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Review

Promising Application of Grape Pomace and Its Agri-Food Valorization: Source of Bioactive Molecules with Beneficial Effects

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Abstract: Grapes, particularly the species *Vitis vinifera* L., are one of the most widely grown crops in the world. Winemaking processes generate a high amount of residues, which currently pose an environmental and economic sustainability problem for companies in the sector. For this reason, solutions are being explored for the development of new products with high-added value derived from the valorization of these residues. One of the wastes produced by winemaking processes is grape pomace, which chemical composition is promising because it is rich in compounds with high antioxidant activity, such as polyphenols (anthocyanins, flavonols, flavan-3-ols, procyanidins), phenolic acids, resveratrol, and fiber. Commonly grape pomace is used to produce distillates and to extract tartaric acid and coloring substances such as enocyanin. Recently, alternative uses of grape pomace have been adopted, such as the production of extracts with antioxidant properties, fermentation substrates, composting and biomass for energy production, and fiber extraction for the development of high-value-added products enriched with bioactive molecules from grape pomace. Here, we discuss how bioactive molecules from grape pomace are involved in various human biological functions and their applications in the agri-food sector.

Keywords: grape pomace; bioactive compounds; polyphenols; biological effects; functional food; waste recovery

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Citation: Caponio, G.R.; Minervini, F.; Tamma, G.; Gambacorta, G.; De Angelis, M. Promising Application of Grape Pomace and Its Agri-Food Valorization: Source of Bioactive Molecules with Beneficial Effects. *Sustainability* **2023**, *15*, 9075. https://doi.org/10.3390/su15119075

Academic Editor: Đurđica Ačkar

Received: 4 May 2023
Revised: 29 May 2023
Accepted: 1 June 2023
Published: 4 June 2023

1. Introduction

Grapes are widely cultivated worldwide; specifically, in Italy, wine grape production occupies about 646,249 hectares of productive area, producing about 73,773,441 hectolitres of wine according to National Institute of Statistics (ISTAT) 2022 data. Thus, the winemaking process generates a considerable volume of different residues, characterized by the presence of biodegradable compounds and suspended solids that, if not properly disposed of, can cause negative environmental and economic impacts, including water pollution, soil degradation, damage to vegetation, energy consumption, and emission of unpleasant gases and odors [1]. Therefore, it is necessary to develop environmentally friendly methods of valorization. The main by-product of the winemaking process includes grape pomace, consisting of stalks, grape seeds, skins, stems, and seeds [2]. Nowadays, an important aspect widely investigated is the promising chemical composition of grape pomace, rich in polyphenols, vitamins, and fibers well-known for their positive biological activities on human health [3–7]. Grape pomace is a complex matrix rich in bioactive compounds and macromolecules (hydroxycinnamic acid, hydroxybenzoic acid, flavonoids, fibers) which, once extracted and evaluated for safety, can be used to formulate new products [3,8]. Particularly, extraction processes represent an important step for the identification, isolation, and recovery of active components from grape pomace, such as solid–liquid extraction for recovery of catechin-enriched grape pomace extracts [2,9]. Figure 1 displayed different extraction methods divided into traditional and non-conventional categories allowing the recovery of bioactive molecules (i.e., polyphenols, flavonoids, tannins, organic acids, terpenes, peptides, and polyunsaturated lipids). Therefore, grace pomace is considered a promising source for obtaining high-value-added materials due to its antioxidant, anti-inflammatory, cardiovascular, anticancer, and antimicrobial properties [8–14]. In recent years, sustainability has driven and promoted research to enhance and valorize grape pomace to support health and well-being, as the high nutritional profile of this by-product allows it to be used as an ingredient for food enrichment. In this regard, innovative biotechnologies have been applied to produce new food products with a high nutritional value from grape pomace, enriched with bioactive compounds, making them functional foods with antioxidant, anti-inflammatory, cytoprotective, and other important biological activities [15,16]. The potential bioactivity of dietary ingested nutraceuticals is strongly influenced by their digestive stability, bioaccessibility, bioavailability, and interaction with the intestinal microbiota [17]. Thus, the valorization of grape pomace is a growing theme not only in the agri-food sector but, in recent years, has also involved other sectors such as the biomedical, cosmetic, and nutraceutical ones. As largely investigated, grape pomaces are rich in bioactive compounds and macromolecules [3,8]. However, researchers and enterprises approaching the valorization of this by-product first need to characterize them. Nevertheless, the characterization of grape pomace is sometimes very complicated and provides only a hazy overview of their huge potential [18,19]. On the contrary, the characterization of matrices derived from grape pomace subjected to different extraction techniques appears relatively easier. It also allows acquiring knowledge about extracts that may become the starting blocks or additional ingredients of novel products, such as functional foods. The current review aims to offer a comprehensive characterization of the grape pomace molecules allowing for ascertaining not only the potential health benefits of the extracts but also the eventual presence of allergens, anti-nutritional factors, and toxins that would make the novel products not safe for all the consumers. Although the grape pomace topic has already been studied, to date, there are no studies that encompassed both biological effects and agri-food application of grape pomace. Specifically, we discuss how bioactive molecules from grape pomace are involved in various human biological functions and their applications in the agri-food sector. Moreover, the inclusion of grape pomace as a fortification element in different edible matrices is reviewed, analyzing its possibilities and limitations also from a sensory and technological point of view, giving a contribution to future studies.

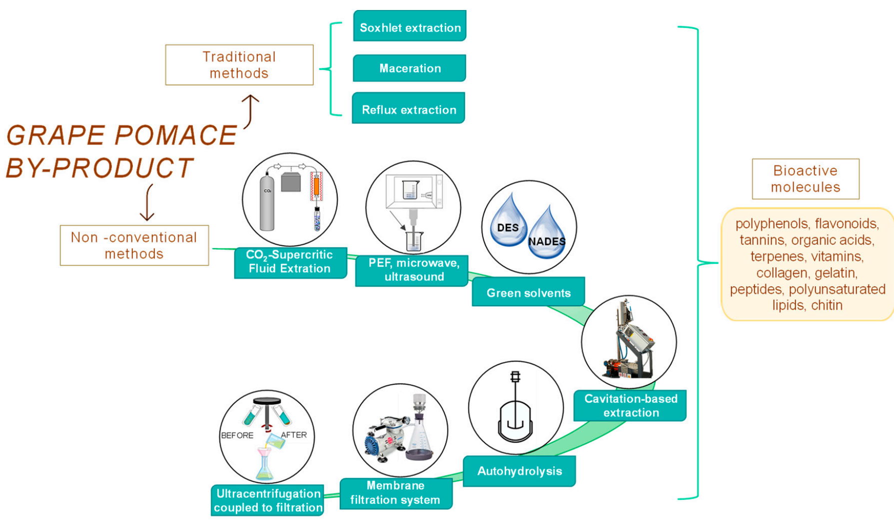

Figure 1. An overview of grape pomace extraction with different methodologies and derived bioactive molecules.

2. Chemical Composition of Grape Pomace

Grape pomace—the main solid residue of winemaking derived from the pressing of fresh grapes in white winemaking and from the pressing of fermented grape pomace in red winemaking—represents 20–25% of the initial weight of the grapes [20]. To date, 9 million tons of grape pomace are produced annually worldwide [21]. The Italian legislation defines grape pomace as “the complex of solid parts of the grape that remain after the crushing and pressing of the grapes, such as skins and seeds, with or without the stalk” [*Official Gazette*, 16 December 1998] including:

- The skin or epicarp—the membrane that encloses the pulp and the seeds—is formed by an epidermis of 6–10 layers of flattened cells, covered with a waxy substance called pruine, an ideal substrate for yeasts and other microorganisms’ growth [22].
- The grape seeds, normally two or three per berry, are covered with a tough epidermis, making them passive to the fermentation process (and distillation to obtain grappa). They represent 25–35% by weight of the fresh destemmed grape pomace and are very rich in antioxidant compounds, mainly linoleic acid, an essential fatty acid belonging to the omega-6 family [23].
- The stem is made up mostly of cellulosic substances, small quantities of simple carbohydrates, and organic and mineral salts; it performs important functions in the transport of all the substances that are deposited in the berries and is characterized by a high content of tannins [24].

Overall, its chemical composition is strongly influenced by grape variety cultivar, stage of ripeness, harvesting, and the type of winemaking process [25,26]. Despite the wide variety of grape pomace being influenced by environmental issues, its composition remains almost consistent among all, mainly consisting of water, followed by sugar, fiber, proteins, and fatty acid [27]. On average, grape pomace consists of the following composition: water 50–70%, cellulose 10–20%, sugars 6–8%, fats 2–4%, organic acids 1–2%, tannins 1–2%, minerals 1–2% [28–30], as well as numerous other substances such as proteins, pectins, coloring substances, aromatic substances, vitamins, and microorganisms. Generally, literature data showed that grape pomace contains total dietary fiber values in the range of 40–50%, crude protein 7–14.5%, crude oil 7–8%, moisture 4.5–11%, crude ash 3–5% (Table 1) [28–30]. Furthermore, as shown in Table 1, grape pomace contains a broad spectrum of mineral substances, mainly represented by calcium, iron, zinc, potassium, and manganese.

Table 1. Proximate composition, TPC, ABTS, and DPPH and mineral substances of average value grape pomace of different varieties (data from Caponio, G.R. et al., 2022 [6]; Antonić, B. et al., 2020 [28]; Mohamed Ahmed, I.A. et al., 2020 [29]; Ribeiro, L.F. et al., 2015 [30]; Spinei, M. and Oroian, M., 2021 [15]; Sousa, E.C. et al., 2014 [31]; John, W.P. et al., 2011 [32]).

