From winery by-product to healthy product: Bioavailability, redox signaling and oxidative stress modulation by wine pomace product

Gisela Gerardi, Mónica Cavia-Saiz, and Pilar Muñiz

Department of Biotechnology and Food Science, Faculty of Sciences, University of Burgos, Plaza Misael Bañuelos, 09001, Spain.

*Corresponding author: Dra. Pilar Muñiz, Plaza Misael Bañuelos, Facultad de Ciencias, Departamento de Biotecnología y Ciencia de los Alimentos, 09001, Burgos, Spain.

E-mail: pmuniz@ubu.es

Phone: +34-947258800 Ext. 8210

Fax: +34-947258831

Email addresses: Gisela Gerardi (mggerardi@ubu.es), Monica Cavia-Saiz (monicacs@ubu.es), Pilar Muñiz (pmuniz@ubu.es).

Abstract

The use of winery by-products, such as wine pomace, to improve human health is attracting increasing interest. The wine pomace is the mainly winery by-products consisted of seeds and skins that suppose an economic and environmental problem and their use as functional ingredient or for pharmaceutical purposes are being increasingly recognized as a good and inexpensive source of bioactive compounds. In this sense, it known the potential health properties of wine pomace products in the prevention of disorders associated with oxidative stress and inflammation such as endothelial dysfunction, hypertension, hyperglycemia, diabetes, obesity, etc. Those effects are due to the bioactive compounds of wine pomace, involved in the maintaining of the cell redox balance through the modulation of oxidative stress and inflammatory process. The mechanisms concern especially modulation of antioxidant/prooxidant activity, improvement of nitric oxide bioavailability, reduction of pro-inflammatory cytokines and modulation of antioxidant/inflammatory signal pathways. This review mainly summarizes the studies that examine the mechanisms of wine pomace products as modulators of oxidative status involved in cell pathologies as well as their potential therapeutic use for cardiovascular diseases. For this purpose, the review provides an overview of the findings related to the wine pomace bioactive compounds profile, their bioavailability and the action mechanisms through which them maintain the redox cell balance involved in health benefits. The review suggests an important role for wine pomace product in cardiovascular diseases prevention and their regular food intake may to attenuate the development and progression of comorbidities associated to cardiovascular diseases.

Keywords: polyphenols, fiber, bioactive compounds, wine by-products, cardiovascular health, signaling pathways, oxidative stress, and wine pomace.

1. Introduction

Food processing wastes are defined as residues or by-products derived from processing raw materials to food (Faustino et al. 2019). Winemaking processing industries generates by-products in the form of peels, seeds, pomace that constitute an important source of nutrients and bioactive compounds (Faustino 2019). The main solid waste from the winemaking industry is a residue from the pressing and/or fermentation process, called wine pomace or grape pomace. The major components of wine pomace are seeds and skins, although it can also contain pulp rest and stems residues. Wine pomace contains a high number of bioactive compounds, with potential health benefits and even various applications, which are responsible of its several biological activities. In this regard, the compounds that mainly contribute to the bioactivity of wine pomace are the polyphenols, as the major bioactive compounds present in wine pomace product, and the dietary fiber. At present, most studies are focused on the use of the wine pomace products in the food industry (Kalli et al., 2018; Lavelli et al., 2016). In that regard, wine pomace can serve as a source of natural additives such as antioxidants and extracts for the preparation of functional foods and dietary supplements. In addition, the incorporation of wine pomace as source of bioactive compounds in the preparation of functional foods leads to the generation of foods with potentially beneficial effects for human health.

An emerging research area is studying the health effect of winery by-products by their role in the improvement of several disorders associated with oxidative stress and inflammation implicated in the increased risk of cardiovascular diseases, aging, obesity, and other chronic diseases (D`Oria et al. 2020). Scientific evidence has supported the beneficial use of wine pomace products in the prevention of this diseases, among others (Balea et al. 2018; De Groote et al. 2012; Gerardi et al. 2020; Del Pino-García et al. 2017b). The health effects of wine pomace products depend of their intake and of the bioaccessibility and bioavailability of their bioactive compounds (Gerardi et al. 2020a; Fraga et al. 2019; Del Pino-García et al. 2016c; Saura-Calixto, Serrano, and Goñi 2007). Thus, the bioavailability of wine pomace bioactive compounds, mainly

polyphenols, varies considerably according to their structure, to their food matrix and by the condition of the host.

The dose and the bioavailability of the bioactive compounds, together with their effects after consumption, have been widely discussed within the scientific community over time. In the first place, the antioxidant compounds can act by either decreasing or by increasing oxidative stress, depending on their concentration, the cellular type, and the conditions. In second place, it is known that polyphenols and other bioactive compounds undergo modifications in the organism, as a consequence of digestion, absorption, and metabolism. Hence, an *in vitro* result will not necessarily correlate with the *in vivo* effects.

The aim of this review article is to provide insights into the relevance of the wine pomace products as source of bioactive compounds, mainly polyphenols, their bioavailability and the role as modulators of cellular response to oxidative stress including signaling pathways, antioxidant implication, and their role to improve oxidative stress-related disorders.

