology* **2023**, *100*, e142–e153. [CrossRef] [PubMed]
150. Kaluza, J.; Harris, H.R.; Linden, A.; Wolk, A. Alcohol Consumption and Risk of Chronic Obstructive Pulmonary Disease: A Prospective Cohort Study of Men. *Am. J. Epidemiol.* **2019**, *188*, 907–916. [CrossRef] [PubMed]
151. Godos, J.; Castellano, S.; Ray, S.; Grosso, G.; Galvano, F. Dietary Polyphenol Intake and Depression: Results from the Mediterranean Healthy Eating, Lifestyle and Aging (MEAL) Study. *Molecules* **2018**, *23*, 999. [CrossRef]
152. Barbería-Latasa, M.; Bes-Rastrollo, M.; Pérez-Araluce, R.; Martínez-González, M.Á.; Gea, A. Mediterranean Alcohol-Drinking Patterns and All-Cause Mortality in Women More Than 55 Years Old and Men More Than 50 Years Old in the "Seguimiento Universidad de Navarra" (SUN) Cohort. *Nutrients* **2022**, *14*, 5310. [CrossRef] [PubMed]
153. Carballo-Casla, A.; Ortolá, R.; García-Esquinas, E.; Oliveira, A.; Sotos-Prieto, M.; Lopes, C.; Lopez-Garcia, E.; Rodríguez-Artalejo, F. The Southern European Atlantic Diet and all-cause mortality in older adults. *BMC Med.* **2021**, *19*, 36. [CrossRef]
154. Grønbaek, M.; Becker, U.; Johansen, D.; Gottschau, A.; Schnohr, P.; Hein, H.O.; Jensen, G.; Sørensen, T.I. Type of alcohol consumed and mortality from all causes, coronary heart disease, and cancer. *Ann. Intern. Med.* **2000**, *133*, 411–419. [CrossRef]
155. Noguer, M.A.; Cerezo, A.B.; Donoso Navarro, E.; Garcia-Parrilla, M.C. Intake of alcohol-free red wine modulates antioxidant enzyme activities in a human intervention study. *Pharmacol. Res.* **2012**, *65*, 609–614. [CrossRef]
156. Giovannucci, E.; Stampfer, M.J.; Colditz, G.A.; Manson, J.E.; Rosner, B.A.; Longnecker, M.P.; Speizer, F.E.; Willett, W.C. Recall and selection bias in reporting past alcohol consumption among breast cancer cases. *Cancer Causes Control* **1993**, *4*, 441–448. [CrossRef] [PubMed]
157. Wu, S.; Li, W.Q.; Qureshi, A.A.; Cho, E. Alcohol consumption and risk of cutaneous basal cell carcinoma in women and men: 3 prospective cohort studies. *Am. J. Clin. Nutr.* **2015**, *102*, 1158–1166. [CrossRef] [PubMed]
158. Papadimitriou, N.; Bouras, E.; van den Brandt, P.A.; Muller, D.C.; Papadopoulou, A.; Heath, A.K.; Critselis, E.; Gunter, M.J.; Vineis, P.; Ferrari, P.; et al. A Prospective Diet-Wide Association Study for Risk of Colorectal Cancer in EPIC. *Clin. Gastroenterol. Hepatol.* **2022**, *20*, 864–873.e13. [CrossRef] [PubMed]
159. Mahamat-Saleh, Y.; Al-Rahmoun, M.; Severi, G.; Ghiasvand, R.; Veierod, M.B.; Caini, S.; Palli, D.; Botteri, E.; Sacerdote, C.; Ricceri, F.; et al. Baseline and lifetime alcohol consumption and risk of skin cancer in the European Prospective Investigation into Cancer and Nutrition cohort (EPIC). *Int. J. Cancer* **2023**, *152*, 348–362. [CrossRef] [PubMed]
160. Heath, A.K.; Muller, D.C.; Brandt, P.A.v.D.; Papadimitriou, N.; Critselis, E.; Gunter, M.; Vineis, P.; Weiderpass, E.; Fagherazzi, G.; Boeing, H.; et al. Nutrient-wide association study of 92 foods and nutrients and breast cancer risk. *Breast Cancer Res.* **2020**, *22*, 5. [CrossRef] [PubMed]
161. Naudin, S.; Li, K.; Jaouen, T.; Assi, N.; Kyrø, C.; Tjønneland, A.; Overvad, K.; Boutron-Ruault, M.-C.; Rebours, V.; Védié, A.-L.; et al. Lifetime and baseline alcohol intakes and risk of pancreatic cancer in the European Prospective Investigation into Cancer and Nutrition study. *Int. J. Cancer* **2018**, *143*, 801–812. [CrossRef] [PubMed]
162. Seidenberg, A.B.; Wiseman, K.P.; Klein, W.M.P. Do Beliefs about Alcohol and Cancer Risk Vary by Alcoholic Beverage Type and Heart Disease Risk Beliefs? *Cancer Epidemiol. Biomark. Prev.* **2023**, *32*, 46–53. [CrossRef] [PubMed]
163. Hay, J.L.; Kiviniemi, M.T.; Orom, H.; Waters, E.A. Moving beyond the "Health Halo" of Alcohol: What Will it Take to Achieve Population Awareness of the Cancer Risks of Alcohol? *Cancer Epidemiol. Biomark. Prev.* **2023**, *32*, 9–11. [CrossRef]
164. Duell, E.J.; Travier, N.; Lujan-Barroso, L.; Clavel-Chapelon, F.; Boutron-Ruault, M.-C.; Morois, S.; Palli, D.; Krogh, V.; Panico, S.; Tumino, R.; et al. Alcohol consumption and gastric cancer risk in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort. *Am. J. Clin. Nutr.* **2011**, *94*, 1266–1275. [CrossRef]
165. Cote, D.J.; Smith, T.R.; Kaiser, U.B.; Laws, E.R., Jr.; Stampfer, M.J. Alcohol intake and risk of pituitary adenoma. *Cancer Causes Control* **2022**, *33*, 353–361. [CrossRef]
166. Bondonno, N.P.; Liu, Y.L.; Zheng, Y.; Ivey, K.; Willett, W.C.; Stampfer, M.J.; Rimm, E.B.; Cassidy, A. Change in habitual intakes of flavonoid-rich foods and mortality in US males and females. *BMC Med.* **2023**, *21*, 181. [CrossRef] [PubMed]

167. Duan, J.; Guo, H.; Fang, Y.; Zhou, G. The mechanisms of wine phenolic compounds for preclinical anticancer therapeutics. *Food Nutr. Res.* **2021**, *65*. [CrossRef] [PubMed]
