Polyphenols from Red and White Grape Pomace

Subjects: Plant Sciences | Integrative & Complementary Medicine

Contributor: Ioana Corina Bocsan, Dan Claudiu Măgureanu, Raluca Maria Pop, Antonia Mihaela Levai, Ștefan Octavian Macovei, Ioana Maria Pătrașca, Veronica Sanda Chedea, Anca Dana Buzoianu

Grape pomace (GP) represents a very reliable source of polyphenols because it could be found globally as a remnant of the wine industry. During the winemaking process, two types of GP are generated: red GP and white GP, according to the produced wine, red or white. Grape pomace represents a viable source of polyphenols, mainly flavanols, procyanidins anthocyanins, and resveratrol which possess antioxidant and anti-inflammatory activities. Multiple differences were observed between red and white GP in terms of their antioxidant and anti-inflammatory activity in both in vitro and in vivo studies. Although most studies are focused on the antioxidant and anti-inflammatory effect of red grape pomace, there are still many variables that need to be taken into consideration, as well as extensive study of the white GP. It was observed that in both in vitro and in vivo studies, the GP polyphenols have a direct antioxidant activity by acting as a free radical scavenger or donating a hydrogen atom. It also possesses an indirect antioxidant and anti-inflammatory activity by reducing mitochondrial reactive oxygen species (ROS) generation, malondialdehyde (MDA), 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), and inhibitor of nuclear factor kappa-B kinase subunit beta (Ikκβ) levels or nitrate oxide-4 (NOX4) expression and by increasing the levels of antioxidants enzymes like superoxide dismutase (SOD), catalase (CAT) glutathione reductase (GRx) and glutathione peroxidase(GPx). Besides these activities, many beneficial effects in ischemic heart diseases were also observed, such as the maintenance of the ventricular function as close as possible to normal, and the prevention of infarcted area extension.

Keywords: antioxidant ; anti-inflammatory ; grape pomace ; polyphenols ; ischemic heart diseases

1. Introduction

Ischemic heart diseases, also known as coronary heart diseases (CAD), alongside stroke and other cardiovascular diseases, are the causes of approximately 17.9 million deaths annually, which represents 32% of the total deaths in the world [1]. Out of these, more than 75% are registered in low and middle-income countries. Furthermore, in accordance with World Health Organization (WHO), ischemic heart disease is the leading cause of global death, with 16% of worldwide deaths, followed by stroke, which is responsible for 11%, respectively. Ischemic heart disease is characterized by narrowing or blockage of one or more coronary arteries, most frequently due to atherosclerosis, which is the main factor that reduced cardiac blood flow. It is clinically manifested by pectoral angina and heart attack [2]. The main incriminated risk factors that promote CAD are tobacco, an unhealthy diet with low fruit and vegetable intake, lack of physical activity, metabolic syndrome, and excessive use of alcohol [1][3]. Besides these, other pathologies like obesity, diabetes mellitus, nephrotic syndrome, and hypothyroidism could associate with dyslipidemia, which is characterized by elevated levels of LDL and total cholesterol and a reduced HDL level. Moreover, it was observed that people with different lifestyles, like workers who have permanent night shifts, are more likely to develop dyslipidemia [4].

All of these risks lead to atherosclerosis. In this term, atherosclerosis is defined as a multifactorial inflammatory disease of the innermost layer of an artery called intima, a build-up of cholesterol plaque, and a loss of the arterial wall elasticity [5]. Therefore, a primary target in the treatment of CAD is represented by the prevention of atherosclerosis development. In this regard, the management of CAD includes lifestyle changes like dietary modification, smoking cessation, and weight reduction alongside classical medication (nitrates, beta-blockers, calcium channel blockers, and angiotensin-converting enzyme inhibitors). Additional comorbidities like diabetes, hypertension, and dyslipidemia are controlled via oral antidiabetics or insulin, antihypertensive drugs, and statins, respectively.

Even if there are many efficient ways of reducing the incidence of associated risk factors, among which the pharmacological and surgical ones with proven results, CAD still represents the main cause of death worldwide. That is why this pathology represents a great interest for many researchers and their efforts are needed in identifying new ways to prevent and treat CAD. In this regard, plants have been always an inexhaustible source of discovering new compounds

with potent pharmacological activities. Shifting from traditional plant utilization, a great alternative is represented by plant waste valorization. This new direction came along with the introduction of the circular economy, an economic system that proposes a reduced use of raw materials and increased reuse and recycling of different components and products already existing [6] (**Figure 1**).