Compounds	Dry Matter Content *	References
Moisture	7.8 ± 4.6 g/100 g	[29,30]
Ash	4.0 ± 1.4 g/100 g	[28,29]
Protein	10.8 ± 5.3 g/100 g	[28,29]
Fat	7.5 ± 0.7 g/100 g	[28,29]
Carbohydrates	25.0 ± 4.2 g/100 g	[30]
Total dietary fiber	45.0 ± 7.1 g/100 g	[29,30]
Insoluble fiber	39.0 ± 32.5 g/100 g	[29,30]
Soluble fiber	7.0 ± 7.1 g/100 g	[29,30]
ABTS	101.5 ± 16.3 μmol TE/g	[6,29,32]
DPPH	96.5 ± 14.8 μmol TE/g	[6,29,32]
TPC	59.5 ± 27.6 mg GAE/g	[29,32]
Calcium	9.9 g/kg	[14,31]
Phosphorous	2.7 g/kg	[14,31]

Table 1. *Cont.*

Compounds	Dry Matter Content *	References
Magnesium	0.8 g/kg	[14,31]
Sodium	0.22 g/kg	[14,31]
Sulfur	1.5 g/kg	[14,31]
Copper	49.0 mg/kg	[14,31]
Zinc	25.0 mg/kg	[14,31]
Iron	361.0 mg/kg	[14,31]
Potassium	140 mg/kg	[31]
Manganese	13.0 mg/kg	[14,31]

* Values are an average value ± SD. ABTS, 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid; DPPH, 2,2-diphenyl-1-picrylhydrazyl; GAE: Gallic acid equivalents; TE: Trolox equivalents; TPC, total phenol content.

2.1. Phenolic Compounds

Grape pomace contains a high content of total phenol content, and antioxidant activity estimated with ABTS and DPPH assays was reported in Table 1 [32]. Of note, the phenolic compounds of grape pomace were strongly impacted by cultivar, genome, soil and climatic conditions, grape maturation, winemaking technology, and extraction method [33]. Considering different cultivars of grape pomaces (Aglianico (AG), Nero di Troia (NT), Cabernet Sauvignon (CS), Merlot (M), Italian Riesling Agner (IRA), and Italian Riesling Bajilo (IRB)) were confirmed a slight difference between different solvent extraction method and total phenol content [4]. As previously evidenced, 80% MeOH and 80% EtOH extracted similar amounts of total phenol content from grape pomace [4]. Moreover, the results of a recent study encompassed a phenolic composition of grape pomace with solvent-free extraction compared with a hydroalcoholic one when subjected to in vitro gastrointestinal digestion [6]. Although the extraction yield of the alcoholic solvent was higher, the Recovery Index % (RI) of each phenolic group (anthocyanins, phenolic acid, flavonoids, stilbenes, and total) in samples extracts before (undigested) and after in vitro digestion (gastric- and intestinal-digested) underlined higher RI values for the samples extracted without alcoholic solvent [6]. Table 2 reported the content of quantified phenolic compounds in 80% EtOH grape pomace extracts belonging to different cultivars. During the winemaking processes, only 30–40% of the phenolic compounds are extracted from different parts of the berry, so a high amount of these compounds remains in grape pomace, amounting to 60–70% of the total phenolic content of the grape. For this reason, grape pomace is an extremely rich source of polyphenols. According to chemical characterization carried out in a recent study by HPLC-DAD quantification, the polyphenolic component of grape pomace is mainly composed of flavonoids (anthocyanins, flavonols, flavanols), phenolic acids (gallic acid, syringic acid), and stilbenes (trans-Resveratrol, ε-Viniferin) [6]. Grape pomace of NT and AG cultivar contained high contents of anthocyanins, especially delphinidin-3-O-glucoside, petunidin-3-O-glucoside, peonidin-3-O-glucoside, malvidin-3-O-acetylglucoside, peonidin-3-O-p-coumarylglucoside, and malvidin-3-O-p-coumarylglucoside. Among other flavonoids, (+)-catechin, hydrated rutin, quercetin-3-glucoside, myricetin, quercetin, kaempferol, and isorhamnetin, and among phenolic acids, gallic acid, and syringic acid were identified and quantified. Moreover, grape pomace contained stilbenes, such as trans-resveratrol and ε-viniferin. Generally, as shown in Table 2, the richness of phenolic compounds is lost in white cultivars of grape pomace, such as IRB and IRA, according to previously published [34]. These results agreed with other studies of chemical characterization of the polyphenolic component of grape pomace [29,35]. Of note, in vitro gastrointestinal digestion of grape pomace allowed an increase in the polyphenolic component and its antioxidant activity, improving the bioavailability and bioaccessibility of polyphenols [6].

Table 2. Quantified sample content (mg/kg dry weight ± SD) of the main phenolic compounds by the UHPLC-DAD analysis in grape pomace extracts of different cultivars [4,6].

	AG	AG-Q	NT	NT-Q	CS	ME	IRA	IRB
Flavonoids								
Anthocyanins								
Delphinidin-3-O-glucoside	2356.4 ± 335.2	231.1 ± 5.1	146.2 ± 2.3	1427.9 ± 1630.3	71.3 ± 0.7	/	/	/
Cyanidin-3-glucoside	296.9 ± 1.8	51.7 ± 0.1	16.6 ± 0.4	27.6 ± 1.5	50.0 ± 0.7	/	/	/
Petunidin-3-O-glucoside	4667.4 ± 102.5	637.9 ± 1.9	365.9 ± 0.4	484.0 ± 23.5	77.5 ± 0.6	/	/	/
Peonidin-3-glucoside	3717.3 ± 98.5	949.4 ± 8.9	127.7 ± 0.6	224.8 ± 8.5	95.0 ± 1.0	/	/	/
Malvidin-3-O-glucoside	35,813.3 ± 850.5	10,775.9 ± 67.0	4908.4 ± 42.3	5306.2 ± 482.7	669.0 ± 3.9	/	/	/
Vitisin A	288.3 ± 1.9	182.9 ± 7.4	120.2 ± 0.3	106.6 ± 3.5	/	/	/	/
Peonidin-3-O-acetylglucoside	340.9 ± 8.5	120.7 ± 3.7	200.8 ± 3.3	240.4 ± 41.6	/	/	/	/
Delphinidin-3-O-*p*-coumarylglucoside	546.0 ± 42.1	273.4 ± 6.9	628.7 ± 2.7	646.3 ± 76.8	/	/	/	/
Malvidin-3-O-acetylglucoside	2210.8 ± 43.1	1008.9 ± 14.2	3126.2 ± 72.1	3150.0 ± 343.2	/	/	/	/
Petunidin-3-O-p-coumarylglucoside	932.5 ± 28.0	607.4 ± 12.6	761.5 ± 25.7	697.8 ± 27.0	/	/	/	/
Peonidin-3-O-*p*-coumarylglucoside	1688.1 ± 35.3	1680.9 ± 13.0	549.9 ± 10.7	637.9 ± 54.7	/	/	/	/
Malvidin-3-O-*p*-coumarylglucoside	15,221.2 ± 302.6	13,992.5 ± 59.6	12,156.2 ± 242.7	9843.4 ± 548.5	/	/	/	/
Total	68,079.2 ± 685.0	30,512.8 ± 108.5	23,108.3 ± 240.1	22,792.9 ± 1140.9	962.8 ± 11.3	/	/	/
Flavonols								
Rutin hydrate	118.5 ± 3.7	105.0 ± 0.6	113.7 ± 28.9	115.2 ± 5.3	18.2 ± 0.2	9.4 ± 0.1	40.3 ± 0.5	8.4 ± 0.1
Quercetin-3-glucoside	31.5 ± 44.5	41.7 ± 0.8	92.5 ± 5.9	106.1 ± 0.1	123.0 ± 1.6	40.3 ± 0.4	234.0 ± 2.8	81.7 ± 0.8
Myricetin	19.6 ± 0.2	22.4 ± 0.3	29.1 ± 1.3	94.7 ± 7.1	1627.0 ± 9.3	/	/	/
Quercetin	14.3 ± 0.1	27.4 ± 0.6	49.7 ± 3.2	91.8 ± 5.2	759.0 ± 6.6	661.0 ± 5.7	/	/
Kaempferol	2.9 ± 0.4	4.9 ± 0.05	9.9 ± 0.7	6.9 ± 9.8	487.0 ± 4.4	473.0 ± 3.3	/	/
Isorhamnetin	13.6 ± 0.1	10.1 ± 0.1	18.7 ± 1.1	19.9 ± 2.4	701.0 ± 4.3	606.0 ± 3.0	/	/
Total	200.4 ± 23.1	211.5 ± 0.5	313.6 ± 28.6	434.6 ± 12.3	3715.2 ± 13.8	1789.7 ± 39.5	274.3 ± 3.1	90.1+ ± 0.7
Flavanols								
(+)-Catechin	20.8 ± 2.6	24.2 ± 0.1	33.9 ± 0.3	47.1 ± 0.4	841.0 ± 8.2	/	992.0 ± 6.1	927.0 ± 9.1
Total	20.8 ± 2.6	24.2 ± 0.1	33.9 ± 0.3	47.1 ± 0.4	841.0 ± 8.2	/	992.0 ± 6.1	927.0 ± 9.1
Phenolic acid								
Gallic acid	638.0 ± 29.8	579.2 ± 19.5	1139.6 ± 19.7	1093.7 ± 2.5	574.0 ± 8.1	607.0 ± 13.0	193.0 ± 2.1	248.0 ± 3.0
Syringic Acid	23.7 ± 0.1	25.5 ± 0.15	20.8 ± 0.2	25.7 ± 0.1	226.0 ± 2.9	432.0 ± 5.0	/	/
Total	661.7 ± 21.1	604.7 ± 13.7	1160.5 ± 13.8	1119.5 ± 1.8	800.0 ± 7.5	1039.0 ± 4.0	193.0 ± 2.05	248.0 ± 3.0
Stilbenes								
trans-Resveratrol	61.2 ± 18.6	34.9 ± 0.2	33.93 ± 0.34	26.37 ± 1.21	9.1 ± 0.1	/	/	/
ε-Viniferin	8.3 ± 0.6	7.6 ± 0.1			/	/	/	/
Total	69.5 ± 12.8	42.4 ± 0.2	33.9 ± 0.2	26.4 ± 0.9	9.1 ± 0.2			

/ = analyzed but not detected; all values are means ± SD. Abbreviation: AG, Aglianico; AG-Q, Aglianico added with oak chips; CS, Cabernet Sauvignon; IRA, Italian Riesling Agner; IRB, Italian Riesling Bajilo; ME, Merlot; NT, Nero di Troia; NT-Q, Nero di Troia added with oak chips.