168. O'Keefe, J.H.; Bybee, K.A.; Lavie, C.J. Alcohol and cardiovascular health: The razor-sharp double-edged sword. *J. Am. Coll. Cardiol.* **2007**, *50*, 1009–1014. [CrossRef] [PubMed]
169. O'Keefe, E.L.; DiNicolantonio, J.J.; O'Keefe, J.H.; Lavie, C.J. Alcohol and CV Health: Jekyll and Hyde J-Curves. *Prog. Cardiov. Dis.* **2018**, *61*, 68–75. [CrossRef] [PubMed]
170. Poli, A. Is drinking wine in moderation good for health or not? *Eur. Heart J. Suppl.* **2022**, *24*, I119–I122. [CrossRef] [PubMed]
171. Rifler, J.P. Is a Meal without Wine Good for Health? *Diseases* **2018**, *6*, 105. [CrossRef] [PubMed]
172. Gerardi, G.; Cavia-Saiz, M.; Muñiz, P. From winery by-product to healthy product: Bioavailability, redox signaling and oxidative stress modulation by wine pomace product. *Crit. Rev. Food Sci. Nutr.* **2022**, *62*, 7427–7448. [CrossRef]
173. Chen, Y.; Wen, J.Y.; Deng, Z.X.; Pan, X.Q.; Xie, X.F.; Peng, C. Effective utilization of food wastes: Bioactivity of grape seed extraction and its application in food industry. *J. Funct. Foods* **2020**, *73*, 104113. [CrossRef]
174. Yang, C.; Han, Y.; Tian, X.; Sajid, M.; Mehmood, S.; Wang, H.; Li, H. Phenolic composition of grape pomace and its metabolism. *Crit. Rev. Food Sci. Nutr.* **2022**, *17*, 1–17. [CrossRef]
175. Spinei, M.; Oroian, M. The Potential of Grape Pomace Varieties as a Dietary Source of Pectic Substances. *Foods* **2021**, *10*, 867. [CrossRef]
176. Panzella, L.; Moccia, F.; Nasti, R.; Marzorati, S.; Verotta, L.; Napolitano, A. Bioactive Phenolic Compounds From Agri-Food Wastes: An Update on Green and Sustainable Extraction Methodologies. *Front. Nutr.* **2020**, *7*, 60. [CrossRef] [PubMed]
177. Ilyas, T.; Chowdhary, P.; Chaurasia, D.; Gnansounou, E.; Pandey, A.; Chaturvedi, P. Sustainable green processing of grape pomace for the production of value-added products: An overview. *Environ. Technol. Innov.* **2021**, *23*, 101592. [CrossRef]
178. Chowdhary, P.; Gupta, A.; Gnansounou, E.; Pandey, A.; Chaturvedi, P. Current trends and possibilities for exploitation of Grape pomace as a potential source for value addition. *Environ. Pollut.* **2021**, *278*, 116796. [CrossRef] [PubMed]
179. Drevelegka, I.; Goula, A.M. Recovery of grape pomace phenolic compounds through optimized extraction and adsorption processes. *Chem. Eng. Process.-Process Intensif.* **2020**, *149*, 107845. [CrossRef]
180. Barba, F.; Zhu, Z.; Koubaa, M.; Sant'Ana, A.; Orlien, V. Green alternative methods for the extraction of antioxidant bioactive compounds from winery wastes and by-products: A review. *Trends Food Sci. Technol.* **2016**, *49*, 96–109. [CrossRef]
181. Jokić, S.; Velić, D.; Bilić, M.; Bucić-Kojić, A.; Planinić, M.; Tomas, S. Modelling of the Process of Solid-Liquid Extraction of Total Polyphenols from Soybeans. *Czech J. Food Sci.* **2010**, *28*, 7. [CrossRef]
182. Yang, C.L.; Shang, K.; Lin, C.C.; Wang, C.; Shi, X.Q.; Wang, H.; Li, H. Processing technologies, phytochemical constituents, and biological activities of grape seed oil (gso): A review. *Trends Food Sci. Technol.* **2021**, *116*, 1074–1083. [CrossRef]
183. Herrero, M.; Mendiola, J.A.; Cifuentes, A.; Ibáñez, E. Supercritical fluid extraction: Recent advances and applications. *J. Chromatogr. A Extr. Technol.* **2010**, *1217*, 2495–2511. [CrossRef]
184. Pinelo, M.; Ruiz-Rodríguez, A.; Sineiro, J.; Señoráns, F.J.; Reglero, G.; Núñez, M.J. Supercritical fluid and solid–liquid extraction of phenolic antioxidants from grape pomace: A comparative study. *Eur. Food Res. Technol.* **2007**, *226*, 199–205. [CrossRef]
185. Jeong, J.; Jung, H.; Lee, S.; Lee, H.; Hwang, K.; Kim, T. Anti-oxidant, anti-proliferative and anti-inflammatory activities of the extracts from black raspberry fruits and wine. *Food Chem.* **2010**, *123*, 338–344. [CrossRef]
186. Casas, L.; Mantell, C.; Rodríguez, M.; de la Ossa, E.J.M.; Roldán, A.; Ory, I.D.; Caro, I.; Blandino, A. Extraction of resveratrol from the pomace of Palomino fino grapes by supercritical carbon dioxide. *J. Food Eng.* **2010**, *96*, 304–308. [CrossRef]
187. Liazid, A.; Guerrero, R.F.; Cantos, E.; Palma, M.; Barroso, C.G. Microwave assisted extraction of anthocyanins from grape skins. *Food Chem.* **2011**, *124*, 1238–1243. [CrossRef]
188. Yu, H.B.; Ding, L.F.; Wang, Z.; Shi, L.X. Study on Extraction of Polyphenol from Grape Peel Microwave-Assisted Activity. *Adv. Mater. Res.* **2014**, *864–867*, 520–525. [CrossRef]
189. Al Bittar, S.; Périno-Issartier, S.; Dangles, O.; Chemat, F. An innovative grape juice enriched in polyphenols by microwave-assisted extraction. *Food Chem.* **2013**, *141*, 3268–3272. [CrossRef] [PubMed]
190. Da Porto, C.; Porretto, E.; Decorti, D. Comparison of ultrasound-assisted extraction with conventional extraction methods of oil and polyphenols from grape (*Vitis vinifera* L.) seeds. *Ultrason. Sonochemistry* **2013**, *20*, 1076–1080. [CrossRef] [PubMed]