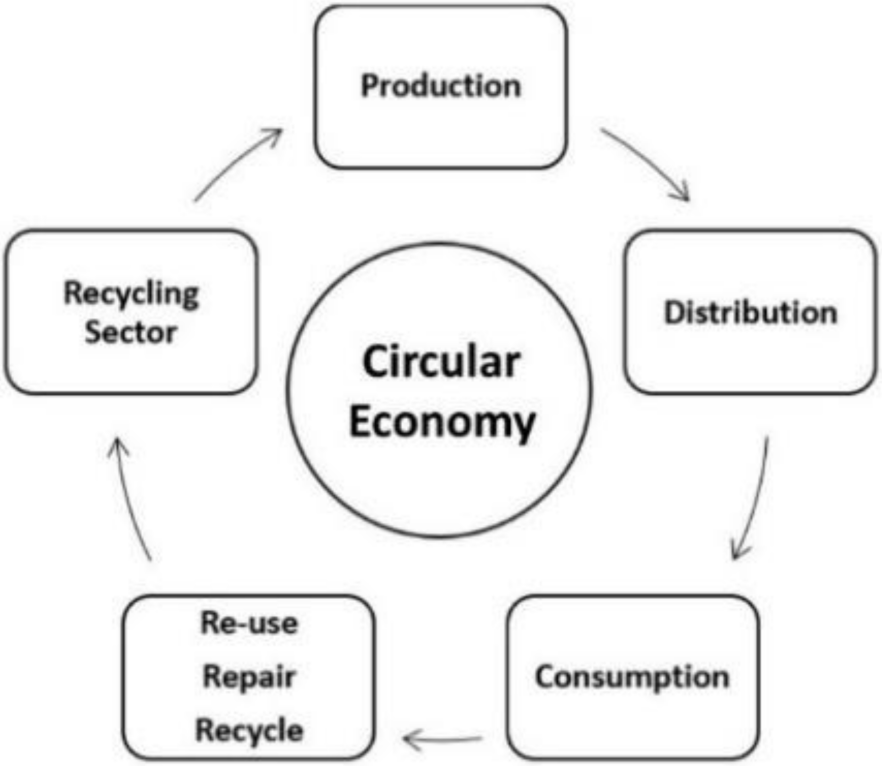


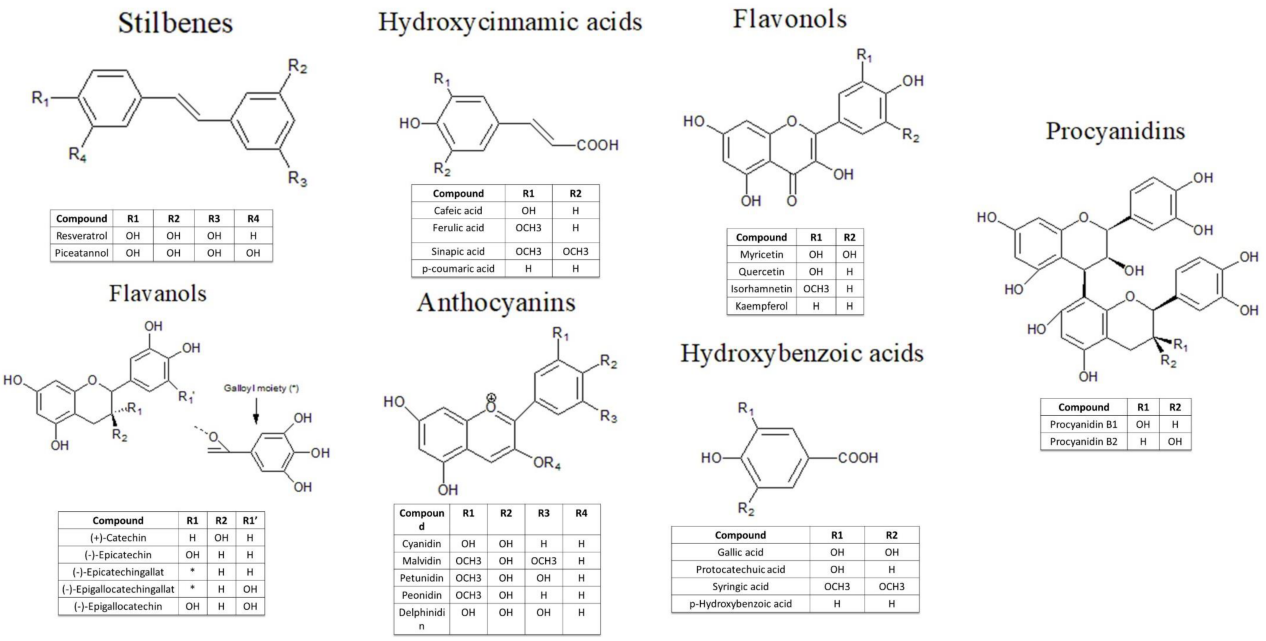
Figure 1. Circular Economy.