2.2. Minor Components

Minor components of grape pomace include non-phenolic antioxidants such as tocopherols and β-carotene. These are molecules with high antioxidant potential that are mainly present in grape seeds. Their content varies depending on grape varietal characteristics and extraction methods; however, the average content of tocopherols ranges from 265 to 454 mg kg^{-1} [36,37]. In addition, grape pomace contains phytosterols mainly found in grape seeds. Of these, the most abundant is β-sitosterol (69.80–61.54%), followed by stigmasterol (11.87–16.03%), campesterol (10.79–9.28%), and sitostanol (3.47–3.97%) [37]. The main biological applications of phytosterols relate to the cardiovascular and metabolic areas due to their marked cholesterol-lowering activities. Phytosterols are effective in inhibiting intestinal absorption of dietary cholesterol, resulting in increased excretion of cholesterol through the feces and subsequent significant reduction in blood concentrations [38]. Furthermore, an important physiological component for its health-promoting characteristics, mainly found in grape pomace, seeds, and stems, is represented by tannins—a class of water-soluble polyphenolic compounds with molecular weights ranging from 120 to 3000 Da [39]. These are non-nitrogenous compounds synthesized at the levels of roots, rhizomes, bark, immature fruits, and seeds. According to their characteristics, tannins are classified into hydrolyzable tannins and condensed tannins. Hydrolyzable tannins consist of a polyol, usually glucose, which can be linked to gallic acid or ellagic acid, forming gallotannins (gallic tannins) and ellagitannins (ellagic tannins), respectively. On the other hand, condensed tannins consist of flavonoids (catechin and epicatechin) and polyphenols with antioxidant action, also called protoanthocyanidins because their acid-catalyzed oxidation gives rise to anthocyanidins [40]. Because of their characteristics, tannins promote the natural balance of the bacterial flora and, at high concentrations, can be considered antibacterial substances [41].

2.3. Dietary Fiber

Dietary fiber is defined as "edible parts of plants or analogous carbohydrates that are resistant to digestion and absorption in the human small intestine with complete or partial fermentation in the large intestine" [42]. Since its consumption is associated with the improvement and control of many diseases, it is considered a beneficial component with a central role in a healthy diet [43]. In this scenario, grape pomace is a highly functional source of fiber, characterized by a good insoluble/soluble fiber ratio and low-calorie content. Research literature reports a high content of hemicellulosic sugars present in the lignocellulosic material of grape skins that, upon enzymatic hydrolysis actions, are converted to xylose and glucose monomers [44,45]. Rhamnose, xylose, mannose, arabinose, galactose, glucose, and uronic acid represent the monosaccharides mainly present in grape pomace, and their composition appears to be rather distributed (Table 3). Comparing different cultivars of grape pomace, red grape pomace was significantly higher in dietary fiber compared to white grape pomace, 51–56% and 17–28%, respectively [46]. Nevertheless, white grape pomace was rich in soluble sugar (55–77% approximately). Scientific evidence classifies the monosaccharide composition of grape pomace in 30% of neutral polysaccharides (cellulose, xyloglucan, arabinan, galactan, xylan, and mannan), 20% of acidic pectin substances, and 15% of insoluble proanthocyanidins, lignin, structural proteins, and phenols [44,47,48]. Of note, grape pomace fiber exerted many beneficial effects correlated to the consumption of fiber on human health [49,50].

Table 3. Composition of monosaccharides (mol%) * of grape pomace of different cultivars.

	Chardonay [a]	Chardonay [b]	*Vitis vinifera* L. [c]	Cabernet Sauvignon [d]	Pinot Noir [e]	Merlot [f]
Glucose	39.1	29.8	62.7	10.7	37.0	8.4
Arabinose	29.8	6.4	5.5	21.2	20.4	0.6
Mannose	8.5	4.8	4.8	19.9	11.8	1.1

Table 3. *Cont.*

	Chardonay [a]	Chardonay [b]	*Vitis vinifera* L. [c]	Cabernet Sauvignon [d]	Pinot Noir [e]	Merlot [f]
Galactose	14.5	3.9	4.9	15.5	8.8	1.2
Xylose	3.5	14.1	20.4	7.7	3.0	2.1
Rhamnose	4.6	0.1	1.7	3.8	2.0	–
Galacturonic acid	–	40.7	–	21.2	17	–

* Average value determinations presented as relative mol%. a, Ferreira C.D.S. et al., 2013 [48]; b, González-Centeno M.R. et al., 2010 [51]; c, Prozil, S.O. et al., 2012 [52]; d, Corbin, K.R. et al., 2015 [53]; e, Beres, C. et al., 2016 [44]; f, Deng, Q. et al., 2011 [46].

2.4. Fatty Acids

Due to the presence of grape seeds in grape pomace, its oil content is higher than that of grape skin, which gives grape pomace an enrichment in fatty acids considered a good source of healthful nutrients with known bioactive activities [12]. Among the fatty acids of grape seeds, the unsaturated fatty acids (linoleic and oleic, respectively 60% and 18–20%) stand out, followed by palmitic acid (5–7%), stearic acid (3%), myristic acid (3%), and palmitoleic and linolenic acid present in lower amounts [29]. Overall, grape pomace is comparable to some oilseeds (sunflower, corn, soy) in terms of acid composition, as they are characterized by a low linolenic acid content [29]. Because scientific evidence reported that high levels of linolenic acid were implicated in unpleasant odor and taste effects, a lower level of linolenic acid in edible oils is preferred [54,55]. Therefore, grape pomace contains polyunsaturated fatty acids (PUFAs) levels of approximately 63.64–73.53%, saturated fatty acids (SFAs) levels of approximately 11.64-14.94%, and monounsaturated fatty acids (MUFAs) levels of approximately 14.19–21.29% [56]. Consequently, grape pomace also has a high ratio of PUFA/SFA and a high ratio of $n-6/n-3$ [29]. In addition, SFAs are all essential fatty acids involved in maintaining the fluidity of the neuronal membrane and in controlling the physiological functions of the brain by preventing the deterioration of brain functions [57]. Grapeseed oil is a product used in both cooking and cosmetics, as it boasts numerous benefits for the human body. Its nutritional qualities are mainly due to its high content of linoleic acid, an omega-6 series essential fatty acid known for its antioxidant and anti-cholesterol properties [58,59]. Indeed, the high linoleic acid content in grape pomace seeds becomes important in the regulation of low-density lipoprotein (LDL)-C metabolism.

2.5. Amino Acids and Biogenic Amines

Grape pomace contains considerable levels of amino acids, including tryptophan, 5-hydroxytryptophan, and L-dopa, some of which are precursors of serotonin and melatonin with important biological activities. Indeed, serotonin is a monoamine neurotransmitter involved in neuromodulation, appetite regulation, and lipid and glucose metabolism [60], whereas melatonin acts on the immune system as a potent scavenger of hydroxyl radicals [61]. A recent chemical characterization study of different grape pomace varieties showed high values of tryptophan, 5-hydroxytryptophan, and L-dopa with values of about 118–153 mg kg^{-1}, 20–80 mg kg^{-1}, and 0.3–27 mg kg^{-1}, respectively. Specifically, the tryptophan values recorded for grape pomace were higher than those of other fruits, as previously published [62]. Microbial decarboxylation of amino acids produces biogenic amines, low molecular weight amine bases with some biological activity. Being biologically active on the nervous and vascular systems, biogenic amines can cause headaches, redness, palpitations, and various allergic reactions in humans depending on their concentration and individual sensitivity. Biogenic amines of fermentative origin can be present in many fermented beverages, such as wine [16]. The most frequent biogenic amines in wine are histamine, tyramine, and 2-phenylethylamine—with the highest toxicity—and putrescine, cadaverine, spermine, and spermidine, which, although not very toxic in themselves, enhance the effects of other biogenic amines and represent possible precursors for the formation of nitrosamines, potentially carcinogenic substances [16]. The toxicity of biogenic amines is related to quantities. Specifically, 440.6 mg kg^{-1} of histamine and 301.8 mg kg^{-1} of tyramine are considered toxic [63]. However, chemical characterization studies of grape pomace recorded values lower than the established limits of biogenic amines, probably due to the absence of undesired fermentation by microorganisms [16]. In addition, grape pomace from Barbera, Chardonnay, Muscat, Müller-Thurgau, Nebbiolo, and Pinot Noir was studied for biogenic amine content, and the results reported values of putrescine, cadaverine, ethanolamine, and ethylamine below the permitted ranges [64]. Therefore, results from the literature suggest a careful selection of grape pomace for obtaining flour and/or extracts for use in the food sector, not only based on their polyphenol and fiber content but also on contaminants that are co-extracted with the compounds of interest.

3. Bioactive Compounds from Grape Pomace and Its Healthy/Functional Applications

Grape pomace components are recognized as bioactive molecules with known beneficial effects on human health (Figure 2). This paragraph encompasses the biological effects related to the grape pomace molecules, such as anti-inflammatory, antioxidant, anti-tumor, antibacterial activity, and anti-hypercholesterolemic activity.