2. Winemaking by-products as source of bioactive compounds

Wine pomace, also called grape pomace, is the main solid by-product from the winemaking industry, is a residue from the pressing and/or fermentation process, and is compound by seeds and skins, although it can also contain pulp rest, and stems residues. It represents about 20-30% of the original grape weight (Ferri et al. 2020). The wine pomace is an important source of bioactive compounds -*"essential and nonessential compounds that are found in nature or are created during the processing of foods or medicinal plants"*-, and modulate many biological activities, providing health benefits (Biesalski et al. 2009; Martín Ortega and Segura Campos 2019).

The main compounds of wine pomace include water, dietary fiber, proteins, essential oils, minerals, soluble sugars, and polyphenols **(Table 1)**. The most important bioactive compounds of wine pomace are polyphenols and fiber (Del Pino-García et al. 2017; Del Pino-García et al.

2016a; Deng, Penner, and Zhao 2011; García-Lomillo et al. 2014; Jin et al. 2018; Saura-Calixto 2011). Their composition depends on the type of grape variety, environmental factors (harvesting, genetic factors, environmental conditions, degree of plant maturation), and on the winery techniques (Aditya et al. 2018; Chamorro et al. 2012; Chedea et al. 2018; De Sales et al. 2018; Doshi et al. 2015; Gerardi 2020a; Gil-Sánchez et al. 2017; González-Paramás et al. 2004; Jara-Palacios et al. 2015; Jara-Palacios et al. 2016; Jara-Palacios et al. 2014; Kadouh et al. 2016; Kammerer et al. 2004; Ky et al. 2014; Lee et al. 2017; Makris, Boskou, and Andrikopoulos 2007; Negro, Tommasi, and Miceli 2003; Peixoto et al. 2018; Pérez-Navarro et al. 2019; Rockenbach et al. 2011; Ruberto et al. 2007; Teixeira 2014; Wei et al. 2017; Zhang et al. 2015; Zhu et al. 2012). These different compositions in these by-products result in products with different valorization and with different potential *in vivo* health effects.

With regard to polyphenolic compounds, red wine pomaces have a greater content than white wine pomaces (**Table 2**). Nevertheless, the lower content of white wine pomace not necessarily reduce their biological activities (Gerardi 2020a; Gerardi et al. 2020b). In that sense, anthocyanins are the most abundant polyphenolic compounds of red wine pomaces, while flavanols are the main in the white wine pomace (Amico et al. 2008; Cantos, Espín, and Tomás-Barberán 2002; Del Pino-García 2017; Teixeira 2014). Anthocyanin content also varies with the contact time in the winemaking process: longer contact times reduces the anthocyanin content of the wine pomaces (Yu and Ahmedna 2013a). In a study with eighteen wine pomace by-products from red and white cultivars, the authors observed a flavanol content of 29-199 mg/100 g of dry matter, where proanthocyanidin B2 was the most abundant among the dimmers, and catechin and epicatechin among the monomers (González-Paramás et al. 2004). As non-anthocyanic polyphenolic in red wine pomaces catechin and epigallocatechin are the most abundant (Gerardi 2020a; Rockenbach 2011). With regard to the phenolic acids, the most abundant are gallic, protocatechuic, vanillic, syringic and gentisic acids, observing some

differences between red and white wine pomaces (Gerardi 2020a; Machado and Domínguez-Perles 2017).

Phenolic content also differs between winery by-products obtained from different wine pomace materials (skins or seeds) (**Table 2**). Some authors observed a higher content of polyphenols in the seed pomaces compared with the skin pomaces (Teixeira 2014). However, other authors showed that skins have more polyphenols than seed pomaces (Del Pino-García 2017; Guaita and Bosso 2019). In general, skin pomaces are richer in phenolic acids, mainly hydroxycinnamic (Carmona-Jiménez et al. 2021; Castillo-Muñoz et al. 2009; Gerardi 2020a; Jara-Palacios 2015; Kammerer 2004; Rockenbach 2011; Teixeira 2014) and stilbenes (resveratrol and piceid) (Katalinić et al. 2010) and in anthocyanins. While flavanols are more predominant in the wine seed pomace (Del Pino-García 2017), with the exception of epigallocatechin that only has been found in the skin pomace (Gerardi 2020a; Rockenbach 2011). Del Pino-García et al. (2017) observed a different flavonols composition between skin and seeds, a higher concentration of monomers than dimmers flavanols in the skin pomace, and the opposite for the wine pomace obtained from the seeds.

Fiber is another type of non-essential compound, present in wine pomace, with important physiological effects (Zhu et al. 2015). There are clear associations between dietary fiber intake and colonic health, gut motility and risk for cardiovascular diseases (Chambers et al. 2018; Das et al. 2020). The polysaccharide fiber type determines its degree of fermentation by the intestinal microbiota (Goñi, Martín, and Saura-Calixto 2005; Palafox-Carlos et al. 2011). The dietary fiber content of wine pomace also varies depending on the grape cultivar, growth climates, and processing conditions. While red wine pomaces are rich in total dietary, fiber (TDF), white varieties have mainly soluble sugars (up to 55%) (**Table 1**) (Deng 2011). For instance, red wine pomace undergoes a period of fermentation whereas white wine pomace is removed before alcoholic fermentation (Moreno, Ballesteros, and Negro 2020). Furthermore, differences

148 in harvest and winemaking practices could explain the different composition between wine
149 pomaces derived from diverse cultivars. Nevertheless, in both types of wine pomaces, the total
150 dietary fiber (TDF) is composed predominantly of insoluble dietary fiber (IDF) (up to 98,5%),
151 while the soluble dietary fiber (SDF) only constitute a small fraction (Deng 2011; Jin et al. 2019;
152 Sheng et al. 2017). The predominance of glucose indicates that cellulose is the major constituent
153 of IDF, while the presence of xylose and galactose in the IDF evidence the existence of
154 hemicellulose, principally in the skin pomace (Deng 2011).