A perfect example of the circular economy's application is represented by the usage of grape pomace (GP). Therefore, it is estimated that annually are used more than 79 million tons of grapes, from which approximately 30% is represented by grape pomace [7][8]. Besides its use as fertilizer or animal feed, another field in which it can be used is the pharmaceutical one, due to the rich amount of bioactive compounds, especially phenolic ones [8]. Thereby, GP is reported to contain high quantities of resveratrol and polyphenols like flavanols: myricetin, quercetin, kaempferol; flavan-3-ols: catechin, epicatechin; cinnamic acids: p-coumaric and benzoic acids: syringic, gallic, and protocatechuic, 4-hydroxybenzoic [9]. It is known that polyphenols, the major compounds in GP waste have well-known antioxidant and anti-inflammatory effects [10]. Previous studies have reported their action on reducing LDL oxidation, inflammation, and platelet activation, all with positive effects in reducing the progression of atherosclerosis [11].

2. Red and White Grape Pomace—Bioactive Compounds

The utilization of grapes has a long history, which dates back to antiquity and spreads to the modern world, especially through their use in the wine industry. That is why there is a variety of literature studies that analyze and characterize grapes, grape derivatives especially wine, and GP composition and content [9][12] (**Figure 2**). It was observed that red grape pomace (RGP) and white grape pomace (WGP) have different phenolic compound fingerprints and different total phenolic content according to the grape cultivar and terroir. This means that all of the pedological, topographical, and geological aspects of a specific physical environment will alter the physical features of the grapes such as tastes, aromas, textures, and appearances [8]. RGP was found to be rich in stilbenes (resveratrol), phenolic acids (gallic acid, protocatechuic acid), flavanols (epigallocatechin), flavanols (myricetin-3-O-rhamnoside) and anthocyanins (delphinidil-3-O-glucoside, cyanidin-3-O-glucoside, petunidin-3-O-glucoside, peonidin-3-O-glucoside, malvidin-3-O-glucoside) [13]. WGP was reported to have high content of phenolic acids (p-hydroxyphenylacetic acid, vanillic acid, homovanillic acid, homoprotocatechuic acid, gentisic acid, syringic acid, 4-O-methylgallic acid, 3-O-methylgallic acid, dihydro-3-coumaric acid, hydroferulic acid, hydrocaffeic acid, isoferulic acid) and flavanols (catechin, epicatechin, procyanidin B1) [13], flavonoid glycoside (hyperoside, isoquercitrin, rutin, quercitrine), flavonoid aglycons (quercetin, luteolin), and protocatechuic acid [14]. It was also reported that WGP has a high quantity of gallic acid, procyanidin B3-4, epicatechin, and procyanidin gallates [15]. In both RGP and WGP was identified a similar amount of caffeic acid, coumaric acid, catechin, and its isomer epicatechin [14], and similar amounts of total tannins [16]. Overall, numerous studies concluded

that RGP contains a higher amount of polyphenols than WGP [17]. However, some studies revealed types of WGP that possessed a greater content of polyphenols than RGP [13].



Compound	R1	R2	R3	R4
Resveratrol	OH	OH	OH	H
Piceatannol	OH	OH	OH	OH

Compound	R1	R2
Cafeic acid	OH	H
Ferulic acid	OCH3	H
Sinapic acid	OCH3	OCH3
p-coumaric acid	H	H

Compound	R1	R2
Myricetin	OH	OH
Quercetin	OH	H
Isorhamnetin	OCH3	H
Kaempferol	H	H

Compound	R1	R2
Procyanidin B1	OH	H
Procyanidin B2	H	OH

Compound	R1	R2	R1'
(+)-Catechin	H	OH	H
(-)-Epicatechin	OH	H	H
(-)-Epicatechingallat	*	H	H
(-)-Epigallocatechingallat	*	H	OH
(-)-Epigallocatechin	OH	H	OH

Compound	R1	R2	R3	R4
Cyanidin	OH	OH	H	H
Malvidin	OCH3	OH	OCH3	H
Petunidin	OCH3	OH	OH	H
Peonidin	OCH3	OH	H	H
Delphinidin	OH	OH	OH	H

Compound	R1	R2
Gallic acid	OH	OH
Protocatechuic acid	OH	H
Syringic acid	OCH3	OCH3
p-Hydroxybenzoic acid	H	H

Figure 2. The chemical composition of principal polyphenols from grape pomace.