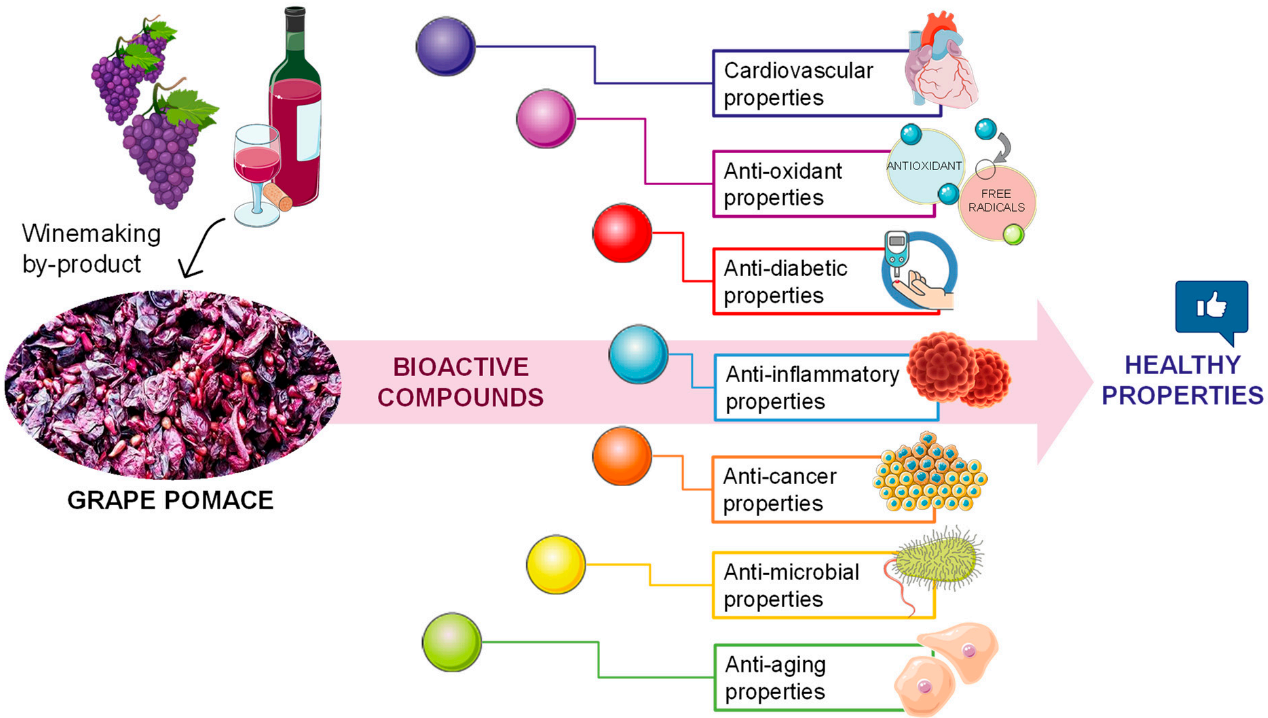

Figure 2. Effects of bioactive molecules of grape pomace on health.

3.1. Cardiovascular Properties

Cardiovascular disease is the leading cause of death worldwide, mainly due to atherosclerosis [65]. The appearance of atherosclerotic plaques causes the narrowing of vessels resulting in reduced blood supply to affected areas promoting ischemic events. To date, therapeutic angiogenesis with colony-forming endothelial cells (ECFCs) represents a new strategy to rebuild the vascular network damaged by ischemia. ECFCs are excellent cells for vascular regeneration due to their pronounced angiogenic ability. However, ECFCs need to be pre-stimulated in vitro with antioxidant substances to enhance this ability. Recent studies have shown that anthocyanin—phenolic acid rich in grapes—promotes the pro-angiogenic effect of these cells [66] and that resveratrol enhances the angiogenesis of cord vein endothelial cells [67]. Moreover, resveratrol also induced the differentiation of vascular progenitor cells into endothelial cells critical for new vessel formation [66]. In addition to the pro-angiogenic effects induced by the bioactive compounds present in grape pomace, they could directly reduce atherosclerosis, as demonstrated by several experimental studies. Thus, grape polyphenols reduce the atherosclerotic process by (i) inhibiting LDL oxidation, reducing LDL and VLDL levels, and increasing HDL levels; (ii) lowering blood pressure; (iii) inhibiting platelet aggregation; (iv) reducing pro-inflammatory processes and activating proteins that prevent cellular senescence [68].

Platelet aggregation is involved in several disease processes, such as stroke and myocardial infarction. Several agonists and adhesion proteins mediate platelet reactivity. Indeed, platelet cell membranes have numerous receptors that mediate their activation upon injury to form platelet plugs and stop bleeding [69]. However, excessive platelet activation activated by several factors such as thrombin, adenosine diphosphate (ADP), adenosine triphosphate (ATP), and collagen may occur in some pathological cases [11,70]. Following platelet activation, G proteins associated with these membrane receptors result in an increase of (Ca +2) in the cell cytosol. This increase releases arachidonic acid (AA), which in turn is converted to thromboxane A 2 (TXA 2) by cyclooxygenase-1 (COX-1) in the platelet cytosol, causing platelet activation and aggregation. This causes the release of certain metabolites that can further aggravate the atherosclerotic lesion. Flavonoids can inhibit platelet activation and aggregation through the inhibition of AA activation or blockade of ADP and collagen [71–73]. For example, resveratrol in 20 healthy volunteers reported antiplatelet effects as it increased nitric oxide (NO) production, which in turn inhibits platelet aggregation as it causes an increase in platelet NO synthase enzyme activity [74].

Grape pomace phenolic extracts showed cardioprotective effects in ex-vitro models in male Winstar rats. Specifically, rat arteries were treated with grape pomace extracts at concentrations ranging from 0.0001 to 0.03 g/L. The extracts resulted in relaxation in aortic rings in a dose-dependent manner through the activation of endothelial nitric oxide synthase. Moreover, the antioxidant activity of the phenolic compounds inhibited the contraction of aortic rings caused by endothelin-1 [75]. In addition, in subjects with high cardiovascular risk and healthy subjects, the culinary use of grape pomace-based condiment significantly reduced blood pressure and fasting blood glucose, assessing its promising strategy against these factors [76]. Obesity certainly stands out among the risk factors leading to atherosclerotic plaque formation. Obese male mice induced to follow a high-fat diet for 12 weeks gained 29% more weight than those given a normal diet. Norton grape extract (GPE) supplementation was observed to lead to a reduction in plasma levels of C-reactive protein and pro-inflammatory action, demonstrating the positive antioxidant effects of GPE in managing these risk factors underlying cardiometabolic imbalances [77].

3.2. Antioxidant and Antidiabetic Properties

The best-known activity of polyphenols is antioxidant activity, which consists in neutralizing free radicals, preventing cellular damage, and the subsequent risk of conditions such as cancer, diabetes, and heart disease [78]. Grape pomace has been studied for its antioxidant and antidiabetic effects. Because hypertension and diabetes are related to a stage of inflammation and increased oxidative stress, a recent study evaluated the effects of grape pomace on attenuating these parameters in hypertensive and diabetic rat models [79]. The results of these experiments showed a positive role of grape pomace polyphenols against endothelial dysfunction and vascular remodeling in rats by decreasing the formation of reactive oxygen species (ROS) (Figure 3). A previous study investigated the mechanisms of the antioxidant activity of grape pomace. Grape pomace extracts at different concentrations were tested on muscle and endothelial cells, evaluating the enzymatic activities of critical antioxidant enzymes, namely catalase (CAT), superoxide dismutase (SOD)1, heme oxygenase 1 (HO-1) and gamma-glutamylcysteine synthetase (GCS). Treatment with grape pomace reduced GCS levels in both cell models. On the other hand, regarding the expression of CAT activity, it had a different trend for the two cell lines, decreasing in muscle cells and conversely increasing in endothelial cells [80].