155 Furthermore, fiber compounds in wine pomaces make chemical bonds with phenolic
156 compounds forming antioxidant dietary fibers (Saura-Calixto 2011). Therefore, the bioactivity of
157 polyphenols and fiber from these wine by-products are interrelated. It is proposed that one of
158 the main functions of dietary fiber is the transport of dietary antioxidant through the digestive
159 tract, allowing their release from the fiber matrix within the colon by the action of bacterial
160 microbiota, generating bioactive metabolites and an antioxidant environment (Saura-Calixto et
161 al. 2010; Urquiaga et al. 2015).

162 **3. Bioavailability and metabolism of bioactive compounds from wine pomace**

163 Bioactive compounds have to survive food processing, in order to exert biological activities, and
164 they have to be released from the food matrix and remain accessible in the gastrointestinal tract,
165 undergo metabolism, and finally reach the target tissue (**Figure 1**). Hence, a bioactive compound
166 cannot produce an effect, unless it is bioavailable -*"the rate and extent to which the bioactive*
167 *compound is absorber and becomes available at the site of action"*- (Rein et al. 2013; F*aDA.*
168 2002) and includes several processes known as LADME phases: liberation from the food matrix,
169 absorption, distribution, metabolism and elimination. The rate and the extent to which different
170 bioactive compounds, obtained from winemaking industry, can be absorbed vary between
171 individuals and could to depend on diet, genetic background, and gut microbiota composition
172 and activity, among others (Fraga 2019; Ozdal et al. 2016; Rein 2013; Teng and Chen 2019).

The wine pomace compounds bioavailability is influenced by their bioaccessibility -*"the fraction of a compound which is released from the food matrix in the gastrointestinal lumen and thereby made available for intestinal absorption"*- (Rein 2013; Saura-Calixto 2007). Bioaccessibility is affected by the composition of food matrix and the interactions between the different components of the food matrix (Fernández-García, Carvajal-Lérida, and Pérez-Gálvez 2009; Neilson and Ferruzzi 2011). Thus, the biological efficiency of wine pomace products, depends on the intake and chemical structures of their bioactive compounds, mainly polyphenols and fiber, that determine their intestinal absorption process (Cantos 2002; Gonzales et al. 2015; Marín et al. 2015; Scalbert et al. 2002) or enzymatic microbial biotransformation (Fraga 2019; Saura-Calixto 2007).

Bioavailability of wine pomace polyphenols depends of dietary intake and differs among winery by-products. Thus, studies in rats evaluated the effect of the intake of different doses of wine pomace on polyphenol bioavailability showed a dose-response effect in the plasma and urine profile of phenolic acids after red wine pomace intake but not after white wine pomace intake (Gerardi 2020a). These authors also observed that the bioavailability of phenolic acids of white wine pomace intake came before that red wine pomace with their maximum in plasma at 2 hours and 4 hours respectively. Furthermore, the wine pomace polyphenol bioavailability is dependent of the intestinal absorption and of their bioactive metabolites resulted of digestive and hepatic metabolic processes. In general, the plasma phenolic profile, after intake of wine pomace product, is dependent of the grape variety, winery process, and even the presence of an extraction process (Alonso et al. 2002; Del Pino et al. 2016; Deng 2011; Gerardi 2020; Jara-Palacios 2015). In this sense, phenolic acids of wine pomace include polymers, esters, and glycosides that are hydrolyzed by gastrointestinal enzymes and further modified by the intestinal microbiota (Castello et al. 2018). The metabolization of these compounds increases their hydrophilicity and facilitates urinary and/or biliary elimination (Manach et al. 2004). Thus, flavonoids such as the anthocyanins, the principal type of phenolic compounds in the red wine

199 pomace, are metabolized in the upper gastrointestinal tract and their metabolites include 4-
200 hydroxyhippuric and ferulic acids derivates, that reach their maximum in plasma at 1-1.5 hours
201 after consumption (Ozdal 2016). In another hand, the anthocyanidins can be metabolized by
202 microbiota into phenolic acids such as syringic, vanillic, protocatechuic, and coumaric acids,
203 thereby contributing to the total content of phenolic acids in the plasma sample (Fernandes et
204 al. 2017). Other wine pomace compounds, flavonols (kaempferol-3-O-rutinoside) and flavanols
205 (epigallocatechin, catechin, epicatechin, procyanidins) also contribute to the total phenolic acid
206 content of plasma derivates from the microbial catabolism (Cueva et al. 2017; Fernandes 2017).
207 It has been suggested that *"colonic metabolism* [of polyphenols] *could be considered as the*
208 *missing link between the consumption of certain polyphenols and their biological activity"* (Rein
209 2013; Williamson and Clifford 2010). The polyphenol elimination can be through two pathways:
210 renal and biliar. Taking these into account, the levels of different phenolic acids in urine not only
211 depend on their urinary excretion ratio, but they also depend on their capacity to bind plasma
212 proteins and the amount eliminated by biliary excretion (Crespy et al. 2003). Polyphenolic
213 metabolites generated after bioavailability showed different biological actions (**Figure 2**) (Del
214 Pino-García 2016c; Gerardi 2020a; Rasines-Perea et al.,2018; Rodriguez Lanzi et al. 2018). These
215 stable metabolites have the potential to act directly as antioxidants or to interfere with signaling
216 pathways, receptors, enzymes and transcription factors (Hunyadi 2019). High levels of phenolic
217 acids in plasma have been associated with a high plasma antioxidant capacity and with a high
218 prevention of lipid peroxidation and nitric oxide bioavailability in rats after oral administration
219 of wine pomace product (Del Pino-García et al 2016b; Gerardi 2020b).