3. Potentially Toxic Effects of Polyphenols from Red and White Grape Pomace

Generally, literature studies focused on GP or GP by-products are emphasizing its health benefits rather than toxic or adverse reactions. Administration of GP may not be an issue in healthy people, but it must be considered in people with certain diseases who are receiving medical treatment [18]. Neag et al., (2019) observed the paradoxical effect of GP polyphenol extract on an animal model of acute kidney injury induced by cisplatin. They reported that when GP, was given alongside cisplatin, for its antioxidant properties, it did not decrease the cisplatin-induced nephrotoxicity, on the contrary, it increased it [19]. The lack of studies reporting the potentially toxic effects of polyphenols from grape pomace could be based on the fact that even if GP presents pro-oxidant activity at a higher dose than the one that presents the antioxidant effect [20][21], that effect is too low to cause changes at the level of an organ or the entire organism, changes that could be highlighted through routine analyses. Thus, this issue should be addressed in terms of precautions rather than acute or chronic toxicity [22].

4. Red and White Grape Pomace—Variability of Total Polyphenols Content and Antioxidant Capacity

It is well-known that GP possesses great antioxidant activity, but it is necessary to find out what are the differences between RGP and WGP to give them an appropriate valorization. Literature studies showed that GP has a strong antioxidant activity, because of the contained phenolic compounds. The antioxidant activity is strongly related to phenolic chemical structures. Thus, the number of existing hydroxyl groups gives them the ability to act as free radical scavengers [23] or to donate an atom of hydrogen [24][25]. Accordingly, several methods for antioxidant activity evaluation have been created over time. The main methods used for GP characterization reported so far were total polyphenol content (TPC), 2,2-Diphenyl-1-picrylhydrazyl (DPPH), 2,2′–azinobis-(3-ethyl-benzothiazoline-6-sulphonic acid) (ABTS), and ferric reducing antioxidant power assay (FRAP) for antioxidant activity (**Table 1**).

Total phenolic content represents the reference assay for measuring the polyphenols in plants or other biological samples, by using the Folin–Ciocalteu assay [24][26]. This method involves a reaction between the polyphenols and a redox reagent. Accordingly, the phenolic content is determined using the spectrophotometric measurement of this reaction [27]. Further, the methods used to determine polyphenols' antioxidant activity content are ABTS, DPPH, and FRAP. These assay methods analyze the antioxidant activity via the donation of a hydrogen atom (ABTS and DPPH) or via electron transfer (FRAP) [28][29].

Due to the variety of antioxidant activity methods that are used, it is very difficult to compare data from the literature. This situation leads to the development of a relevant correlation method, which could allow their comparison. In this case, Xu

et al., (2016), in their study regarding the phenolic compounds extracted from four GP varieties, identified antioxidants and compounds with antibacterial properties and also developed a correlation method between TPC, DPPH, and ABTS [30]. They observed that between TPC and ABTS there is a significant positive correlation, but none between these and DPPH. A probable cause for this could be the fact that there are differences between the phenolic compounds involved in each method. Thus, it was reported that flavonoids and tannins contributed to the determination of antioxidant activity via ABTS, while in the case of DPPH anthocyanins, they had a major contribution. In comparison to this study, Marchante et al., (2018) observed that in the measurement of antioxidant activity using the DPPH method, a higher contribution was brought by (−)-epigallocatechin, while in the case of the ABTS method by flavan-3-ol monomers. Furthermore, they did not observe any differences between the contribution to the determination of ABTS and DPPH methods for (+)-catechin, (+)-gallocatechin, (+)-epigallocatechin, (+)-catechin gallate, (−)-epicatechin gallate, procyanidin B1, galloylated dimers, flavan-3-ol dimers, flavan-3-ol total oligomers, total flavan-3-ols, and trans-resveratrol-glucoside. Moreover, they also observed that the compound with the highest antioxidant property was (+)-catechin gallate, followed by (−)-epicatechin gallate, (+)-gallocatechin, (+)-catechin, and (−)-epigallocatechin [31].

Xia et al., (2019), also addressed the necessity of comparing and correlating the values of the different methods used in polyphenols quantification. To eliminate the variations of these values, the authors also chose to determine the antioxidant activity by using all the above-described methods. Thus, Xia et al., (2019), evaluated the TPC and measured the antioxidant assay using ABTS, DPPH, and FRAP of skin and seeds from 31 different cultivars of grapes. Firstly, they observed that the grape seeds have more polyphenols and more antioxidant activity as assayed via DPPH, ABTS, and FRAP than grape skins. Secondly, they observed that the European species have higher antioxidant properties than the American, Asian, or hybrid ones [10].