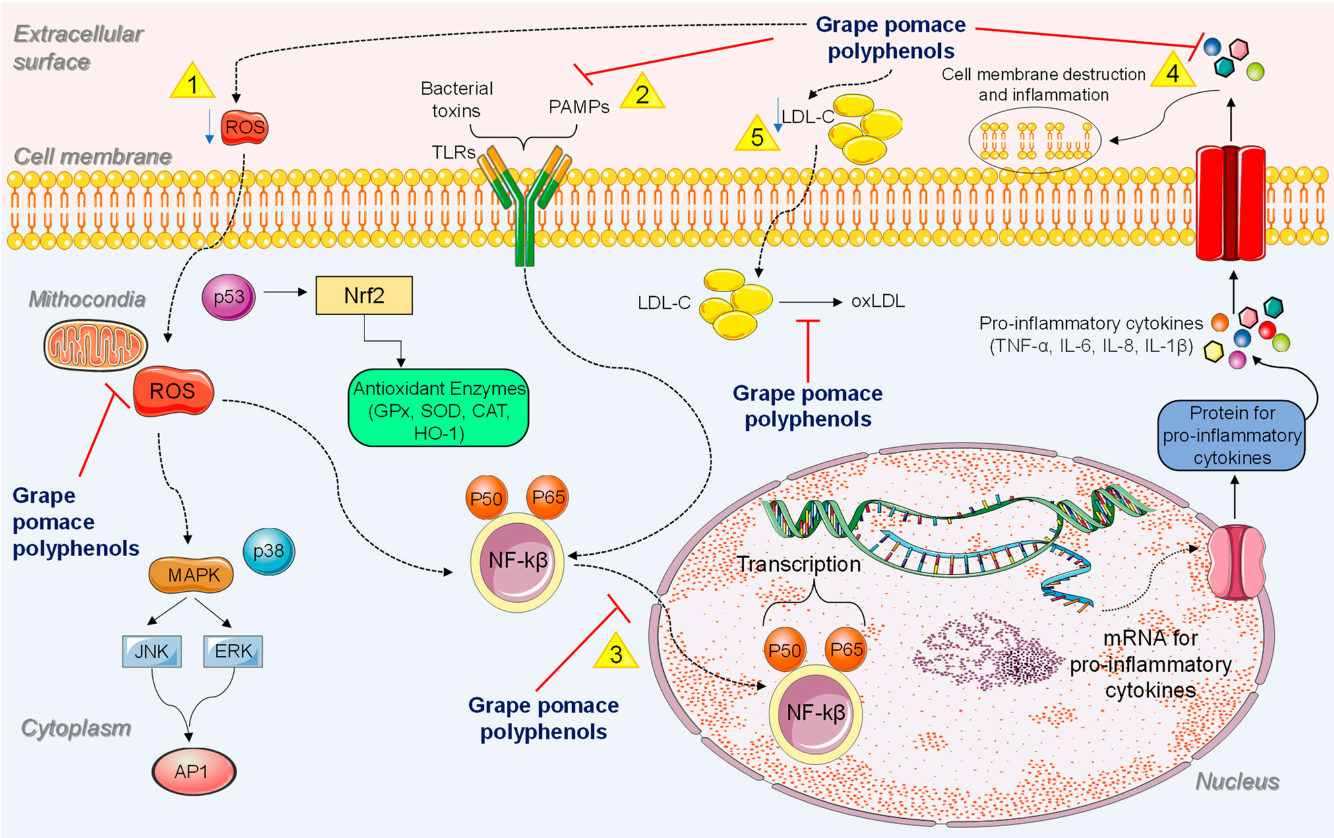

Figure 3. Effects of grape pomace polyphenols. (1) Polyphenols reduce the production of ROS. ROS diffused in the cell or exploded from mitochondria stimulate the activation of MAPKs, NF-κβ MAPKs, and NF-κβ determine the inflammatory transcription factor characteristics of pro-inflammatory mediators. Transcription of antioxidant enzymes is determined by the dissociation of Nrf2. (2) Polyphenols inhibit the activation of TLRs by bacterial toxins and PAMPs, which in turn activates NF-κβ. (3) polyphenols inhibit the NF-κβ pathway leading to the release of pro-inflammatory cytokines, which (4) cause cell membrane destruction and inflammation. (5) Polyphenols reduce LDL-C levels and the formation of oxLDL. Arrows indicate activation, and perpendicular lines indicate inhibition. Blu arrows indicate a decrease. Abbreviations: AP1, activator protein 1; CAT, catalase; ERK, extracellular-signal-regulated kinase; GPx, glutathione peroxidase; HO-1 heme oxygenase 1; IL-1β, interleukin-1β; IL-6, interleukin-6; IL-8 interleukin-8; JNK, c-Jun N-terminal kinases; LDL-C, low-density lipoprotein cholesterol; MAPK, mitogen-activated protein kinases; NF-κβ, nuclear factor κ light chain enhancer of activated B cells; Nrf2, nuclear factor erythroid 2 related factor 2; oxLDL, Oxidized LDL; PAMPs, pathogen-associated molecular patterns; ROS, reactive oxygen species; SOD, superoxide dismutase; TLRs, Toll-like receptors; TNF-α, tumor necrosis factor-α.

An important aspect concerns the different effects of polyphenols, which may have antioxidant or pro-oxidant activity depending on the dose of administration. Specifically, resveratrol—one of the most extensively studied polyphenols—showed mixed results in the literature, largely due to differences in administration doses and duration of treatment. Many of the dose-dependent responses induced by resveratrol, in vitro and in vivo, lead to positive responses at low doses and cytotoxic responses at high doses that could be explained by a dose-response effect [81,82]. In certain cases, resveratrol showed pro-oxidant effects by causing DNA damage in colon cancer cells through topoisomerase II and activation of ataxia-telangiectasia mutated kinase, triggering apoptosis [83,84].

Moreover, phenolic substances in grape pomace are involved in blood glucose control in diabetes as they act by delaying the hydrolysis of complex sugars and promoting a decrease in the release of glucoside units into the blood [85]. The study showed that grape pomace polyphenols, mainly catechin, peonidine-3-O-acetylglucoside, quercetin-3-O-glucuronide, and isorhamnetin-3-O-glucoside, can inhibit α-amylase maintaining normal blood glucose levels. Furthermore, while these polyphenols inhibited pancreatic and salivary α-amylases, no inhibitory action was found on α-glucosidase levels [85]. On the contrary, another study demonstrated inhibition of α-glucosidase levels in male diabetic C57BLKS/6NCr mice treated with streptozocin to induce diabetes and subsequently fed with grape pomace extract (400 mg/kg body weight). The introduction of grape pomace resulted in a 35% suppression of postprandial hyperglycemia through the inhibition of intestinal α-glucosidases. Thus, the hypoglycemic activities of grape pomace extract suggest how bioactive compounds derived from grape pomace can be used in the management of diabetes [86].

Moreover, grape pomace had a positive effect on the modulation of some metabolic parameters associated with a high fructose content (HF) diet. Specifically, the plasma profile of glucose, insulin, and triglycerides was evaluated in 40 rats fed both with an HF diet and HF + grape pomace at a low level (HF + LP) or a high level (HF + HP). In the first case, an increase in the plasma levels was observed, while in the groups treated with grape pomace, this increase was reduced. Postprandial plasma triglyceride levels were also higher in HF mice compared to HF + LP and HF+HP groups. In addition, the HF group showed an increase in glucose intolerance and insulin resistance (by 25%) assessed with the homeostatic model assessment (HOMA) index. The inclusion of a grape pomace-based diet restored insulin sensitivity and glucose tolerance. Therefore, grape pomace, due to the high content of polyphenols, acts not only with hypoglycemic effects but also improves the imbalances associated with serious forms of diabetes [87].

3.3. Anti-Inflammatory Properties

Oxidative stress activates redox-sensitive inflammatory molecules that amplify the inflammatory response of cytokines, chemokines, and lymphokines by inducing vascular inflammation [88]. Several findings reported that resveratrol—the main compound extracted from the skin and seeds of grape varieties—has potent anti-inflammatory and immunomodulatory properties [89,90]. Generally, the anti-inflammatory effects of grape pomace polyphenols are achieved in several pathways, including reducing the generation of mitochondrial reactive oxygen species (ROS), tumor necrosis factor-alpha (TNF-α), interleukin-1-beta (IL-1β), interleukin-6 (IL-6), nuclear factor kappa light chain enhancer of activated B cells (NF-κβ) (Figure 3) [91,92].

Of particular interest is the ability to reduce obesity-related disorders through the use of grape pomace extracts showing a reduction in inflammation and oxidative stress as a result of gut microbiota regulation leading to potential clinical benefits. Since obesity is associated with inflammation and oxidative stress [93], a clinical study investigated the effects of bioactive compounds in grape pomace on the reduction of obesity through their antioxidant and anti-inflammatory actions [79]. Specifically, Wistar rats were subjected to a high-fat diet for 14 weeks coupled with the administration of 100 mg of grape pomace/kg body weight. Following constant weekly monitoring of liver antioxidant and lipid status, fat, and adipocyte size, the results obtained showed a significant reduction in body weight and abdominal adipose area, a decrease in blood glucose, liver weight, and lipids, increase in antioxidant status and subsequent reduction in adipocyte size by down-regulating the NF-κB pathway.

Moreover, Merlot grape pomace extracts were tested in arthritic rat models to evaluate the inflammation response and investigate the effect on oxidative states. Administration of 250 mg of grape pomace extract/kg body weight for 23 days reported significant changes in inflammation-related pathways and biomarkers, suggesting its potential use as a food additive [94].

TNF-α, IL-1, IL-6, IL-8, and C-reactive protein (CRP) are known inflammatory markers, among which IL-1 and TNF-α are the most important cytokines that induce NF-kB expression, i.e., the potential target in inflammatory diseases [95]. In this regard, scientific evidence highlighted the effect of Petit Verdot grape pomace extract in reducing TNF-α and IL-1β levels in peritoneal fluid evaluated in two models of acute inflammation [96]. The anti-inflammatory effect of grape pomace in combination with tannase was also confirmed in subsequent studies conducted on Caco-2 cells [97,98]. The results showed the ability of tannase-treated grape pomace to inhibit IL-1β-induced NF-κB activation.

The anti-inflammatory effect of grape pomace extracts was evaluated in vitro by monitoring the expression of inflammatory molecules (TNF-α, IL-1β, iNOS) on N13 microglia cells stimulated with lipopolysaccharide and treated with grape pomace extracts. The results of the experiments reported decreased mRNA levels of the above-mentioned inflammatory molecules [99]. Of note, the anti-inflammatory effects of grape pomace mainly concern red grape pomace, whereas white grape pomace is less studied. Little scientific evidence exists in the literature on the anti-inflammatory properties of white grape pomace. However, white grape pomace polyphenols, primarily gallic acid, procyanidin B3-4, and epicatechin, have been reported to reduce TNF-α-induced inflammation in human embryonic kidney HEK293 cells [100].

3.4. Anti-Cancer Properties

The anti-cancer activity of grape pomace polyphenols has been reported in the context of their preventive effects on several diseases, which has led to the commercialization of several polyphenol-rich food supplements [101]. The effects of grape pomace polyphenols on cancer have been extensively investigated. Scientific literature reported results obtained in different cancer models, mainly prostate cancer and colorectal cancer. Resveratrol was studied for the prevention and treatment of human cancer on human prostate cancer DU145 cells. Indeed, treatment with resveratrol at different concentrations (12.5, 25, and 50 μM) in DU145 cells resulted in a dose-dependent inhibition of cell growth by inducing morphological changes and cell death by apoptosis [102]. The apoptotic effects of resveratrol were confirmed by protein and mRNA expression, showing inhibition of D-type cyclins and cyclin-dependent kinase (Cdk) 4 and the increase of tumor suppressor p53 and inhibitor of the CDk p21. In addition, increased levels of Bax were recorded [99]. Similar results were observed in a subsequent study in colonic carcinogenesis models in mice treated with the carcinogenic compound azoxymethane/dextran sulfate sodium. Grape pomace treatment reduced tumor size and suppressed the expression of inflammatory cytokines, reducing the levels of p53 and cyclin D1 [103]. Recently, the molecular mechanisms underlying this effect in the same models and the microbiota-derived metabolites that mediate the beneficial effects of grape pomace have been studied [104]. Metabolomics analysis based on gas chromatography-mass spectrometry revealed an upregulation of gene expression downstream of the farnesoid X receptor by decreasing fecal urease activity. Furthermore, an upregulation of the enzyme involved in DNA repair MutS Homolog 2 and a relative similarity of the DNA damage marker were obtained following treatment with grape pomace.