191. Drosou, C.; Kyriakopoulou, K.; Bimpilas, A.; Tsimogiannis, D.; Krokida, M. A comparative study on different extraction techniques to recover red grape pomace polyphenols from vinification byproducts. *Ind. Crops Prod.* **2015**, *75*, 141–149. [CrossRef]
192. Wang, J.; Wang, K.; Wang, Y.; Lin, S.; Zhao, P.; Jones, G. A novel application of pulsed electric field (PEF) processing for improving glutathione (GSH) antioxidant activity. *Food Chem.* **2014**, *161*, 361–366. [CrossRef] [PubMed]
193. Jeyamkondan, S.; Jayas, D.S.; Holley, R.A. Pulsed electric field processing of foods: A review. *J. Food Prot.* **1999**, *62*, 1088–1096. [CrossRef]
194. Brianceau, S.; Turk, M.; Vitrac, X.; Vorobiev, E. Combined densification and pulsed electric field treatment for selective polyphenols recovery from fermented grape pomace. *Innov. Food Sci. Emerg. Technol. App. Food Process* **2015**, *29*, 2–8. [CrossRef]
195. Wan, J.; Coventry, J.; Swiergon, P.; Sanguansri, P.; Versteeg, C. Advances in innovative processing technologies for microbial inactivation and enhancement of food safety-pulsed electric field and low-temperature plasma. *Trends Food Sci. Technol. Nat. Safe Foods* **2009**, *20*, 414–424. [CrossRef]

196. Barba, F.J.; Brianceau, S.; Turk, M.; Boussetta, N.; Vorobiev, E. Effect of Alternative Physical Treatments (Ultrasounds, Pulsed Electric Fields, and High-Voltage Electrical Discharges) on Selective Recovery of Bio-compounds from Fermented Grape Pomace. *Food Bioprocess Technol.* **2015**, *8*, 1139–1148. [CrossRef]
197. Corrales, M.; Toepfl, S.; Butz, P.; Knorr, D.; Tauscher, B. Extraction of anthocyanins from grape by-products assisted by ultrasonics, high hydrostatic pressure or pulsed electric fields: A comparison. *Innov. Food Sci. Emerg. Technol.* **2008**, *9*, 85–91. [CrossRef]
198. Dordoni, R.; Duserm Garrido, G.; Marinoni, L.; Torri, L.; Piochi, M.; Spigno, G. Enrichment of Whole Wheat Cocoa Biscuits with Encapsulated Grape Skin Extract. *Int. J. Food Sci.* **2019**, *2019*, 9161840. [CrossRef] [PubMed]
199. Pasqualone, A.; Bianco, A.M.; Paradiso, V.M. Production trials to improve the nutritional quality of biscuits and to enrich them with natural anthocyanins. *CyTA –J. Food* **2013**, *11*, 301–308. [CrossRef]
200. Mildner-Szkudlarz, S.; Bajerska, J.; Zawirska-Wojtasiak, R.; Górecka, D. White grape pomace as a source of dietary fibre and polyphenols and its effect on physical and nutraceutical characteristics of wheat biscuits. *J. Sci. Food Agric.* **2013**, *93*, 389–395. [CrossRef] [PubMed]
201. Acun, S.; Gül, H. Effects of grape pomace and grape seed flours on cookie quality. *Qual. Assur. Saf. Crops Foods* **2014**, *6*, 81–88. [CrossRef]
202. Bender, A.B.B.; Speroni, C.S.; Salvador, P.R.; Loureiro, B.B.; Lovatto, N.M.; Goulart, F.R.; Lovatto, M.T.; Miranda, M.Z.; Silva, L.P.; Penna, N.G. Grape Pomace Skins and the Effects of Its Inclusion in the Technological Properties of Muffins. *J. Culin. Sci. Technol.* **2017**, *15*, 143–157. [CrossRef]
203. Šporin, M.; Avbelj, M.; Kovač, B.; Možina, S.S. Quality characteristics of wheat flour dough and bread containing grape pomace flour. *Food Sci. Technol. Int.* **2018**, *24*, 251–263. [CrossRef]
204. Tolve, R.; Simonato, B.; Rainero, G.; Bianchi, F.; Rizzi, C.; Cervini, M.; Giuberti, G. Wheat Bread Fortification by Grape Pomace Powder: Nutritional, Technological, Antioxidant, and Sensory Properties. *Foods* **2021**, *10*, 75. [CrossRef]
205. Bianchi, F.; Lomuscio, E.; Rizzi, C.; Simonato, B. Predicted Shelf-Life, Thermodynamic Study and Antioxidant Capacity of Breadsticks Fortified with Grape Pomace Powders. *Foods* **2021**, *10*, 2815. [CrossRef]
206. Nowak, J.Z. Oxidative stress, polyunsaturated fatty acids-derived oxidation products and bisretinoids as potential inducers of CNS diseases: Focus on age-related macular degeneration. *Pharmacol. Rep.* **2013**, *65*, 288–304. [CrossRef] [PubMed]
207. Hoye, C.; Ross, C. Total Phenolic Content, Consumer Acceptance, and Instrumental Analysis of Bread Made with Grape Seed Flour. *J. Food Sci.* **2011**, *76*, S428–S436. [CrossRef] [PubMed]
208. Lavelli, V.; Kerr, W.L.; García-Lomillo, J.; González-SanJosé, M.L. Applications of Recovered Bioactive Compounds in Food Products. In *Handbook of Grape Processing By-Products*; Galanakis, C.M., Ed.; Academic Press: Cambridge, MA, USA, 2017; Volume 10, pp. 233–266.
209. Tolve, R.; Pasini, G.; Vignale, F.; Favati, F.; Simonato, B. Effect of Grape Pomace Addition on the Technological, Sensory, and Nutritional Properties of Durum Wheat Pasta. *Foods* **2020**, *9*, 354. [CrossRef] [PubMed]
210. Sant'Anna, V.; Christiano, F.D.P.; Marczak, L.D.F.; Tessaro, I.C.; Thys, R.C.S. The effect of the incorporation of grape marc powder in fettuccini pasta properties. *LWT-Food Sci. Technol.* **2014**, *58*, 497–501. [CrossRef]
211. Lavelli, V.; Torri, L.; Zeppa, G.; Fiori, L.; Spigno, G. Recovery Of Winemaking By-Products For Innovative Food Applications. *Ital. J. Food Sci.* **2016**, *28*, 542–564.