220 The health contribution of bioavailability of wine pomace fiber is mainly by microbial
221 fermentation of no-digestible carbohydrates that contribute to the production of bioactive
222 compounds. In general the main effects of dietary fiber is to prolong the gastric emptying time
223 and to retard the absorption of nutrients and to reduce glucose and cholesterol levels (Birkett
224 et al. 1997; Fuller et al. 2016; Lecumberri et al. 2007; Llobera and Cañellas 2007; Oh et al. 2019;

225 Stewart et al. 2010). In the colon, the dietary fiber is fermented by the microbiota and enhances
226 the production of microbial metabolites, such as short-chain fatty acids (SCFAs) providing a
227 source of energy for colonocytes and by passing through the colonic epithelium into the
228 bloodstream, they also influence lipid, glucose and cholesterol metabolism through effects on
229 G protein-coupled receptors (Barber et al. 2020). A study of red wine pomace bioavailability in
230 rats showed that after 4 weeks of consumption, the contents of SCFAs in fecal rats increase a 20
231 % mainly due to the higher butyric acid concentration (Del Pino 2016c). Furthermore, these
232 authors observed that the relative faecal content of butyric acid in diabetic rats was increased,
233 and acetic acid was decreased, obtaining a molar ratio of butyric:propionic:acetic acid similar to
234 no diabetic rats. Considering that, dietary fiber acts entrapping polyphenols in their matrix and
235 because of that, the gastrointestinal enzymes cannot release the fiber-associated polyphenols,
236 and the polyphenols are not bioavailable in the gut and small intestine until colonic bacterial
237 fermentation (Saura-Calixto 2007). Short chain fatty acids (SCFAs) are the mainly bioactive
238 compounds released due to partial or complete fermentation of TDF and they can act
239 synergistically with polyphenols modulating the expression of genes involved in certain diseases
240 (Tang et al. 2011).

241 **4. Wine pomace modulates the oxidative stress response through redox signaling pathways**

242 Growing evidence indicates that the bioactive compounds such as polyphenolic metabolites
243 might modulate redox state systems *in vivo* (Fraga, Oteiza, and Galleano 2018). Cell oxidative
244 stress is classified by its intensity, from physiological oxidative stress or eustress to toxic
245 oxidative stress or distress with biomolecule damage and disrupted redox signaling
246 (pathological). Sarsour, Kalen, and Goswami (2014) along with Niki (2016) proposed the term
247 oxidative eustress, as a definition of beneficial cell responses to oxidant generation including
248 redox processes which regulate normal physiological functions. In contrast, oxidative distress
249 was defined as *"a cell response resulting from irreversible modifications and damage to*

biomolecules under pathological conditions". In addition, there are many sub-forms of oxidative stress, associated with their different forms and ways in which they are generated.

In physiological concentrations, reactive oxygen and nitrogen species (RONS) can act as signaling molecules in redox signaling pathways and have essential functions at basal levels including cell metabolism, gene expression, cell cycle progression, cell survival, proliferation and differentiation, cytoskeletal organization, immune defense angiogenesis, and vessel relaxation, among others (**Figure 3A**), (Battino et al. 2018; Belleza et al. 2018; Bogdan 2015; Moldogazieva et al. 2018; Schieber and Chander 2014; Takada 2003; Tu et al. 2019; Zhang et al. 2019b). Excessive levels of RONS can produce changes in redox status acting as signals that inducing cellular damage and various diseases including inflammation, autoimmunity, tumorigenesis, endothelial dysfunction, atherosclerosis, and hypertension, kidney fibrosis, among others (**Figure 3B**). This excessive increase in the levels of RONS lead to oxidative stress, which is a mediator of oxidative damage of biological targets and modulation of pathways such as the mediated by transcription factors AP-1 (activator protein 1), NF-κB and Nrf2 (Sies 2018; Yin et al. 2017).

In this regard, the modulation of the cell redox state by wine pomace is due mainly to the polyphenolic metabolites resulted from their bioavailability by direct or indirect mechanisms. The direct mechanism involves the reaction with RONS giving a less reactive product or the chelation of transitions metals (Fe^{2+} or Cu^{+}). This direct activity is attributed to the presence of hydroxyl groups in the benzene ring that are capable of donating either one hydrogen or a single electron to RONS, thereby stabilizing the free radical molecules (Forman, Davies, and Ursini 2014; Sandoval-Acuña, Ferreira, and Speisky 2014). Nevertheless, a growing body of evidence indicates that the bioactivity of wine pomace polyphenols might also related oxidant/antioxidant production (Fraga 2018). Depending on their concentrations, chemical structures and under the conditions that favor their autoxidation, at high pH, at high concentrations of transition metals or at high concentration of oxygen, some polyphenols also

act as prooxidants *in vitro* (Ayuda-Durán et al. 2019; Jara-Palacios et al. 2013; Pizzino et al. 2017; Tang and Halliwell 2010). Moreover, the prooxidant effect of grape pomace extract might be beneficial because it triggers the preconditioning mechanisms (Gems and Partridge 2008; Veskoukis et al. 2012). Still, further studies are necessary for evaluated the therapeutic effect of grape pomace product under distress oxidative conditions.