Even though the majority of studies determined that RGP possesses a higher polyphenolic content and antioxidant activity (Costa et al., 2018, Sagdic et al., 2011, Xu et al., 2016), there is no sufficient evidence yet to affirm that RGP is superior to WGP. Winkler et al., (2015) observed that even though the RGP cultivated in Rhineland-Palatinate, Germany had a higher TPC than WGP, the differences were not significant [32]. Further, Cerda-Carrasco et al., (2015) who investigated GP obtained from *Vitis vinifera* sp. cultivated in Maipo Valley, Chile, observed that two types of white grapes, Sauvignon Blanc and Chardonnay, had higher phenolic content and antioxidant capacity than the two red types, Cabernet Sauvignon and Carménère [15].

It can be concluded that both GP varieties represent great sources for further valorization, their prior analysis being a key step in directing toward the appropriate use, because of their large variation in terms of phenolic content and antioxidant activity.

Table 1. Comparison of total polyphenols content (TPC) and antioxidant capacity of red and white grape pomace polyphenols extracts.

Grape Pomace (GP)		TPC (mg GAE */g GP)	Antioxidant Capacity DPPH (µmol TE **/g GP)	ABTS (µmol TE/g GP)	FRAP (µmol F_eSO_4 * $7H_2O$/g GP)	References
Vitis vinifera sp. Cultivated in Maipo Valley, Chile						
White	Sauvignon Blanc	19	120	-	-	[15]
	Chardonnay	17	90	-	-	
Red	Cabernet Sauvignon	14	60	-	-	
	Carménère	13	70	-	-	

Grape Pomace (GP)		TPC (mg GAE */g GP)	Antioxidant Capacity DPPH (µmol TE **/g GP)	ABTS (µmol TE/g GP)	FRAP (µmol F_eSO_4 * $7H_2O$/g GP)	References
Vitis vinifera sp. cultivated in Virginia, USA						
White	Vidal Blanc (hybrid variety)	55.5	7.71	334	-	[30]
	Viognier (*Vitis vinifera* sp.)	99.1	3.54	951	-	
Red	Cabernet Franc (*V. vinifera* sp.)	153.8	11.2	1013	-	
	Chambourcin (hybrid variety)	92.0	28.2	378	-	
Vitis vinifera sp. cultivated in Rhineland-Palatinate, Germany						
White	4 varieties of Pinot Blanc and 6 of Riesling	48	-	-	-	[32]
Red	5 varieties of Dornfelder, 5 of Pinot noir and 2 of Portugais bleu	58	-	-	-	
Vitis vinifera sp. cultivated in Blacksburg, Crozet, Floyd VA, USA						
White	Viognier	11.8	-	-	-	[33]
	Vidal Blanc	12.5	-	-	-	
	Niagara	24.8	-	-	-	
	Petit Manseng	32.1	-	-	-	
Red	Petit Verdot	64.8	-	-	-	
	Merlot	35.8	-	-	-	
	Cabernet Franc	36.1	-	-	-	
	Chambourcin	10.4	-	-	-	
White	unknown varieties	90.51	-	-	1619	[34]
Red	unknown varieties	107.40	-	-	1886	

Grape Pomace (GP)		TPC (mg GAE */g GP)	Antioxidant Capacity DPPH (µmol TE **/g GP)	ABTS (µmol TE/g GP)	FRAP (µmol F_eSO_4 * $7H_2O$/g GP)	References
Vitis vinifera sp. cultivated in Cappadocia district of Nevsehir province (Emir), Tokat province (Narince), Sarkoy-Murefte district of Trakya region (Gamay), Ankara province (Kalecik Karasi), Elazig province (Okuzgozu), Turkey						
White	Emir	75.5	-	-	-	[35]
	Narince	138.1	-	-	-	
	Gamay	255.4	-	-	-	
Red	Kalecik Karasi	205.7	-	-	-	
	Okuzgozu	281.4	-	-	-	
Vitis vinifera sp. cultivated in Blackstone, VA, USA						
White	Chardonnay	24.5	-	-	-	[36]
Red	Cabernet Franc	30.4	-	-	-	
Vitis vinifera sp. cultivated in Cantine Cantele, Apulia Region, Southern Italy						
White	Fiano	127.06	-	-	-	[37]
Red	Negramaro	127.87	-	-	-	
Vitis vinifera sp. cultivated in Paros, Greece						
White	Monemvassia	4.49	-	-	0.32	[38]
	Mandilaria	5.1	-	-	0.31	
Red	Aidani mavro	0.25	-	-	0.21	

* GAE—gallic acid equivalent ** TE—Trolox equivalent.

5. Red and White Grape Pomace—In Vitro Antioxidant and Anti-Inflammatory Activities

The fact that many studies investigating GP have shown that it possesses intense antioxidant activity has been a key factor in drawing the attention of researchers to continue the findings and to focus on the beneficial antioxidant and anti-inflammatory activities within the in vitro studies as presented in **Table 2**. Most literature data reports the antioxidant activity of GP on cells exposed to different oxidative stress factors or/and the anti-inflammatory activity on cells subjected to different proinflammatory factors.