212. Balli, D.; Cecchi, L.; Innocenti, M.; Bellumori, M.; Mulinacci, N. Food by-products valorisation: Grape pomace and olive pomace (pâté) as sources of phenolic compounds and fiber for enrichment of tagliatelle pasta. *Food Chem.* **2021**, *355*, 129642. [CrossRef] [PubMed]
213. Codină, G.G.; Zaharia, D.; Stroe, S.-G.; Ropciuc, S. Influence of calcium ions addition from gluconate and lactate salts on refined wheat flour dough rheological properties. *CyTA-J. Food* **2018**, *16*, 884–891. [CrossRef]
214. Mironeasa, S.; Codina, G.; Mironeasa, C. The effects of wheat flour substitution with grape seed flour on the rheological parameters of the dough assessed by Mixolab. *J. Texture Stud.* **2012**, *43*, 40–48. [CrossRef]
215. Rashwan, A.K.; Osman, A.I.; Chen, W. Natural nutraceuticals for enhancing yogurt properties: A review. *Environ. Chem. Lett.* **2023**, *21*, 1907–1931. [CrossRef]
216. Barakat, H.; Hassan, M.F.Y. Chemical, Nutritional, Rheological, and Organoleptical Characterizations of Stirred Pumpkin-Yoghurt. *Food Nutr. Sci.* **2017**, *8*, 746–759. [CrossRef]
217. O'Connell, J.E.; Fox, P.F. Significance and applications of phenolic compounds in the production and quality of milk and dairy products: A review. *Int. Dairy J.* **2001**, *11*, 103–120. [CrossRef]
218. Demirkol, M.; Tarakci, Z. Effect of grape (*Vitis labrusca* L.) pomace dried by different methods on physicochemical, microbiological and bioactive properties of yoghurt. *LWT Food Sci. Technol.* **2018**, *97*, 770–777. [CrossRef]
219. Tseng, A.; Zhao, Y. Wine grape pomace as antioxidant dietary fibre for enhancing nutritional value and improving storability of yogurt and salad dressing. *Food Chem.* **2013**, *138*, 356–365. [CrossRef] [PubMed]
220. Silva, F.A.; do Egypto, R.D.; de Souza, E.L.; Voss, G.B.; Borges, G.D.; dos Santos Lima, M.; Pintado, M.M.; da Silva Vasconcelos, M.A. Incorporation of phenolic-rich ingredients from integral valorization of Isabel grape improves the nutritional, functional and sensory characteristics of probiotic goat milk yogurt. *Food Chem.* **2022**, *369*, 130957. [CrossRef] [PubMed]
221. Marchiani, R.; Bertolino, M.; Ghirardello, D.; McSweeney, P.L.H.; Zeppa, G. Physicochemical and nutritional qualities of grape pomace powder-fortified semi-hard cheeses. *J. Food Sci. Technol.* **2016**, *53*, 1585–1596. [CrossRef] [PubMed]

222. Tami, S.H.; Aly, E.; Darwish, A.A.; Mohamed, E.S. Buffalo stirred yoghurt fortified with grape seed extract: New insights into its functional properties. *Food Biosci.* **2022**, *47*, 101752. [CrossRef]
223. Gaglio, R.; Restivo, I.; Barbera, M.; Barbaccia, P.; Ponte, M.; Tesoriere, L.; Bonanno, A.; Attanzio, A.; Di Grigoli, A.; Francesca, N.; et al. Effect on the Antioxidant, Lipoperoxyl Radical Scavenger Capacity, Nutritional, Sensory and Microbiological Traits of an Ovine Stretched Cheese Produced with Grape Pomace Powder Addition. *Antioxidants* **2021**, *10*, 306. [CrossRef]
224. Chouchouli, V.; Kalogeropoulos, N.; Konteles, S.J.; Karvela, E.; Makris, D.P.; Karathanos, V.T. Fortification of yoghurts with grape (*Vitis vinifera*) seed extracts. *LWT-Food Sci. Technol.* **2013**, *53*, 522–529. [CrossRef]
225. Marchiani, R.; Bertolino, M.; Belviso, S.; Giordano, M.; Ghirardello, D.; Torri, L.; Piochi, M.; Zeppa, G. Yogurt Enrichment with Grape Pomace: Effect of Grape Cultivar on Physicochemical, Microbiological and Sensory Properties. *J. Food Qual.* **2016**, *39*, 77–89. [CrossRef]
226. Karaaslan, M.; Ozden, M.; Vardin, H.; Turkoglu, H. Phenolic fortification of yogurt using grape and callus extracts. *LWT-Food Sci. Technol.* **2011**, *44*, 1065–1072. [CrossRef]
227. Zhou, Y.J.; Wang, Q.Y.; Wang, S.J. Effects of rosemary extract, grape seed extract and green tea polyphenol on the formation of n-Nitrosamines and quality of western-Style smoked sausage. *J. Food Process Preserv.* **2020**, *44*, e14459. [CrossRef]
228. García-Lomillo, J.; González-SanJosé, M.L. Applications of Wine Pomace in the Food Industry: Approaches and Functions. *Compreh. Rev. Food Sci. Food Saf.* **2017**, *16*, 3–22. [CrossRef]
229. García-Lomillo, J.; Gonzalez-SanJose, M.L.; Del Pino-García, R.; Ortega-Heras, M.; Muñiz-Rodríguez, P. Antioxidant effect of seasonings derived from wine pomace on lipid oxidation in refrigerated and frozen beef patties. *LWT* **2017**, *77*, 85–91. [CrossRef]
230. Ryu, K.; Shim, K.; Shin, D. Effect of Grape Pomace Powder Addition on TBARS and Color of Cooked Pork Sausages during Storage. *Korean J. Food Sci. Res.* **2014**, *34*, 200–206. [CrossRef] [PubMed]
231. Riazi, F.; Zeynali, F.; Hoseini, E.; Behmadi, H. Effect of Dry Red Grape Pomace as a Nitrite Substitute on the Microbiological and Physicochemical Properties and Residual Nitrite of Dry-cured Sausage. *Nutr. Food Sci. Res.* **2016**, *3*, 37–44. [CrossRef]
232. Garrido, J.; Borges, F. Wine and grape polyphenols—A chemical perspective. *Food Res. Intern.* **2013**, *54*, 1844–1858. [CrossRef]
233. Bobko, M.; Haščí k, P.; Kročko, M.; Trembecká, L.; Mendelova, A.; Tkáčová, J.; Czako, P.; Tóth, T. Effect of grape seed extract on quality of raw-cooked meat products. *Potr. Slovak J. Food Sci.* **2017**, *11*, 517–521. [CrossRef]
234. Guerra-Rivas, C.; Vieira, C.; Rubio, B.; Martínez, B.; Gallardo, B.; Mantecón, A.R.; Lavín, P.; Manso, T. Effects of grape pomace in growing lamb diets compared with vitamin E and grape seed extract on meat shelf life. *Meat Sci.* **2016**, *116*, 221–229. [CrossRef]
235. Selani, M.M.; Contreras-Castillo, C.J.; Shirahigue, L.D.; Gallo, C.R.; Plata-Oviedo, M.; Montes-Villanueva, N.D. Wine industry residues extracts as natural antioxidants in raw and cooked chicken meat during frozen storage. *Meat Sci.* **2011**, *88*, 397–403. [CrossRef]