Grape pomace also showed anti-proliferative activity in Caco-2 and SW620 cells following fermentation processes to obtain a maximum yield of phenolic compounds [104]. The fermented grape pomace reduced cell growth by about 60% at the different concentrations tested by inducing changes in the cell cycle [104]. The effect of grape pomace polyphenols subjected to in vitro gastrointestinal digestion was also studied and recognized as a method to increase the bioaccessibility and bioavailability of polyphenols [17]. A recent study aimed to test the phenolic compounds of grape pomace, following the in vitro gastrointestinal digestion, previously analyzed for both antioxidant activity and phenolic composition by UHPLC-DAD, on colon cancer cell lines at different degrees of differentiation (HT29 and SW480) [105]. Experiments confirmed the anti-proliferative and pro-apoptotic effects of digested grape pomace extract. Interestingly, both colorectal cancer cell lines produced a significant increase in Bax, Bax/Bcl-2 ratio, and caspase-3 and a significant decrease in Bcl-2. The effects of grape pomace on cell proliferation agree with previous works confirming a dose-dependent action. In a previous study, concentrations of 10, 25, 50, and 100 μg/mL of grape pomace extract were tested on Caco-2 cells treated for 24, 48, and 72 h. The results showed a significant dose-dependent cell proliferation inhibition effect at concentrations of 25, 50, and 100 μg/mL of grape pomace, with no differences between the different hours of exposure [13]. Furthermore, the grape pomace tested on Caco-2, HT-29 cells, resulted in the overexpression of a Ptg2 gene encoding cyclooxygenase-2—a protein involved in inflammation related to some colorectal cancers [106].

3.5. Anti-Microbial Properties

In addition to the above-mentioned health attributes as antioxidant and anti-inflammatory agents, grape pomace polyphenolic extracts have shown effective antimicrobial capacity. The antimicrobial action of grape pomace polyphenols can be traced to both direct activities against pathogens through damage to their bacterial cell and the inhibition of certain virulent factors [107]. A previous in vitro study showed that resveratrol exerted a potent antimicrobial activity [108]. The antimicrobial activity of grape pomace extracts makes them potentially useful in products for the food, pharmaceutical, cosmetic, and biomedical industries. Six different bacterial strains, including three Gram-positive bacteria (*Staphylococcus aureus*, *Enterococcus faecalis*, and *Listeria monocytogenes*), three Gram-negative bacteria (*Escherichia coli*, *Pseudomonas aeruginosa*, and *Salmonella enteridis*) and three yeasts (*Enteritidis*, *Candida krusei* and *Candida tropicalis*) were used to evaluate the antimicrobial effect of grape pomace. The main results confirmed their positive effect against Gram-positive compared to Gram-negative bacteria and yeasts [108]. Further studies confirmed similar results, highlighting the inhibitory effects of grape pomace also on other bacterial species such as *Helicobacter pylori*, *Streptococcus sanguis*, and *Bacillus cereus* [109–111]. In addition, the antimicrobial effects of grape pomace polyphenols were tested in combination with a probiotic to evaluate the growth of pathogenic microorganisms such as *Escherichia coli*, *Bacillus megaterium*, and *Listeria monocytogenes*. The probiotic *Lactiplantibacillus plantarum* (*L. plantatum*) showed an increase of one logarithmic cycle after 24 h of incubation with grape pomace; moreover, pathogenic microorganisms were inhibited by the synergistic action of grape pomace and *L. plantatum*, reduced by three logarithmic cycles [6]. Therefore, these results suggest the enhancement of grape pomace also in new applications of the agri-food chain for the control of food quality and safety parameters.

3.6. Anti-Aging Properties

Polyphenols are substances often associated with cosmetics as they possess a high antioxidant power that counteracts the formation of free radicals, blocking the process of premature skin aging and fighting external exogenous factors that undermine the health and beauty of the skin [112]. By defending the skin from damage by ultraviolet rays, smog, and the aggressive action of external weather agents such as wind, humidity, or temperature changes, polyphenols help to keep the surface lipid barrier and protein structures of skin cells strong. In this regard, numerous studies have been conducted on grape pomace polyphenols to identify phytochemicals and potential applications of bioactive compounds for skin care products, which can produce high-value ingredients useful for cosmetic formulations. The bioactive compounds of grape pomace, as previously reported, are mainly polyphenols such as catechin, epicatechin, gallic acid, resveratrol, fatty acids, and vitamins. Grape pomace acts with inhibitory effects on the activity of collagenase and elastase, proteolytic enzymes related to skin aging [27]. Wittenauer et al. (2015) conducted a study evaluating grape pomace polyphenols for their antioxidant effects, showing high antiradical capabilities [113]. In addition to antioxidant potential, a cosmetic application was tested using grape pomace as an inhibitor of the activity of proteolytic enzymes such as collagenase and elastase, which are linked to skin aging. These enzymes are responsible for the degradation of dermal protein structures, thus confirming their suitability for anti-aging cosmetic preparations. In this study, the best results of enzyme inactivation were obtained with hydrophilic polyphenols, such as low molecular weight phenolic acids, particularly gallic acid [113].

4. Grape Pomace for Agri-Food Use

Alternative uses of grape pomace have recently been adopted, as fertilizer for fields, composted, distilled, used to produce tartaric acid, cream of tartar (potassium bitartrate) and dyes, added to animal feed or used for energy production, and as a colorant through the extraction of enocyanin [18,114]. In recent years, there has been a growing interest in specific compounds obtained from grape pomace and a growing interest by the wine industries in reducing the impact of their products and reducing the volume of waste and disposal costs. This has led to an increased interest in research for more efficient utilization of these by-products rich in high-value-added substances. Several bioactive compounds are found in grape pomace and grape seeds, including proteins, polyphenols, and polyunsaturated fatty acids, which are used in numerous applications in various fields, such as cosmetics and nutraceuticals. Therefore, it becomes important to develop methods that allow these by-products to be used in a comprehensive, large-scale, and economical way. Grape pomace can be valorized by following different strategies due to its chemical characteristics and the presence of a wide variety of high-value-added compounds. Different applications of grape pomace are listed and described as follows.

4.1. Biogas and Bioethanol

Grape pomace is used to produce grappa, and after distillation, their oligosaccharide can be reused to produce bioethanol. The possibility of reusing grape pomace as a source of energy substances has grown in recent years with a focus on low-impact energies [115]. Comparing the cellulose content of grape pomace with other agricultural biomasses, it seems possible to use grape pomace for biogas and bioethanol production. Anaerobic digestion for biofuel production is particularly suitable for processing grape pomace, as it has a high content of nutrient-rich organic matter and considerable energy potential. In producing bioenergy from grape pomace, however, it is necessary to consider the variability of the biomass used, as different substrate characteristics lead to different results in biogas production. Grape type, origin, and treatments undergone during the winemaking process are factors that influence substrate variability [116]. During the anaerobic digestion process, grape pomace undergoes biochemical reactions that lead to the production of simple monomers, their conversion to volatile fatty acids and then to acetates, hydrogen, and carbon dioxide, and finally to the production of biogas by methanogenic bacteria [117]. It was shown that the presence of lignin in grape pomace does not allow its degradation under anaerobic conditions, resulting in lower methane yields [118]. In contrast, was demonstrated a yield of 420 L methane/kg volatile solids using a continuously stirred reactor for 20 days [119]. Anaerobic digestion of grape pomace is used as a fuel source to produce low-cost energy. Because biogas is produced at lower temperatures than other thermal conversion technologies, this allows for lower economic investment and improved plant functionality. A low-voltage dynamic process simulation system produced 94 MWh per 1000 t of crushed grapes [120]. In addition, the economic aspect related to the costs of anaerobic digestion was examined in a subsequent study, which showed lower costs than distillation, confirming the potential of pomace for energy valorization [121]. Another alternative for biofuel production is the fermentation of sugars by the yeast *Saccharomyces cerevisiae*. Ethanol can be obtained from the fermentation of residual sugars, and in addition, the hydrolysis of complex polysaccharides into more digestible sugars can lead to an improvement of the nutritional values of these by-products, making them more suitable for use in animal feed. Grape pomace contains a considerable amount of carbohydrates, most of which are soluble monosaccharides (glucose and fructose) and complex polysaccharides (pectins, heteroxylans, xyloglucans, and cellulose). Soluble carbohydrates can be converted directly to ethanol through fermentation, with yields exceeding 270 L/ton of ethanol; alternatively, yields can be increased by subjecting grape pomace to acid pre-treatment followed by enzymatic hydrolysis. Overall, grape pomace has the potential for bioethanol production, with yields varying by grape pomace type, 211 L/ton and 400 L/ton of ethanol from red and white pomace, respectively [53].