Table 2. In vitro antioxidant and anti-inflammatory activity of grape pomace polyphenols extracts.

Materials	Polyphenols Extracts	Models	Antioxidant and Anti-Inflammatory Activity	References
Grape pomace from different red *Vitis vinifera* species				
GP from *Vitis vinifera* L. Cagnulari cv. from Santa Maria La Palma, Alghero, Italy	Water/ethanol (60:40, *v*/*v*) extract containing: - anthocyanins (malvidin, peonidin-3-O-glucoside, malvidin-3-(6-acetyl)-glucoside, M-3-G)	H_2O_2-induced oxidative damage in human umbilical vein endothelial cells	- increased cells viability - reduced ROS levels	[39]
GP from *Vitis vinifera* L. Batiki Tyrnavou cv. from Greece	Ethanol extract containing: - flavan-3-ols (catechin, epicatechin, epicatechin-3-gallate) - anthocyanidins (malvidin, cyanidin, petunidin, delphinidin) - anthocyanins (peonidin-3-O-glucoside, myrtillin, oenin, kuromanin) - phenolic acids (caftaric acid, gallic acid) - flavanols (quercetin, kaempferol)	Tert-butyl hydroperoxide-induced oxidative damage in muscle cells (C2C12)	- reduced TBARS, ROS and protein carbonyls levels - increased GSH levels	[40]
		Tert-butyl hydroperoxide-induced oxidative damage in endothelial cells (EA.hy926)	- reduced TBARS and protein carbonyls levels - increased GSH levels	
GP from *Vitis vinifera* seeds	-	UV radiation-induced oxidative stress in human keratinocytes cells (HaCaT cells)	- decreased ROS levels - decreased apoptosis proteins levels - decreased Bax-α pro-apoptotic protein levels - decreased NF-kB p65 protein levels	[41]

Materials	Polyphenols Extracts	Models	Antioxidant and Anti-Inflammatory Activity	References
GP from *Vitis vinifera* from Valea Calugareasca	Acetone extract containing: - flavonoids (catechins, procyanidins, epicatechins) * higher concentration for procyanidin dimer and epicatechin	Intestinal inflammation model: LPS-inflammation induced in Caco-2 intestinal cells Symbiotic combination with *Lactobacillus sp*. as probiotic	- down-regulation of chemokines and cytokines proteins and genes expression - up-regulation of TIMP1 and TIMP2 genes expression - down-regulation of JNK1, ERK1/2, Akt/P70S6K/mTOR, MAPK, NF-κB and Nrf2 expression	[42]
GP from *Vitis vinifera* variety Montepulciano from Chieti, Italy	Water extract containing: - gallic acid, caftaric acid, caffeic aicd, syringic acid, coumaric acid, ferulic acid, catechin, epicatechin, chlorogenic acid	H_2O_2-induced oxidative damage in HypoE22 rat hypothalamus cells	- averted the down-regulation of BDNF gene expression - averted up-regulation of COX-2 gene expression and decreased PGE2 levels	[43]
GP from *Vitis vinifera* L. varieties from Emilia Romagna region, Italy	Natural deep eutectic solvents (NaDESs) extract containing: - anthocyanins (malvidin)	Menadione-induced oxidative damage in keratinocyte cells from human skin (HaCaT cells)	- improved cells viability - reduced IL-8 levels	[44]
GP from *Vitis vinifera* L., cv Negramaro from Azienda Agricola Cantele, Guagnano, Lecce, Italy	Methanol/ethanol (80:20, *v*/*v*) extract containing: - caffeic acid, caftraic acid, cutaric acid, gallic acid, catechin, epicatechin, kampferol, oenin, quercetin, rutin, t-resveratrol	LPS and TNF-α-induced inflammation in human colorectal adenocarcinoma-derived intestinal epithelial cells (Caco-2 cells) and human microvascular endothelial cells (HMEC-1 cells)	- decreased IL-6 and MCP-1 levels - down-regulation of MMP-9 and MMP-2 expression - down-regulation of the mRNA levels of the cytokines (IL-1β and TNF-α), the chemokines (CXCL-10 and M-CSF), COX-2 VCAM-1, ICAM-1 - down-regulation of the NF-κB signaling pathways - reduced ROS levels	[45]