236. Shirahigue, L.D.; Plata-Oviedo, M.; De Alencar, S.M.; D'Arce, M.A.B.R.; De Souza Vieira, T.M.F.; Oldoni, T.L.C.; Contreras-Castillo, C.J. Wine industry residue as antioxidant in cooked chicken meat. *Int. J. Food Sci. Technol.* **2010**, *45*, 863–870. [CrossRef]
237. Sáyago-Ayerdi, S.G.; Brenes, A.; Goñi, I. Effect of grape antioxidante dietary fibre on the lípido oxidation of raw and cooked Chicken hamburgers. *LW-Food Sci. Technol.* **2009**, *42*, 971–976. [CrossRef]
238. Sánchez-Alonso, I.; Jiménez-Escrig, A.; Saura-Calixto, F.; Borderías, A.J. Effect of grape antioxidant dietary fibre on the prevention of lipid oxidation in miced fish: Evaluation by different methodologies. *Food Chem.* **2007**, *101*, 372–378. [CrossRef]
239. Özvural, E.; Vural, H. Grape seed flour is a viable ingredient to improve the nutritional profile and reduce lipid oxidation of frankfurters. *Meat Sci.* **2011**, *88*, 179–183. [CrossRef] [PubMed]
240. Choi, Y.; Choi, J.; Han, D.; Kim, H.; Lee, M.; Kim, H.; Lee, J.; Chung, H.; Kim, C. Optimization of replacing pork back fat with grape seed oil and rice bran fibre for reduced-fat meat emulsion systems. *Meat Sci.* **2010**, *84*, 212–218. [CrossRef] [PubMed]
241. Özalp Özen, B.; Eren, M.; Pala, A.; Özmen, İ.; Soyer, A. Effect of plant extracts on lipid oxidation during frozen storage of minced fish muscle. *Int. J. Food Sci. Technol.* **2011**, *46*, 724–731. [CrossRef]
242. Cilli, L.; Contini, L.; Sinnecker, P.; Lopes, P.; Andréo, M.; Neiva, C.; Nascimento, M.; Yoshida, C.; Venturini, A. Effects of grape pomace flour on quality parameters of salmon burger. *J. Food Process Preserv.* **2020**, *44*, e14329. [CrossRef]
243. Pazos, M.; Gallardo, J.M.; Torres, J.L.; Medina, I. Activity of grape polyphenols as inhibitors of the oxidation of fish lipids and frozen fish muscle. *Food Chem.* **2005**, *92*, 547–557. [CrossRef]
244. Sánchez-Alonso, I.; Jiménez-Escrig, A.; Saura-Calixto, F.; Borderías, A.J. Antioxidant protection of white grape pomace on restructured fish products during frozen storage. *LWT-Food Sci. Technol.* **2008**, *41*, 42–50. [CrossRef]
245. Sánchez-Alonso, I.; Borderías, J.; Larsson, K.; Undeland, I. Inhibition of hemoglobin-mediated oxidation of regular and lipid-fortified washed cod mince by a white grape dietary fibre. *J. Agric. Food Chem.* **2007**, *55*, 5299–5305. [CrossRef]
246. Urquiaga, I.; Troncoso, D.; Mackenna, M.J.; Urzúa, C.; Pérez, D.; Dicenta, S.; de la Cerda, P.M.; Amigo, L.; Carreño, J.C.; Echeverría, G.; et al. The Consumption of Beef Burgers Prepared with Wine Grape Pomace Flour Improves Fasting Glucose, Plasma Antioxidant Levels, and Oxidative Damage Markers in Humans: A Controlled Trial. *Nutrients* **2018**, *10*, 1388. [CrossRef]
247. Lavelli, V.; Sri Harsha, P.S.C.; Torri, L.; Zeppa, G. Use of winemaking by-products as an ingredient for tomato puree: The effect of particle size on product quality. *Food Chem.* **2014**, *152*, 162–168. [CrossRef] [PubMed]
248. Phan, M.A.T.; Bucknall, M.P.; Arcot, J. Interferences of anthocyanins with the uptake of lycopene in Caco-2 cells, and their interactive effects on anti-oxidation and anti-inflammation in vitro and ex vivo. *Food Chem.* **2019**, *276*, 402–409. [CrossRef] [PubMed]

249. Dordoni, R.; Cantaboni, S.; Spigno, G. Walnut paste: Oxidative stability and effect of grape skin extract addition. *Heliyon* **2019**, *5*, e02506. [CrossRef] [PubMed]
250. Friedman, M. Chemistry, Biochemistry, and Safety of Acrylamide. A Review. *J. Agric. Food Chem.* **2003**, *51*, 4504–4526. [CrossRef] [PubMed]
251. Xu, C.; Yagiz, Y.; Marshall, S.; Li, Z.; Simonne, A.; Lu, J.; Marshall, M.R. Application of muscadine grape (Vitis rotundifolia Michx.) pomace extract to reduce carcinogenic acrylamide. *Food Chem.* **2015**, *182*, 200–208. [CrossRef] [PubMed]
252. Teng, J.; Hu, X.; Tao, N.; Wang, M. Impact and inhibitory mechanism of phenolic compounds on the formation of toxic Maillard reaction products in food. *Front. Agr. Sci. Eng.* **2018**, *5*, 321. [CrossRef]
253. Rózek, A.; Achaerandio, I.; Güell, C.; López, F.; Ferrando, M. Use of commercial grape phenolic extracts to supplement solid foodstuff. *LWT Food Sci. Technol.* **2010**, *43*, 623–631. [CrossRef]
254. Guerrero, R.L.F.; Smith, P.; Bindon, K.A. Application of insoluble fibres in the fining of wine phenolics. *J. Agric. Food Chem.* **2013**, *61*, 4424–4432. [CrossRef]
255. Shinagawa, F.B.; de Santana, F.C.; Torres, L.R.O.; Mancini, J. Grape seed oil: A potential functional food? *Food Sci. Technol.* **2015**, *35*, 399–406. [CrossRef]
256. Auger, C.; Gérain, P.; Laurent-Bichon, F.; Portet, K.; Bornet, A.; Caporiccio, B.; Rouanet, J.M. Phenolics from commercialized grape extracts prevent early atherosclerotic lesions in hamsters by mechanisms other than antioxidant effect. *J. Agric. Food Chem.* **2004**, *52*, 5297–5302. [CrossRef]
257. Tournour, H.H.; Segundo, M.A.; Magalhães, L.M.; Barreiros, L.; Queiroz, J.; Cunha, L.M. Valorization of grape pomace: Extraction of bioactive phenolics with antioxidant properties. *Ind. Crops Prod.* **2015**, *74*, 397–406. [CrossRef]
258. Rodriguez-Rodriguez, R.; Justo, M.L.; Claro, C.M.; Vila, E.; Parrado, J.; Herrera, M.D.; de Sotomayor, M.A. Endothelium-dependent vasodilator and antioxidant properties of a novel enzymatic extract of grape pomace from wine industrial waste. *Food Chem.* **2012**, *135*, 1044–1051. [CrossRef] [PubMed]
259. Scola, G.; Conte, D.; Spada, P.W.D.-S.; Dani, C.; Vanderlinde, R.; Funchal, C.; Salvador, M. Flavan-3-ol Compounds from Wine Wastes with in Vitro and in Vivo Antioxidant Activity. *Nutrients* **2012**, *2*, 1048–1059. [CrossRef] [PubMed]
260. Ed Nignpense, B.; Chinkwo, K.A.; Blanchard, C.L.; Santhakumar, A.B. Polyphenols: Modulators of Platelet Function and Platelet Microparticle Generation? *Int. J. Mol. Sci.* **2019**, *21*, 146. [CrossRef] [PubMed]