The indirect mechanisms of wine pomace polyphenols can be by inhibition of oxidant enzymes, activation enzymatic and non-enzymatic antioxidant systems and regulation of gene expression of antioxidants by interaction with redox signaling pathways **(Figure 4)** (Del Pino-García 2016; Del Pino-García 2017b; García-Lomillo 2014; Kabir, Sultana, and Kurnianta 2015; Zhang et al. 2011).

Some authors observed a modulation of the Nrf2/NF-κB crosstalk by bioavailability fractions of wine pomace in culture cells with a consequent increase in the expression of antioxidant molecules and reduction of pro-oxidant and pro-inflammatory pathways (Del Pino-García 2016; Gerardi et al. 2019). Moreover, wine pomace bioavailability fraction upregulates Nrf2 pathway while downregulate NF-κB pathways by both regulating their gene expression and by their activation and nuclear translocation (Gerardi 2019). The mechanism of action is acting directly or on transmembrane receptors and trigger the activation or inhibition of signal transduction kinases/phosphatases (**Figure 4**). In that regards, different studies showed that wine pomace polyphenols activate protein kinases MAPK (ERK1/2, p38 and JNK) or PI3K/Akt involved in the modulation of AMPK/FOXO1/mTOR/SIRT1 pathways and later activation of transcription factors Nrf2/NF-κB, AP-1, HIF-1α, p53, Wnt/β-catenin (Bak, Jun, and Jeong 2012; Chen et al. 2017; Chung et al. 2010; Dai et al. 2018; Del Pino-García 2016b; Haegeman et al. 2010; Kårlund et al. 2015; Maleki, Crespo, and Cabanillas 2019; Vargas et al. 2018; Wang, Zhong, and Zhao 2017; Weng and Yen 2012). Thus, flavonols presents in wine pomace inhibit MAPK pathways stimulated by IL-1β or INF-γ in inflammatory rheumatoid arthritis by reduction of the ERK1/2,

p38 and JNK phosphorylation (Mateen et al. 2016). In contrast, wine pomace activate MAPK (p38 and ERK1/2), through changes in redox status cell, in human umbilical vein endothelial cells (HUVECs) by modulating the Nrf2/HO-1 gene expression (Cao et al. 2019; Gerardi 2019). Other flavonoids presents in wine pomace product such as quercetin inhibits PTEN phosphatase and PI3K/Akt/eNOS pathway (Cao 2019) involved in angiogenesis and tumor growth (Bjørklund and Chirumbolo 2017; Maaliki et al. 2019).

Wine pomace product also modulate the cell redox status by regulation of the Nrf2 and NF-κB transcription factors and modulating superoxide dismutase (SOD1 and SOD2), catalase (CAT), HO-1 expression, among others (Del Pino-García 2016; Gerardi 2019; Goutzourelas 2015; Groh et al. 2020; Hegazy et al. 2019). In that regards, the presence of wine pomace flavonoids such as quercetin, flavanols, resveratrol and, proanthocyanidins activate Nrf2 by direct modulation (Fraga 2018) or via up-regulation of their mRNA and stabilization of Nrf2 protein. Moreover, it has been observed that wine pomace metabolites improved the redox balance, ameliorated protein oxidation, lipid peroxidation and cell membrane damage, and restored the balance between endothelial RONS and NO production in hyperglycemic cells through gene modulation of SOD1, SOD2, CAT, HO-1, NOX4, cyclooxygenase 2 (COX2) and endothelial nitric oxide synthase (eNOS) (Del Pino-García 2016; Gerardi 2019). Additionally, wine pomace by modulation of cell redox status, inhibit the NF-κB activation, and as consequence have the inhibition of specific steps in the NF-κB cascade (Gerardi 2019). In that regard, different authors have observed that some polyphenols presents in wine pomace as epicatechin interacts with NF-κB and reduces the binding of NF-κB to the DNA κB site (Fraga 2018; Mateen 2016).

Wine pomace can moreover modulate redox signaling, by their inhibitory effects on enzymes that generate RONS (**Figure 4**) such as NOX, NOS, COX, or LOX (Gerardi 2019). This could to be explained by the presence of polyphenols epicatechin or anthocyanins that reduce the RONS generation and act as competitive inhibitor of the NOX and inflammatory cyclooxygenase (COX)

enzymes (Furuuchi et al. 2018; Gómez-Guzmán et al. 2012). In that regard, the decreased of NOX activation by wine pomace product in aorta, heart, liver, kidney and adipose tissue, could have preventive effect on oxidative damage generated in hypertension, endotoxemia or diet-induced obesity (Fraga 2018). In addition, wine pomace prevents cell membrane alterations, by reducing lipid oxidation due to RONS, and regulates calcium fluxes that prevent NOX and protein kinase C (PKC) activation (Fraga 2018; Verstraeten et al. 2008). Another wine pomace mechanism of action is to modulate the levels of nitric oxide synthase (NOS) by activation of eNOS (Gerardi 2020). In contrast, it attenuates the expression of iNOS after different inflammatory stimuli and modulates uncontrolled immune response (Cao 2019; Fraga 2018; Maaliki 2019).