4.2. Bio-Fertilizer

In addition to biofuel production, grape pomace is also used for compost production. Composting is a commonly used treatment for the disposal of biological residues, and it is a process in which organic material is decomposed by aerobic microbial activity under mesophilic conditions by stabilizing organic substrates at thermophilic temperatures. Burg et al. (2014) investigated the feasibility of targeting grape pomace for composting [122]. In this study, the composting process of compost masses consisting of different percentages of grape pomace, waste plant material, chips, and manure was monitored. Each compost mass was subjected to a sanitization/remediation process at 45 °C for 5 days. The authors showed that the composting process represents an effective use of grape pomace, asserting that the resulting compost is considered a high-quality organic fertilizer, comparable in terms of chemical values to other organic composts. However, one of the limiting factors is the acidic pH of the grape pomace, which requires adjustment before processing for composting. Experiments conducted by Paradelo et al. (2013) showed a low volume of nitrogen available for microbial activity and failure to achieve thermophilic conditions leading to a pH toward neutrality [123]. More recently, models of co-composting grape pomace with other organic materials have been evaluated. The results of a study by Zhang and Sun (2016) showed the good performance of grape pomace compost added to sugarcane bagasse and the good chemical characteristics of water content and carbon/nitrogen ratio [124]. Therefore, the compost produced had higher microbial and enzymatic activity and shorter lignocellulosic degradation times than the control. Further work on co-composting grape pomace was studied in combination with municipal solid waste in equal amounts [125]. The combination of the two organic materials produced a neutralization of the acidic pH of grape pomace resulting in a product rich in nitrogen and phosphorus. In addition, the addition of grape pomace to municipal solid waste had less impact on odor emissions compared to composting municipal waste alone. In addition, red and white grape pomace were evaluated for soil pest inactivation. While white grape pomace showed good soil pest inactivation characteristics, in contrast, red grape pomace was not suitable as it induced undesirable soil methanogenesis [126]. Because the presence of polyphenols in grape pomace compost can cause phytotoxic effects in the soil, the vermicomposting technique is considered a viable alternative to using pomace as a fertilizer. Vermicomposting with grape pomace in reactors for 112 days resulted in a reduction of the polyphenolic content by about 80% and an increase in pH to neutral values [127].

4.3. Tartaric Acid

Another interesting product recovered from grape pomace is tartaric acid. Techniques for recovering tartaric acid from grape pomace involve the extraction by hydrochloric acid and subsequent precipitation of tartrate with calcium salts, which is converted to tartaric acid by sulfuric acid. The extraction efficiency of tartaric acid from grape pomace can be affected by several factors, including the temperature conditions used, pH level, and calcium chloride levels. Hot water provides higher yields of tartaric acid/kg grape pomace, as well as specific pH values of 6.8 and high calcium chloride rates [115]. The recovery yield of tartaric acid varies between 50 and 75 g of tartaric acid/kg of grape pomace [128]. Due to its antioxidant, pH regulator, and preservative properties, tartaric acid is widely applied in various food categories, including dairy products, edible oils and fats, fish and meat products, fruits and vegetables, and soft and alcoholic beverages. Potassium tartrates are also used in baked goods because of their ability to react with sodium bicarbonate to produce carbon dioxide without requiring fermentation processes [128].

4.4. Natural Dyes

A further field of application of grape pomace concerns its use as a source of natural dyes. The use of grape pomace as a colorant in the food industry depends on several factors: the method of extraction of the anthocyanin component and the characteristics of the food product to which the enocyanin is to be added. A study conducted by Bechtold et al. (2007)

evaluated the different extraction capabilities of anthocyanin dyes from grape pomace of different grape varieties, using aqueous extraction to compensate for the consumption of chemicals used in textile dyeing processes [129]. In addition, an optimized dyeing procedure was used to evaluate the correlation between the concentration of anthocyanins extracted and the intensity of the preserved color. Among the grape pomace tested, those belonging to the Blauburger grape variety presented the highest concentration of extracted anthocyanins (126 mg dm^{-3}), followed by Cabernet Sauvignon (75 mg dm^{-3}) and Blauer Burgunder (70 mg dm^{-3}). The amount of extracted anthocyanins was comparable to that determined on other matrices, such as blueberries. In addition, the extracts were compared with commercial reactive dyes to estimate the color intensity of the extracted substance. Particularly, anthocyanins extracted from Blauburger showed comparable color intensity to commercial reagents. Dyeing tests had not yielded promising results, as the color yield was unsatisfactory. However, by adopting a pre-dye with 30% of tannin, intense red/purple shades could be obtained on cotton fabrics [129]. A more recent study evaluated to define an optimal dyeing process from anthocyanins extracted from grape pomace using an aqueous extraction [130]. The main results showed that the optimal factors of the dyeing process are the temperature of 100 °C, the duration of 55 min, and the pH of 8. Another study evaluated the ultrasonic technique to use the anthocyanins extracted from grape pomace, achieving a good color rendition of fabrics dyed with grape pomace compared to conventional dyeing [130]. In addition, color changes of anthocyanins as a function of the pH of the medium and color stability in terms of intensity and hue following acetylation, polymerization, and condensation reactions are well known [131]. Moreover, the color changes of anthocyanins as a function of the pH of the medium and the stability of the color in terms of intensity and shade following acetylation, polymerization, and condensation reactions are well known [132]. In addition, the presence of sulfites in the food can lead to a drastic decrease in color due to anthocyanin–sulfite discoloration reactions [129]. Despite these problems, enocyanin has always been used as a colorant in the food sector on matrices such as milk, ice cream, beverages, juices, jams, and other food preparations, and has stable characteristics when added at concentrations between 20 and 60 ppm [129].

4.5. Oxidative Stability and Shelf-Life Improvement

Since modern society promotes the valorization of by-products and food waste to support human health, research focuses on the development of innovative biotechnologies to produce new food with a higher nutritional value starting from grape pomace, enriched with bioactive compounds displaying antioxidant, anti-inflammatory, cytoprotective, and other important biological activities. Amendola et al. (2010) studied the chemical and physical characteristics of a phenolic extract obtained from grape pomace of red grape cultivars [132]. The extract was obtained by hydroalcoholic extraction and subsequent freeze-drying and showed stable total phenolic content and antioxidant activity when stored at 25 °C in a closed container protected from light for up to 300 days. Spigno et al. (2013), taking advantage of these results, studied the ability of phenolic extract as a natural additive to improve the shelf-life of hazelnut paste [133]. To test the protection from lipid oxidation of the product with the addition of freeze-dried grape pomace extracts, the hazelnut paste was stored at 60 °C for 5 days, thus accelerating the rancidity process of the product. The authors demonstrated the effectiveness of a pomace extract in improving the shelf-life of hazelnut paste by inhibiting its oxidation, despite the limited solubility of the extract in a matrix containing a high lipid concentration.

Other scientific evidence showed the application of grape pomace powder to control oxidative stability, such as in the production of cured meat products. The grape pomace polyphenols play an antibacterial role and do not negatively affect the production of cured meats [134]. In these studies, grape pomace flour was used to replace nitrites and nitrates as a source of polyphenols in making salami. The addition of polyphenols delayed the oxidative reactions that lead to the onset of unpleasant and altering flavors and odors of normal fermentation, as measured by the thiobarbituric acid reactive substances index

(TBARS) [135]. Lipid oxidation is one of the main factors contributing to the worsening shelf-life of meat preparations. It is divided into two phases: primary oxidation, which induces the formation of hydroperoxides, conjugated dienes, and trienes, and secondary oxidation, which involves the release of volatile compounds. As a result, sensory quality is significantly reduced, as are nutritional value and technological properties [136]. In addition, phenolic extracts from grape pomace are also used as substitutes for synthetic antioxidants in the production of processed meats, such as hamburgers, showing good oxidative stability and color characteristics [137,138]. Positive effects of grape pomace flour have also been obtained on the quality parameters of salmon burgers in terms of oxidative stability, physicochemical, and sensory characteristics [139]. Moreover, grape pomace extract has been shown to minimize changes in flavor, color, texture, and lipid oxidation during the freezing of seafood products [140,141]. The grape pomace activity of protecting and stabilizing oxidative processes was also confirmed in beef by feeding animals with grape pomace for 90 days [142]. The main results showed the positive effect of the grape pomace diet on increasing antioxidant activity and reducing coliform. In addition, the grape pomace diet resulted in reduced oxidation of meat lipids and proteins, with lower TBARS values. On the contrary, breadsticks fortified with different percentages of grape pomace powder (5% and 10%) showed a decreasing trend in shelf-life probably due to pro-oxidant molecules or the presence of polyunsaturated fatty acids, although giving breadsticks a higher fiber content [143].

4.6. Source of Fiber

As largely investigated, grape pomace allows for increasing fiber content when added to foods. Recently, grape pomace flour has been used to make leavened bakery products, such as pizza bases, with high nutritional value. In the study conducted by Difonzo et al. (2023), the authors partially replaced wheat flour with grape pomace flour in amounts of 15, 20, and 25% [144]. The pizza bases were analyzed for polyphenol content, antioxidant activity, physico-chemical characteristics, and volatile compounds. Experimental products with the addition of grape pomace flour presented higher polyphenol content and antioxidant activity and high fiber content (6 g/100 g) already with 15% of flour substitution, allowing the nutritional claim "enriched in fiber". From a technological point of view, pizza bases with the addition of grape pomace flour showed different textural aspects for hardness and chewability parameters. Moreover, since the aroma and flavor of grape pomace can affect the acceptability of the product, a sensory analysis of the pizza bases was conducted, showing pungent and musty notes due to the presence of some volatile compounds determined, such as aldehydes, alcohols, and esters, correlated with the parameters of astringency and acidity. A similar technological application of grape pomace flour involved its use in the production of muffins with reduced fat content and increased fiber content. The resulting muffins had good characteristics of polyphenolic content, fiber content, and antioxidant activity [145]. Other scientific studies have focused on the use of grape pomace flour in unleavened bakery products, such as breadsticks [146]. In this study, technological approaches were implemented to produce fortified breadsticks by replacing wheat flour with 0.5 and 10 g 100 g^{-1} of grape pomace flour. The authors characterized the experimental samples for functional attributes (fiber content and antioxidant activity), rheological characteristics, and sensory attributes. The results of these analyses, according to further study [143], showed the promising characteristics of grape pomace flour in the production of fiber-rich and bioactive fortified breadsticks. Another application case involving the use of grape pomace flour to produce bread evaluated the nutritional and sensory characteristics [147]. Grape pomace used in this study belonged to different vine cultivars and was substituted for white flour at the rate of 5% and 10%. The fiber content of the bread was affected by the different grape pomace cultivars, showing a significant increase in insoluble fiber with the addition of 10% Cabernet Franc and Cabernet Sauvignon grape pomace. In addition, the sensory aspect is a key parameter for consumer acceptability. Sensory evaluations had shown significant effects on panelists' preferences for aroma, flavor, and texture parameters of bread-related to the different grape pomace cultivars rather than to the percentage of substitution. Overall, the grape pomace cultivar Cabernet Sauvignon showed the best preferences in color, aroma, and texture compared to the others, achieving similar acceptability values to those of white bread.