261. De Lange, D.W.; van Golde, P.H.; Scholman, W.L.G.; Kraaijenhagen, R.J.; Akkerman, J.W.N.; Van De Wiel, A. Red wine and red wine polyphenolic compounds but not alcohol inhibit ADP-induced platelet aggregation. *Eur. J. Intern. Med.* **2003**, *14*, 361–366. [CrossRef] [PubMed]
262. Olas, B.; Wachowicz, B.; Stochmal, A.; Oleszek, W. The polyphenol-rich extract from grape seeds inhibits platelet signaling pathways triggered by both proteolytic and non-proteolytic agonists. *Platelets* **2012**, *23*, 282–289. [CrossRef] [PubMed]
263. Bijak, M.; Sut, A.; Kosiorek, A.; Saluk-Bijak, J.; Golanski, J. Dual anticoagulant/antiplatelet activity of polyphenolic grape seeds extract. *Nutrients* **2019**, *11*, 93. [CrossRef]
264. Shanmuganayagam, D.; Beahm, M.R.; Osman, H.E.; Krueger, C.G.; Reed, J.D.; Folts, J.D. Grape seed and grape skin extracts elicit a greater antiplatelet effect when used in combination than when used individually in dogs and humans. *J. Nutr.* **2002**, *132*, 3592–3598. [CrossRef]
265. Moschona, A.; Liakopoulou-Kyriakides, M. Encapsulation of biological active phenolic compounds extracted from wine wastes in alginate-chitosan microbeads. *J. Microencapsul.* **2018**, *35*, 229–240. [CrossRef]
266. Rivera, K.; Salas-Pérez, F.; Echeverría, G.; Urquiaga, I.; Dicenta, S.; Pérez, D.; de la Cerda, P.; González, L.; Andia, M.E.; Uribe, S.; et al. Red Wine Grape Pomace Attenuates Atherosclerosis and Myocardial Damage and Increases Survival in Association with Improved Plasma Antioxidant Activity in a Murine Model of Lethal Ischemic Heart Disease. *Nutrients* **2019**, *11*, 2135. [CrossRef]
267. Hogan, S.; Zhang, L.; Li, J.; Sun, S.; Canning, C.; Zhou, K. Antioxidant rich grape pomace extract suppresses postprandial hyperglycemia in diabetic mice by specifically inhibiting alpha-glucosidase. *Nutr. Metab.* **2010**, *7*, 1. [CrossRef] [PubMed]
268. Urquiaga, I.; D'Acuña, S.; Pérez, D.; Dicenta, S.; Echeverría, G.; Rigotti, A.; Leighton, F. Wine grape pomace flour improves blood pressure, fasting glucose and protein damage in humans: A randomized controlled trial. *Biol. Res.* **2015**, *48*, 49. [CrossRef] [PubMed]
269. Draijer, R.; de Graaf, Y.; Slettenaar, M.; de Groot, E.; Wright, C. Consumption of a Polyphenol-Rich Grape-Wine Extract Lowers Ambulatory Blood Pressure in Mildly Hypertensive Subjects. *Nutrients* **2015**, *7*, 3138–3153. [CrossRef] [PubMed]
270. Del Pino-García, R.; Gerardi, G.; Rivero-Pérez, M.D.; González-SanJosé, M.L.; García-Lomillo, J.; Muñiz, P. Wine pomace seasoning attenuates hyperglycaemia-induced endothelial dysfunction and oxidative damage in endothelial cells. *J. Funct. Foods* **2016**, *22*, 431–445. [CrossRef]
271. Flammer, A.J.; Sudano, I.; Wolfrum, M.; Thomas, R.; Enseleit, F.; Périat, D.; Kaiser, P.; Hirt, A.; Hermann, M.; Serafini, M.; et al. Cardiovascular effects of flavanol-rich chocolate in patients with heart failure. *Eur. Heart J.* **2012**, *33*, 2172–2180. [CrossRef] [PubMed]
272. Wang, S.; Mateos, R.; Goya, L.; Amigo-Benavent, M.; Sarriá, B.; Bravo, L. A phenolic extract from grape by-products and its main hydroxybenzoic acids protect Caco-2 cells against pro-oxidant induced toxicity. *Food Chem. Toxicol.* **2016**, *88*, 65–74. [CrossRef] [PubMed]

273. Tomé-Carneiro, J.; Gonzálvez, M.; Larrosa, M.; García-Almagro, F.J.; Avilés-Plaza, F.; Parra, S.; Yáñez-Gascón, M.J.; Ruiz-Ros, J.A.; García-Conesa, M.T.; Tomás-Barberán, F.A.; et al. Consumption of a grape extract supplement containing resveratrol decreases oxidized LDL and ApoB in patients undergoing primary prevention of cardiovascular disease: A triple-blind, 6-month follow-up, placebo-controlled, randomized trial. *Mol. Nutr. Food Res.* **2012**, *56*, 810–821. [CrossRef]
274. De Oliveira, W.P.; Biasoto, A.C.T.; Marques, V.F.; dos Santos, I.M.; Magalhães, K.; Correa, L.C.; Shahidi, F. Phenolics from Winemaking By-Products Better Decrease VLDL-Cholesterol and Triacylglycerol Levels than Those of Red Wine in Wistar Rats. *J. Food Sci.* **2017**, *82*, 2432–2437. [CrossRef]
275. Razavi, S.-M.; Gholamin, S.; Eskandari, A.; Mohsenian, N.; Ghorbanihaghjo, A.; Delazar, A.; Argani, H. Red grape seed extract improves lipid profiles and decreases oxidized low-density lipoprotein in patients with mild hyperlipidemia. *J. Med. Food* **2013**, *16*, 255–258. [CrossRef]
276. Park, E.; Edirisinghe, I.; Choy, Y.Y.; Waterhouse, A.; Burton-Freeman, B. 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. *Br. J. Nutr.* **2016**, *115*, 226–238. [CrossRef]
277. Pasini, F.; Chinnici, F.; Caboni, M.F.; Verardo, V. Recovery of oligomeric proanthocyanidins and other phenolic compounds with established bioactivity from grape seed by-Products. *Molecules* **2019**, *24*, 677. [CrossRef] [PubMed]
278. Sapwarobol, S.; Adisakwattana, S.; Changpeng, S.; Ratanawachirin, W.; Tanruttanawong, K.; Boonyarit, W. Postprandial blood glucose response to grape seed extract in healthy participants: A pilot study. *Pharmacogn. Mag.* **2012**, *8*, 192–196. [CrossRef] [PubMed]
279. Montagut, G.; Onnockx, S.; Vaqué, M.; Bladé, C.; Blay, M.; Fernández-Larrea, J.; Pujadas, G.; Salvadó, M.J.; Arola, L.; Pirson, I. Oligomers of grape-seed procyanidin extract activate the insulin receptor and key targets of the insulin signaling pathway differently from insulin. *J. Nutr. Biochem.* **2010**, *21*, 476–481. [CrossRef]
280. Kaur, M.; Agarwal, C.; Agarwa, R. Anticancer and cancer chemopreventive potential of grape seed extract and other grape-based products. *J. Nutr.* **2009**, *139*, 1806S–1812S. [CrossRef] [PubMed]