Recently, the wine pomace epigenetic modulation by regulation of HDACs and NMTs activity or by microRNAs expression is of great interest as news mechanism of action (Arora, Sharma, and Tollefsbol 2019; Lubecka et al. 2018; Milenkovic, Deval, and Gouranton 2012; Ratovitski 2017; Sheng et al. 2019; Su et al. 2017). In that regards, some human studies of supplementation with wine pomace showed changes in the expression of several miRNAs related to glucose metabolism (miRNA-130a-3p, miRNA-122-5p, miRNA-34a-5p, miRNA191-5p and miRNA-342-3p) (Gil-Sánchez et al. 2018; Ramos-Romero et al. 2021). In addition, miRNA regulation by wine pomaces was also observed against inflammatory processes, including the upregulation of mir-376c, which regulates the expression of mRNA of inflammatory chemokines, chemokine receptors, interleukins, and interleukin receptors (Gessner et al. 2017). In addition, epigenetic modulation of individual compounds that are present in the wine pomace, it has been more studied. Thus, epigallocatechin gallate (EGCG) increased the expression of miR-133a/b and reduce Smad3 signaling leading to the amelioration of inflammation and fibrosis in rats with prostatic hyperplasia (Zhou et al. 2018). Several *in vitro* and *in vivo* studies showed the effect of compounds such as quercetin in the modulation of multiple cancer-associated miRNA including let-7, miR-155, and miR21 leading to the reduction of cancer initiation and development (Kim et al. 2019). Furthermore, resveratrol controls cancer proliferation by inducing tumor-suppressive

352 miRNAs such as miRNA-34, miRNA-663, and miRNA-744 (Esmerina Tili et al. 2013; Farooqi,
353 Khalid, and Ahmad 2018; Otsuka, Yamamoto, and Ochiya 2018)..

354 **5. Wine pomace as modulator of oxidative stress-related disorders**

355 Disorders associated with oxidative stress by changes in cell redox equilibrium have
356 consequences at different levels, including cellular, tissue, and systemic alterations. First, the
357 modification of the redox status in the cells leads to the pathological expression of molecules,
358 such as proinflammatory cytokines and oxidant enzymes, which alter the function and the
359 structure of different tissues (epithelial, muscular, nervous tissue). Those pathological
360 alterations are exacerbated by persistent oxidative stress that alters proteins and other cellular
361 components, causing cellular dysfunction (Aykin-Burns et al. 2009; Dalle-Donne et al. 2006;
362 Dikalov et al. 2014; Kuo et al. 2014; Tang et al. 2013; Valko et al. 2007; Welch 2008). Cells
363 progressively lose their physiological activities and can finally to induce apoptosis to cytotoxic
364 levels of oxidative stress or activate the proliferation of cells at levels of oxidative stress
365 persistent. Both options alter the physiological functions of the tissue and cause organ failure
366 and systemic diseases (**Figure 5**).

367 The capacity of wine pomace to modulate the oxidative stress through redox signaling pathways
368 plays an important role in the prevention of chronic diseases involved in cardiovascular diseases
369 include endothelial dysfunction, inflammation, hypertension, hyperglycemia, and obesity (Cani
370 et al. 2012; Del Pino-García 2016b; Gerardi 2020; Pal, Naissides, and Mamo 2004).

371 ***Endothelial dysfunction***

372 Endothelium is a selectively permeable barrier between the vascular wall and the bloodstream
373 that regulates vascular tone, cell growth, vascular wall permeability, and interaction between
374 leukocytes, thrombocytes, and the vessel wall (Endemann and Schiffrin 2004; Yang, Chang, and
375 Wei 2016).

The endothelial dysfunction can be considered a consequence of three interrelated processes: impaired nitric oxide (NO) signaling with eNOS uncoupling, oxidative stress, and inflammation (**Figure 6**) (Ding et al. 2004; Higashi et al. 2009). Endothelial dysfunction is associated with the development of atherosclerosis, hypertension, and cardiovascular events. It is likewise associated with aging-related disorders such as erectile dysfunction, renal dysfunction, Alzheimer´s disease, and retinopathy (Burnett 2006; Coleman et al. 2008; Karbach et al. 2014; Price et al. 2004; Steven et al. 2019) (**Figure 7**).

Wine pomace obtained from by-products showed great potential as source of bioactive compounds that protect the vascular endothelial function against endothelial dysfunction by stimulating Nrf2/ARE pathway and inhibiting the IKK/IκB/NF-κB pathway (Gerardi 2019). Wine pomace product in endothelial cells mediated up-regulation of cellular antioxidant genes (HO-1, NQO-1, SOD, CAT) through the promotion of the transcriptional activity of Nrf2 and down-regulation of the inflammatory process gene expression (COX-2, NADPH oxidase) mediated by NF-κB pathway. This modulation by wine pomace products could be due to the content of phenolic compounds such ferulic acid that decrease the phosphorylation of NF-κB under conditions of oxidative stress (Cao et al. 2015), or by the content of stilbenes that could to attenuate the phosphorylation, acetylation and nuclear translocation of NF-κB studies (Chung 2010; Shanmugam, Kannaiyan, and Sethi 2011).