Materials	Polyphenols Extracts	Models	Antioxidant and Anti-Inflammatory Activity	References
GP from *Vitis vinifera* cv Pinot noir from Cautín valley, La Araucanía Region, Chile	Ethanol extract containing: - hydroxybenzoic acids (gallic acid, protocatechuic acid) - flavanol (catechin) - hydroxycinnamic acid (ferulic acid) - flavanols (quercetin, quercetin-3-rutinoside, quercetin-3-galactoside, quercetin-3-glucoside, kaempferol-3-glucoside) - anthocyanins (malvidin-3-glucoside, peonidin-3-glucoside, delphinin-3-glucoside, petunidin-3-glucoside, cyanidin-3-glucoside)	Polycyclic aromatic hydrocarbons-induced cytotoxicity in endothelial cells	- increased cells viability - down-regulation of Nrf2 expression	[46]
Grape pomace from different white *Vitis vinifera* species				
GP from *Vitis vinifera* cv Chardonnay from Lowden, WA, USA	-	H_2O_2-induced oxidative damage in human colonic epithelial cells (Caco-2 cells)	- decreased ROS levels	[47]
Red grape pomace versus White grape pomace				

Materials	Polyphenols Extracts	Models	Antioxidant and Anti-Inflammatory Activity	References
GP from *Vitis vinifera* varieties from Quinta da Cavadinha, Pinhão, Portugal Red: Tinto Cão, Tinta Barroca White: Malvasia Fina, Moscatel Branco	Methanol/distilled water (70:30, *v*/*v*) extract containing: - flavanols (isorhamnetin-3- O-(6-O-feruloyl)-glucoside, quercetin-3-O-glucuronide, quercetin-3-O-rutinoside, kaempferol-3-O-rutinoside, kaempferol-3-O-gluco- side) - cinnamic acid (caftaric acid) - anthocyanins (malvidin-3-O-glucoside, malvidin-3-O-(6-O-caffeoyl)-glucoside, malvidin-3-O-rutinoside) - stilbene (Σ-viniferin)	H_2O_2-induced oxidative damage in human keratinocytes (HaCaT cells)	- increased GSH levels, where WGP from Malvasia Fina had the highest capacity to increase it - decreased ROS levels, where RGP from Tinto Cão had the highest capacity to decrease it - decreased LPO levels, where WGP from Malvasia Fina had the highest capacity to decrease it	[48]

Abbreviations: TIMP1/2—matrix metalloproteinase inhibitors 1/2; MAPK—Mitogen-activated protein kinase; JNK1—c-Jun N-terminal kinase; ERK1/2—Extracellular signal-regulated kinase 1/2; Akt—protein kinase B; P70S6K—ribosomal protein S6 kinase; mTOR—mammalian target of rapamycin; Nrf2—nuclear factor erythroid 2–related factor 2; ROS–Reactive oxygen species; TBARS- Thiobarbituric acid reactive substances; GSH –Glutathione; BDNF—brain-derived neurotrophic factor; PGE2—Prostaglandin E2; LPO—Lipid peroxidation; NF-kB –nuclear factor kappa-light-chain-enhancer of activated B cells; LPS—lipopolysaccharide; TNF-α—tumor necrosis factor; IL-6—Interleukin-6; MCP-1—monocyte chemoattractant protein-1; MMP—matrix metalloproteinases; IL-1β—Interleukin-1-beta; CXCL-10—C-X-C motif chemokine ligand 10; M-CSF—macrophage colony-stimulating factor; COX-2– cyclooxygenase-2; VCAM-1– Vascular Cell Adhesion Molecule 1; ICAM-1– Intercellular Adhesion Molecule 1; H_2O_2—hydrogen peroxide.

6. Red and White Grape Pomace—In Vivo Antioxidant and Anti-Inflammatory Activities

Taking into consideration that several studies have demonstrated a beneficial impact on metabolic syndrome, which is a key factor in many health-related issues [49][50][51][52][53][54], for reducing cardiovascular disease risk factors such as TMAO (trimethylamine N-oxide) [55], hypertension, and hyperglycemia [56], it is necessary to find out if all of these are supported by in vivo studies. Thus, the literature can provide valuable information about the anti-inflammatory and antioxidant activity that GP possesses in various experimental studies [57][58][59].

The liver is the main antioxidant site for neutralizing most oxygen-free radicals. For this reason, the liver also plays a key role in maintaining the oxidant/antioxidant balance. This balance can be disturbed by diseases such as atherosclerosis, diabetes, and cancer, which induce oxidative stress. This state occurs when there is an increase in the production of free radicals, which can damage biomolecules such as lipids (lipid peroxidation), proteins (peptide chain fragmentation and electrical charge alteration), and DNA (purine and pyrimidine bases degradation, mutations, translocations or deletion) [60]. An additional measure in combating these pathological changes is brought by antioxidants, including GP, which is known to have a strong antioxidant effect. Thus, many studies have aimed to investigate the effects of GP on liver redox homeostasis.