281. Ono, K.; Condron, M.M.; Ho, L.; Wang, J.; Zhao, W.; Pasinetti, G.M.; Teplow, D.B. Effects of grape seed-derived polyphenols on amyloid beta-protein self-assembly and cytotoxicity. *J. Biol. Chem.* **2008**, *283*, 32176–32187. [CrossRef] [PubMed]
282. Charradi, K.; Mahmoudi, M.; Bedhiafi, T.; Jebari, K.; El May, M.; Limam, F.; Aouani, E. Safety evaluation, anti-oxidative and anti-inflammatory effects of subchronically dietary supplemented high dosing grape seed powder (GSP) to healthy rat. *Biomed. Pharmacother.* **2018**, *107*, 534–546. [CrossRef] [PubMed]
283. Cádiz-Gurrea, M.D.L.L.; Borrás-Linares, I.; Lozano-Sánchez, J.; Joven, J.; Fernández-Arroyo, S.; Segura-Carretero, A. Cocoa and Grape Seed Byproducts as a Source of Antioxidant and Anti-Inflammatory Proanthocyanidins. *Int. J. Mol. Sci.* **2017**, *18*, 376. [CrossRef] [PubMed]
284. Rauf, A.; Imran, M.; Abu-Izneid, T.; Iahtisham-Ul-Haq; Patel, S.; Pan, X.; Naz, S.; Sanches Silva, A.; Saeed, F.; Rasul Suleria, H.A. Proanthocyanidins: A comprehensive review. *Biomed. Pharm.* **2019**, *116*, 108999. [CrossRef]
285. Kruger, M.J.; Davies, N.; Myburgh, K.H.; Lecour, S. Proanthocyanidins, anthocyanins and cardiovascular diseases. *Food Res. Int.* **2014**, *59*, 41–52. [CrossRef]
286. Iriondo-DeHond, M.; Blázquez-Duff, J.M.; Del Castillo, M.D.; Miguel, E. Nutritional Quality, Sensory Analysis and Shelf Life Stability of Yogurts Containing Inulin-Type Fructans and Winery Byproducts for Sustainable Health. *Foods* **2020**, *9*, 1199. [CrossRef]
287. Zhang, X.-H.; Huang, B.; Choi, S.-K.; Seo, J.-S. Anti-obesity effect of resveratrol-amplified grape skin extracts on 3T3-L1 adipocytes differentiation. *Nutr. Res. Pract.* **2012**, *6*, 286–293. [CrossRef] [PubMed]
288. Ismail, A.F.M.; Moawed, F.S.M.; Mohamed, M.A. Protective mechanism of grape seed oil on carbon tetrachloride-induced brain damage in γ-irradiated rats. *J. Photoch. Photobio.* **2015**, *153*, 317–323. [CrossRef]
289. Ismail, A.F.M.; Salem, A.A.M.; Eassawy, M.M.T. Hepatoprotective effect of grape seed oil against carbon tetrachloride induced oxidative stress in liver of γ-irradiated rat. *J. Photoch. Photobio.* **2016**, *160*, 1–10. [CrossRef] [PubMed]
290. Asadi, F.; Shahriari, A.; Chahardah-Cheric, M. Effect of long-term optimal ingestion of canola oil, grape seed oil, corn oil and yogurt butter on serum, muscle and liver cholesterol status in rats. *Food Chem. Toxicol.* **2010**, *48*, 2454–2457. [CrossRef] [PubMed]
291. Nguyen, A.V.; Martinez, M.; Stamos, M.J.; Moyer, M.P.; Planutis, K.; Hope, C.; Holcombe, R.F. Results of a phase I pilot clinical trial examining the effect of plant-derived resveratrol and grape powder on Wnt pathway target gene expression in colonic mucosa and colon cancer. *Cancer Manag. Res.* **2009**, *1*, 25–37.
292. Elshaer, M.; Chen, Y.; Wang, X.J.; Tang, X. Resveratrol: An overview of its anti-cancer mechanisms. *Life Sci.* **2018**, *207*, 340–349. [CrossRef]
293. Wang, L.-S.; Stoner, G.D. Anthocyanins and their role in cancer prevention. *Cancer Lett.* **2008**, *269*, 281–290. [CrossRef]
294. Lala, G.; Malik, M.; Zhao, C.; He, J.; Kwon, Y.; Giusti, M.M.; Magnuson, B.A. Anthocyanin-rich extracts inhibit multiple biomarkers of colon cancer in rats. *Nutr. Cancer* **2006**, *54*, 84–93. [CrossRef]
295. Tian, Q.; Xu, Z.; Sun, X.; Deavila, J.; Du, M.; Zhu, M. Grape pomace inhibits colon carcinogenesis by suppressing cell proliferation and inducing epigenetic modifications. *J. Nutr. Biochem.* **2020**, *84*, 108443. [CrossRef]
296. Mišković Špoljarić, K.; Šelo, G.; Pešut, E.; Martinović, J.; Planinić, M.; Tišma, M.; Bucić-Kojić, A. Antioxidant and antiproliferative potentials of phenolic-rich extracts from biotransformed grape pomace in colorectal Cancer. *BMC Complement. Med. Ther.* **2023**, *23*, 29. [CrossRef]

297. Singletary, K.W.; Jung, K.J.; Giusti, M. Anthocyanin-rich grape extract blocks breast cell DNA damage. *J. Med. Food.* **2007**, *10*, 244–251. [CrossRef] [PubMed]
298. Luo, J.; Song, S.; Wei, Z.; Huang, Y.; Zhang, Y.; Lu, J. The comparative study among different fractions of muscadine grape 'Noble' pomace extracts regarding anti-oxidative activities, cell cycle arrest and apoptosis in breast cancer. *Food Nutr. Res.* **2017**, *61*, 1412795. [CrossRef]
299. Silva, A.; Silva, V.; Igrejas, G.; Gaivao, I.; Aires, A.; Klibi, N.; Dapkevicius, M.; Valentao, P.; Falco, V.; Poeta, P. Valorization of Winemaking By-Products as a Novel Source of Antibacterial Properties: New Strategies to Fight Antibiotic Resistance. *Molecules* **2021**, *26*, 2331. [CrossRef]
300. Shan, B.; Cai, Y.-Z.; Brooks, J.D.; Corke, H. Potential application of spice and herb extracts as natural preservatives in cheese. *J. Med. Food* **2011**, *14*, 284–290. [CrossRef] [PubMed]
301. Shahidi, F.; Ambigaipalan, P. Phenolics and polyphenolics in foods, beverages and spices: Antioxidant activity and health effects—A review. *J. Funct. Foods* **2015**, *18*, 820–897. [CrossRef]
302. Mattio, L.M.; Dallavalle, S.; Musso, L.; Filardi, R.; Franzetti, L.; Pellegrino, L.; D'Incecco, P.; Mora, D.; Pinto, A.; Arioli, S. Antimicrobial activity of resveratrol-derived monomers and dimers against foodborne pathogens. *Sci. Rep.* **2019**, *9*, 19525. [CrossRef] [PubMed]
303. De Vries, K.; Strydom, M.; Steenkamp, V. Bioavailability of resveratrol: Possibilities for enhancement. *J. Herb. Med.* **2018**, *11*, 71–77. [CrossRef]
304. Tsali, A.; Goula, A.M. Valorization of grape pomace: Encapsulation and storage stability of its phenolic extract. *Powder Technol.* **2018**, *340*, 194–207. [CrossRef]
305. Domínguez, R.; Pateiro, M.; Munekata, P.E.S.; McClements, D.J.; Lorenzo, J.M. Encapsulation of Bioactive Phytochemicals in Plant-Based Matrices and Application as Additives in Meat and Meat Products. *Molecules* **2021**, *26*, 3984. [CrossRef]