4.7. Source of Pectins

Among the fermentable soluble fibers of grape pomace, pectins are of particular interest for food applications. Grape pomace is an unconventional source of pectins, which makes it promising for use in food formulations, such as condiments, toppings, and yogurt. In fact, the pectin content of grape pomace is about 3.92 g/100 g of pomace [148]. Therefore, grape pomace, in addition to conferring good properties of antioxidant activity and fiber content, is considered a good source of pectin used as an additive in the food industry to improve texture and rheology [15]. The recovery of certain bioactive molecules from grape pomace is a crucial aspect to better use them in the food sector. The extraction yield of pectins from grape pomace depends on various factors, including the type of solvent used [15]. The principal solvents used for pectin extraction are water and buffers, acids, bases, and calcium chelators. Scientific evidence confirms that among the acids, citric acid allows to obtain better yields [149,150]. Furthermore, the ultrasonic extraction technique conferred higher pectin extraction yields than conventional techniques [151]. Another aspect that influences the extraction of pectins concerns the variety of grape pomace. Red grape pomace varieties produce a higher amount of extracted pectin than white grape pomace [46]. Pectin is a highly perishable substance, and its activity is strongly influenced by storage conditions. In this context, a recent study evaluated the effects of different drying methods on the physio-chemical characteristic of extracted pectin from grape pomace [152]. Among convective drying, freeze drying, infrared radiation drying, and solar drying, freeze-drying and convection drying reported the highest extraction yields. Freeze-drying allowed us to obtain a higher antioxidant capacity and a high reducing sugar content, respectively, 7238 μmol TE/100 g and 19.8%. Instead, convective drying had the best characteristics in terms of galacturonic acid content and molecular weight.

4.8. Prebiotic Effects

Probiotics and grape pomace are a combination considered ideal for amplifying the benefits of yogurt consumption by incorporating fiber and antioxidants. Several scientific studies have verified the viability of this option. A recent study evaluated the enrichment of grape pomace flour in yogurt by also testing consumer preferences [153]. Unfermented grape pomace from three different cultivars (Chardonnay, Muscat, and Pinot Noir) was added in amounts of 60 g/kg to a whole yogurt. Analyses conducted up to three weeks of storage at 4 °C showed a significant increase in antioxidant content compared to the control yogurt without the addition of grape pomace. In addition, microbiological analyses reported survival in the presence of grape pomace of starter strains and *Streptococcus thermophilus* and *Lactiplantibacillus delbrueckii* subsp. *bulgaricus*, without negative influences. However, in terms of the organoleptic profile, yogurt enriched with grape pomace achieved lower acceptability scores than the control yogurt, foreshadowing the need for further improvement. Specifically, yogurt with grape pomace was perceived as excessively sour in taste and grainy in texture, making it necessary to reduce the particle size of grape pomace and change the flavor by adding sweeteners or using yogurt with lower acidity. On the contrary, Karnopp et al. (2017) reported a 79% acceptability index for yogurt enriched with grape pomace flour, indicating its use as a promising alternative to increase the functional properties of yogurt [154]. In the area of dairy products, Pinot Noir pomace obtained from white winemaking obtained good results in fermented milk in terms of viable cell growth of *L. rhamnosus*, with no significant differences for *S. thermophilus* [155]. Although grape pomace conferred a significant increase in antioxidant activity to fermented milk, the samples tested were not favorable for the survival of *L. acidophilus*. Overall, the use of white Pinot noir pomace in fermented milk containing *L. rhamnosus* imparted good flavor, color, and overall acceptability characteristics to the products. These results agree with those of a later study, also conducted on different types of pomaces (Pinot Noir, Freisa, Croatina, and Barbera). The protective effect of grape pomace phenolic extract on the survival of lactobacilli (*L. acidophilus*) was principally confirmed with Freisa, Croatina, and Barbera varieties [156]. Moreover, the prebiotic effect of grape pomace polyphenols was studied in combination with probiotic *Lactiplantibacillus* sp. for its anti-inflammatory properties, emphasizing a synergy action between prebiotics and probiotics [157]. Furthermore, grape pomace extract has been used in food preparations not only to increase the content of antioxidants and fibers but also as a lipid oxidation controller, monitoring and extending the shelf-life of yogurt and salad dressings [158]. Grape pomace fermentation is recognized as a technique to increase the functionality of polyphenolic extracts by imparting prebiotic character. Grape pomace from the Malbec and Tannat varieties have been studied for their prebiotic characteristics. Aqueous grape pomace extracts fermented by fungal-produced hydrolytic enzymes have been tested on *L. casei* growth detecting prebiotic activity [159]. Since it is well known that encapsulation of polyphenols is a viable alternative to increase their bioaccessibility and bioavailability [7,17], a recent study evaluated the effects of a micro-encapsulated pomace extract added in coconut water on the growth of probiotic bacteria [160]. The results suggested a positive effect on the growth of bifidobacteria and lactobacilli, with no negative influence on the sensory aspect in terms of aroma and flavor.

5. Limitation: Research Gaps

In addition to the real advantages related to grape pomace reuse, such as high efficiency in disposal management and enrichment of bioactive molecules and antioxidant substances [2,25], based on experimental data, researchers have pointed to some limits as critical points in the use of grape pomace.

Given the increasing consumption of new foods based on grape pomace waste, the importance of ensuring food safety in the context of new and more sustainable processing technologies is well-known. However, from a nutritional point of view, the use of novel foods derived from grape pomace waste potential could be a limitation due to the poor digestibility of matrices rich in fiber, polyphenols, availability of essential amino acids that is difficult to balance [161] Another issue is the possible presence of contaminants or other compounds such as anti-nutritional factors, toxins, biogenic amines that negatively impact the human health [16,161]. Therefore, it is important to understand what and how many anti-nutritional compounds are present in grape pomace and apply purification technologies to make it optimal for new food production. Moreover, given the large number of bioactive components in grape pomace with biological properties on human health that can replace synthetic additives, its use as a source of functional ingredients allows the definition of "functional foods". Recent trends show interest in studies on grape pomace flours rich in fiber, phenolic compounds, and minerals. Although sensory aspects and taste are not key factors in defining a functional food, attention to consumer satisfaction is of paramount importance. Therefore, understanding how much the consumer is willing to compromise between the "original" taste of food and its derivative with functional components that provide health benefits plays a key role. To date, scientific evidence makes it possible to expand research to achieve foods with grape pomace that are sensory acceptable. At the same time, scientific research should focus on health aspects to demonstrate the real effect of grape pomace on various diseases and health alterations.

6. Conclusions

The scientific works considered in this review highlight the growing focus on waste minimization in the food supply chain that aims to reuse by-products as a source of bioactive molecules in the perspective of a circular economy. The chemical composition of grape pomace makes it promising for various uses (i.e., biogas and bioethanol production, bio-fertilizer, tartaric acid, natural dyes, source of pectins, fibers and oxidative stability regulating molecules, and source of bioactive molecules with prebiotic effects). Therefore, grape pomace contains large amounts of bioactive components with biological properties on human health that can replace synthetic additives, combining health benefits (e.g., cardiovascular health, antioxidants, and anti-inflammatory properties) and technological use. In this scenario, the use of grape pomace as a source of functional ingredients is a promising field for the formulation of so-called "functional foods". The attention to the sensory aspect and consumer satisfaction is of paramount importance. Therefore, further studies could help define better protocols for the use of pomace in the agri-food sector.

Author Contributions: Conceptualization, G.R.C.; data curation, G.R.C.; investigation, G.R.C.; writing—original draft preparation, G.R.C. and M.D.A.; writing—review and editing, G.R.C., F.M., G.T., G.G. and M.D.A.; visualization, F.M., G.T. and G.G.; supervision, M.D.A. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by a Project funded under the National Recovery and Resilience Plan (NRRP), Mission 4 Component 2 Investment 1.3—Call for proposals No. 341 of 15 March 2022 of the Italian Ministry of University and Research funded by the European Union—NextGenerationEU; Award Number: Project code PE00000003, Concession Decree No. 1550 of 11 October 2022 adopted by the Italian Ministry of University and Research, CUP H93C22000630001, Project title "ON Foods—Research and innovation network on food and nutrition Sustainability, Safety and Security—Working ON Foods", by SNIPS-PSR Puglia 2014–2020 Sm 16.2 DdS:94250034553, and by project SYSTEMIC "an integrated approach to the challenge of sustainable food systems: adaptive and mitigatory strategies to address climate change and malnutrition", Knowledge hub on Nutrition and Food Security, has received funding from national research funding parties in Belgium (FWO), France (INRA), Germany (BLE), Italy (MIPAAF), Latvia (IZM), Norway (RCN), Portugal (FCT), and Spain (AEI) in a joint action of JPI HDHL, JPI-OCEANS and FACCE-JPI launched in 2019 under the ERA-NET ERA-HDHL (n° 696295).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Data are contained within the article.

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

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