7. Ischemic Heart Diseases—What We Know So Far and What Can Be Improved

When it comes to ischemic heart diseases, the literature refers to them as coronary artery diseases (CAD). Thereby, CAD is characterized as a pathological process caused by the accumulation of atherosclerotic plaque in the intimal wall of the arteries. This accumulation could lead to a complete or incomplete obstruction of the arteries, resulting in an imbalance between myocardial oxygen demand and supply. Other causes that could induce CAD are microvascular dysfunction and a spasm of the coronary arteries. This pathology is considered to be a chronic and progressive disease [2][61].

7.1. Risk Factors

The principal risk factors that contribute to the appearance and progression of atherosclerosis and coronary artery diseases are smoking, diet, weight gain, and physical activity. Among risk factors, tobacco is responsible for more than 8 million death per year. According to WHO, over 80% of tobacco users are from low-middle-income countries, and, taking into consideration that 75% of total deaths of cardiovascular events are registered also in low- and middle-income countries, there is a possible correlation between smoking and cardiovascular death causes. It was observed that smoking cessation leads to a reduction of 36% in CAD-induced mortality. For this matter, besides behavioral counseling, there is also pharmacological support to encourage smoking cessation [61][62]. Another risk factor is represented by an unhealthy diet. For the prevention of several diseases, a dietary plan that includes fruits, vegetables, polyunsaturated fats, fish, and fiber is recommended, along with avoiding a high quantity of refined carbohydrates, saturated, fat and red meat [61]. Nonetheless, physical inactivity represents a major risk factor for CAD and stroke. Both diet and physical activity modulate weight management, which represents one of the most life-long risks of all because a close correlation between body weight and lipid profile has been demonstrated in several studies. Increased body weight may also disturbs the lipid profile, which, could lead to atherosclerosis. According to WHO, over 39 million children under 5 years are obese, and over 1.9 billion adults are overweight, of which over 650 million are obese [63]. Therefore, it was demonstrated that patients who are overweight or obese are more likely to develop cardiovascular diseases than patients with a normal BMI (20–25 kg/m^2) [61]. Considering these, a healthy lifestyle behavior would decrease the risk of cardiovascular events.

7.2. Diagnostics

When it comes to diagnostic methods, there is basic testing, which includes resting ECG, and echocardiography and biochemical tests such as a lipid profile and myocardial injury markers—troponins T and I. In addition to imagistic testing, if the echocardiography is inconclusive cardiac magnetic resonance may be taken into consideration [61]. In the last years, the medical scientific community tried to develop a way for less invasive and less expensive screening for this pathology. In this direction, a risk-estimation system was created and validated, the well-known SCORE system [61].

7.3. Management

The aims of pharmacological management are to reduce the symptoms associated with coronary artery diseases and to prevent major acute cardiovascular events like myocardial infarction. Starting from here, there are two types of therapy: for and for no life-threatening CAD, the second one is usually referred to it as long-term medication. For life-threatening CAD, the gold standard is percutaneous coronary intervention, within 2 h from the appearance of symptoms associated with antiplatelet and anticoagulant therapy. An alternative to percutaneous coronary intervention is fibrinolystic drugs such as alteplase or reteplase. The long-term medication includes numerous classes of drugs such as: anti-ischemic drugs, which include nitrates, beta-blockers, and calcium channel blockers; antiplatelet drugs like aspirin and clopidogrel; anticoagulant drugs, which include heparin and low molecular weight heparins, warfarin, dabigatran. All of these treatments come with side effects such as hypotension, headache (nitrates), fatigue, bradycardia, bronchospasm, heart block, peripheral vasoconstriction (beta-blockers), headache and ankle edema (calcium channel blockers), and increased risk of bleeding (antiplatelet and anticoagulant drugs) [61][64].

7.4. Potential New Therapy

Taking all of the above into consideration, even with the fact that the major risk factors are well-known and there is a continuous progression in diagnostic methods and pharmacological management, ischemic heart diseases remain one of the major causes of mortality and morbidity so far. Accordingly, there still exists the demand and necessity for alternative therapy to be found. That is why, when taking into consideration the oxidative stress and inflammation associated with all the mechanisms that induce ischemic heart diseases, it is a good premise that the polyphenols from GP could be used as adjuvant therapy. Even though the antioxidant and anti-inflammatory effects of the polyphenols from GP are well-known, there is still a lack of information when it comes to the pharmacological activities, especially their pharmacokinetics and

pharmacodynamics. Looking in this direction, it is necessary to conduct studies for this purpose, firstly on animals, and, if the results are promising, to take the next step, and, eventually, to conduct trials on patients with ischemic heart diseases.

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