306. Glampedaki, P.; Dutschk, V. Stability studies of cosmetic emulsions prepared from natural products such as wine, grape seed oil and mastic resin. *Colloid. Surf. A* **2014**, *460*, 306–311. [CrossRef]
307. Wittenauer, J.; Mäckle, S.; Sußmann, D.; Schweiggert-Weisz, U.; Carle, R. Inhibitory effects of polyphenols from grape pomace extract on collagenase and elastase activity. *Fitoterapia* **2015**, *101*, 179–187. [CrossRef] [PubMed]
308. Marino, A.; Battaglini, M.; Desii, A.; Lavarello, C.; Genchi, G.; Petretto, A.; Ciofani, G. Liposomes loaded with polyphenol-rich grape pomace extracts protect from neurodegeneration in a rotenone-based in vitro model of Parkinson's disease. *Biomater. Sci.* **2021**, *9*, 8171–8188. [CrossRef]
309. Davidov-Pardo, G.; McClements, D.J. Nutraceutical delivery systems: Resveratrol encapsulation in grape seed oil nanoemulsions formed by spontaneous emulsification. *Food Chem.* **2015**, *167*, 205–212. [CrossRef] [PubMed]
310. Hübner, A.A.; Sarruf, F.D.; Oliveira, C.A.; Neto, A.V.; Fischer, D.C.H.; Kato, E.T.M.; Lourenço, F.R.; Baby, A.R.; Bacchi, E.M. Safety and Photoprotective Efficacy of a Sunscreen System Based on Grape Pomace (*Vitis vinifera* L.) Phenolics from Winemaking. *Pharmaceutics* **2020**, *12*, 1148. [CrossRef]
311. Jakobek, L.; Matić, P. Non-covalent dietary fiber—Polyphenol interactions and their influence on polyphenol bioaccessibility. *Trends Food Sci. Technol.* **2019**, *83*, 235–247. [CrossRef]
312. Pérez-Jiménez, J.; Serrano, J.; Tabernero, M.; Arranz, S.; Díaz-Rubio, M.E.; García-Diz, L.; Goñi, I.; Saura-Calixto, F. Bioavailability of Phenolic Antioxidants Associated with Dietary Fiber: Plasma Antioxidant Capacity After Acute and Long-Term Intake in Humans. *Plant Foods Hum. Nutr.* **2009**, *64*, 102–107. [CrossRef] [PubMed]
313. Ferreira, C.S.; Pinho, M.N.; Cabral, L. Solid-liquid extraction and concentration with processes of membrane technology of soluble fibers from wine grape pomace. Técnico Lisboa. 2013. Available online: https://api.semanticscholar.org/CorpusID:189801481 (accessed on 7 September 2023).
314. Zhang, L.; Zhu, M.; Shi, T.; Guo, C.; Huang, Y.; Chen, Y.; Xie, M. Recovery of dietary fiber and polyphenol from grape juice pomace and evaluation of their functional properties and polyphenol compositions. *Food Funct.* **2017**, *8*, 341–351. [CrossRef] [PubMed]
315. Zhu, F.; Du, B.; Zheng, L.; Li, J. Advance on the bioactivity and potential applications of dietary fibre from grape pomace. *Food Chem.* **2015**, *186*, 207–212. [CrossRef]
316. Valiente, C.; Arrigoni, E.; Esteban, R.; Amadò, R. Grape Pomace as a Potential Food Fiber. *J. Food Sci.* **1995**, *60*, 818–820. [CrossRef]
317. Dias, J.F.; Simbras, B.D.; Beres, C.; dos Santos, K.O.; Cabral, L.M.C.; Miguel, M.A.L. Acid Lactic Bacteria as a Bio-Preservant for Grape Pomace Beverage. *Front. Sust. Food Syst.* **2018**, *2*, 58. [CrossRef]
318. Ageyeva, N.; Tikhonova, A.; Burtsev, B.; Biryukova, S.; Globa, E. Grape pomace treatment methods and their effects on storage. *Foods Raw. Mat.* **2021**, *9*, 215–223. [CrossRef]
319. Ayed, N.; Yu, H.-L.; Lacroix, M. Using gamma irradiation for the recovery of anthocyanins from grape pomace. *Rad. Phys. Chem.* **2000**, *57*, 277–279. [CrossRef]
320. Tseng, A.; Zhao, Y. Effect of different drying methods and storage time on the retention of bioactive compounds and antibacterial activity of wine grape pomace (Pinot Noir and Merlot). *J. Food Sci.* **2012**, *77*, H192–H201. [CrossRef] [PubMed]
321. Sokač, T.; Gunjević, V.; Pušek, A.; Tušek, A.J.; Dujmić, F.; Brnčić, M.; Ganić, K.K.; Jakovljević, T.; Uher, D.; Mitrić, G.; et al. Comparison of Drying Methods and Their Effect on the Stability of Graševina Grape Pomace Biologically Active Compounds. *Foods* **2022**, *11*, 112. [CrossRef] [PubMed]

322. MohdMaidin, N.; Oruna-Concha, M.J.; Jauregi, P. Surfactant TWEEN20 provides stabilisation effect on anthocyanins extracted from red grape pomace. *Food Chem.* **2019**, *271*, 224–231. [CrossRef]
323. Torri, L.; Piochi, M.; Marchiani, R.; Zeppa, G.; Dinnella, C.; Monteleone, E. A sensory- and consumer-based approach to optimize cheese enrichment with grape skin powders. *J. Dairy Sci.* **2016**, *99*, 194–204. [CrossRef] [PubMed]
324. Soares, S.; Brandão, E.; Guerreiro, C.; Soares, S.; Mateus, N.; de Freitas, V. Tannins in Food: Insights into the Molecular Perception of Astringency and Bitter Taste. *Molecules* **2020**, *25*, 2590. [CrossRef]
325. McRae, J.M.; Kennedy, J.A. Wine and Grape Tannin Interactions with Salivary Proteins and Their Impact on Astringency: A Review of Current Research. *Molecules* **2011**, *16*, 2348–2364. [CrossRef]
326. Canett-Romero, R.; Osuna, A.; Sánchez, M.; Castro, R.; León-Martínez, L.; León-Gálvez, R. Characterization of cookies made with deseeded grape pomace. *Arch. Latinoam. Nutr.* **2004**, *54*, 93–99.
327. Caponio, G.R.; Noviello, M.; Calabrese, F.M.; Gambacorta, G.; Giannelli, G.; De Angelis, M. Effects of Grape Pomace Polyphenols and In Vitro Gastrointestinal Digestion on Antimicrobial Activity: Recovery of Bioactive Compounds. *Antioxidants* **2022**, *11*, 567. [CrossRef]
328. Čuš, F.; Česnik, H.B.; Bolta, Š.V.; Gregorčič, A. Pesticide residues in grapes and during vinification process. *Food Control* **2010**, *21*, 1512–1518. [CrossRef]
329. Hou, X.; Xu, Z.; Zhao, Y.; Liu, D. Rapid analysis and residue evaluation of six fungicides in grape wine-making and drying. *J. Food Comp. Anal.* **2020**, *89*, 103465. [CrossRef]
330. Moncalvo, A.; Marinoni, L.; Dordoni, R.; Duserm Garrido, G.; Lavelli, V.; Spigno, G. Waste grape skins: Evaluation of safety aspects for the production of functional powders and extracts for the food sector. *Food Addit. Contam. Part A* **2016**, *33*, 1116–1126. [CrossRef]