Wine pomace product also inhibits the endothelial dysfunction by increasing the nitric oxide levels and decreasing superoxide production (Rahman, Biswas, and Kirkham 2006; Son et al. 2010). Thus, in *ex vivo* studies, arteries were treated with grape pomace extract at concentrations of 0.1-30 mg/L observing a relaxation in aortic rings in dose-dependent mechanisms by the activation of eNOS (Rodriguez-Rodriguez et al., 2012). The activation of eNOS phosphorylation by wine pomace was observed as resulted PI3K/Akt pathway activation (Gerardi 2019; Gerardi 2020). On the other hand, the wine pomace mechanism involved in the

401 reduction of superoxide production is by reduction of the NADPH oxidase activity through the
402 interaction with MAPK and downregulation of transcription factors, such as NF-kB (Hussain et
403 al. 2016). Furthermore, wine pomace could prevent endothelial permeability increase and cell
404 infiltration by improving endothelial cell-cell junctions. Wine pomace products showed a
405 protective effect on adherent junction in endothelial cells cultures by increasing the expression
406 of endothelial cadherin (VE-cadherin) (Gerardi 2020b).

407 Endothelial dysfunction is also associated with proinflammatory and prothrombic states that
408 results in aberrant endothelium activation (Crimi, Ignarro, and Napoli 2007; Steven 2019).
409 Inflammation is a biological adaptive response of vascular tissues to any alteration of tissue
410 integrity, in order to restore homeostasis through the induction of various repair mechanisms
411 and results in the increased of the expression of pro-inflammatory mediators cytokines and
412 RONS (**Figure 8**) (Lugrin et al. 2014). Chronic inflammation is involved in the pathogenesis of
413 several diseases such as type 2 diabetes, cardiovascular diseases, and obesity-related disorders
414 (Hussain 2016) (**Figure 9**).

415 Wine pomace diet supplementation modulates the systemic inflammatory status by the
416 reduction in the expression of several proinflammatory cytokines (TNF-α; IL-1) (Gerardi et. al.
417 2020c; Rivera et al. 2019; Rodriguez-Morgado et al 2015). Rats fed with high fat diets and
418 supplemented daily with 100 mg wine pomace product /Kg body weight for seven weeks
419 modulate the inflammatory process by reduction of cytokines TNF-α and IL-1 (Gerardi 2020c).
420 The mechanism through which the polyphenols of thr wine pomace exert their anti-
421 inflammatory action was described by different authors (Balea et al. 2020; Rivera 2019; Bettaieb
422 et al. 2016; Fechtner et al. 2017; Martins et al. 2017; Medina-Remón et al. 2015; Yahfoufi et al.
423 2018; Zhang and Tsao 2016). Wine pomace polyphenols can inhibit the arachidonic acid
424 metabolizing enzymes like cyclooxygenases (COX) and lipoxygenases (LOX) reducing the
425 production of inflammation mediators including prostaglandins, and leukotrienes. Other

426 mechanisms involved in the anti-inflammatory activity of wine pomace include suppression of
427 NF-κB and AP-1 activation, inhibition of iNOS, activation of antioxidant enzymes, and stimulation
428 of MAPK, PKC and Nrf2 (Bode and Dong 2013; Del Pino-García 2016b; Hussain 2016; Nishizuka
429 et al. 2011; Vezza et al. 2016).

430 ***Hypertension***

431 Vascular alterations associated with hypertension include endothelial dysfunction, vascular
432 smooth muscle cells (VSMCs) stiffness and adhesion, increased vascular RONS, and endothelin
433 1 (ET-1) expression (**Figure 10**) (Endemann 2004; Larivie`re, Thibault, and Schiffrin 1993; Schiffrin
434 2012; Touyz and Schiffrin 2004; Xu and Touyz 2006).

435 The anti-hypertensive actions of wine pomace extract have been reported in various studies
436 (Cassidy et al. 2011; Del Pino-García et al. 2017a; Gerardi 2020; He 2017; Javkhedkar et al. 2015;
437 Maaliki 2019; Paredes et al. 2018). The action mechanism involves reduction of angiotensin I-
438 converting enzyme (ACE) activity and gene modulation of SOD, HO-1, NOX4, and eNOS (Del Pino-
439 García 2017a; Rasines-Perea 2018). These effects could be due to the synergy effect of the
440 phenolic compounds such as resveratrol, flavan-3-ols, flavonols, anthocyanidins and their
441 degradation metabolites (Appeldoorn 2009;Edwards et al. 2015; Loft et al. 2008; Patel et al.
442 2013).

443 Furthermore, the intake of wine pomace is associated with lowering systolic blood pressure. In
444 this regard flavonols of wine pomace, such as epicatechin, increased eNOS activity and reduced
445 superoxide production in the aorta of spontaneously hypertensive rats (Galleano, Puzserova,
446 and Balis 2013). Other wine pomace compounds, EGCG activats PI3K/Akt/NO/cGMP and inhibits
447 phosphodiesterase (PDE) activity, modulating vascular contractibility (Álvarez et al. 2006;
448 Romano and Lograno 2009). Quercetin showed that improves endothelial function, modulates
449 RAAS, regulates VSMC contractibility, increases aortic eNOS and NO plasma, and suppresses
450 RONS production by NADPH oxidases.

Wine pomace also prevent cardiovascular risk factors associates with the vascular remodeling and endothelial function activity (Del Pino-Garcia 2016; Gerardi et al 2010; Spinetti et al., 2010;). Vascular remodeling is an active process that response to physiological and pathological changes in the hemodynamics conditions as consequence of different stimuli like hypertension, and other inflammatory diseases (Van Varik et al., 2012). Large central arteries of hypertensive rats undergo arteriosclerotic changes with outward hypertrophic remodeling characterized by increased cross sectional area and lumen diameter (O'Rourke and Hashimoto, 2007). The diet supplementation with wine pomace used in models of hypertensive and streptozotocin-diabetic rats prevents the vascular remodeling by reducing of wall aortic thickness, cross sectional area and wall/lumen ratio, and decreases ROS and increases eNOS activation (Garrido and Borges 2013; Gerardi 2020; Serino-Salazar 2019; Spinetti 2010). Thus, the reduction of this alteration by the wine pomace could contribute to a less incidence of cardiovascular complications. Several mechanisms are involved in the activity of wine pomace including reduction of the gene expression of angiotensin converting enzyme (ACE), NADPH oxidase activity inhibition, reduced expression of NF-kB, stimulation of SOD2 and increased NO production (Del Pino-Garcia 2016; Gerardi 2019; Gerardi 2020; Serino-Salazar 2019; Spinetti 2010). Hence, there is a reduction of prooxidant and proinflammatory activity with a decrease of the reactive oxygen species and the inhibition of mitogen activated protein kinases (MAPK) activity that leads to inhibition of the growth of SMCs and the vascular remodeling (Balasuriya and Rupasinghe, 2011; Del Pino-Garcia 2017; Stangl 2007).

Hyperglycemia

Hyperglycemia implies the alteration of normal glucose levels and constitutes one of the main characteristics of diabetes. Hyperglycemia is also commonly linked to hyperlipidemia and obesity. Both, diabetes and hyperlipidemia are cardiovascular risk factors associated with inflammatory processes, by inducing the expression of proteins and inflammatory molecules in the endothelium that leads to leukocyte adhesion and infiltration. The autoxidation of glucose

has a dual role in the pathogenesis of hyperglycemia. On the one hand, the oxidation of monosaccharides such as glucose produces many types of RONS, thereby contributing to the oxidative stress (Exner et al. 2001; Hunt, Dean, and Wolff 1988). On the other hand, the oxidation of glucose participates in protein glycosylation contributing to protein damage (Wolff and Dean 1987) (**Figure 11**).

Wine pomace decreases hyperglycemia and improves insulin secretion, and insulin sensitivity (Aryaeian, Sedehi, and Arablou 2017; Del Pino-García 2016; Del Pino-García 2016b). The possible mechanisms include decrease of intestinal absorption of glucose; inhibition of carbohydrate digestion; stimulation of insulin secretion; modulation of glucose release from the liver; activation of insulin receptors and glucose uptake; and modulation of intracellular signaling pathways and gene expression. Winery by-products studied by Doshi (2015) showed antioxidant and insulinotropic effects, leading to an increase in the release of insulin in isolated mice pancreatic islets. Kadouh (2016) suggested potential effects of the red wine pomace in the prevention and treatment of diabetes through inhibition of α-glucosidase in rat intestines.

In addition, the protective effects of the wine pomace in hyperglycemic cells include the modulation of several signaling pathways. The mechanisms through which the polyphenols could regulate the Nrf2 and NF-κB pathways in the hyperglycemic cells are as follows: 1) Nrf2 and NF-κB activities might depend on the modulation exerted by several kinases such as Akt, PKA, PKC, MAPK that phosphorylate Nrf2 and NF-κB at specific sites; 2) might increase the expression of sirtuins (SIRT1 and SIRT2) that regulate the deacetylation of the NF-κB transcription factor, leading to a reduction of ROS and inflammatory cytokines. In addition, the inhibition of Nrf2 ubiquitination by SIRT1 might increases Nrf2 availability, favoring nuclear translocation of Nrf2 (Huang, Gao, and Wei 2017); 3) The activator CBP complex is used by both transcription factors, thus an overexpression of Nrf2 induced by bioactive compounds of wine pomace might limits the availability of CBP complexes for NF-κB (Wardyn, Ponsford, and

Sanderson 2015). The reduction of pro-oxidant and proinflammatory actions of Ang II, and NADPH oxidase involves less generation of RONS, decreased activity of the MAPK and consequent reduction of the protooncogens c-fos, c-jun and c-myc that leads to reduce growth of the remodeling (Domínguez-Avila et al. 2016; Schiffrin 2012).

Obesity

Obesity is described as a state of chronic low-grade inflammation and is related to increased vascular risk, due to vascular alterations such as endothelial dysfunction, vascular stiffening, and vascular remodeling, dysregulation of adipose tissue signaling, altered metabolism such as insulin resistance and hyperlipidemia, and hypertension (Reho and Rahmouni 2017). Oxidative stress is associated with the development of co-morbidities in obesity. Alterations in several signaling pathways are observed, including excessive RONS production, rennin-angiotensin-aldosterone-system (RAAS) activation, inflammatory/immune signaling, and reduced NO bioavailability and activity. Various factors contribute to oxidative stress in obesity and they are summarized in **Figure 12** (Manna and Jain 2015).

The anti-obesity effects of wine pomace products obtained from by-products of the food industry have been observed by various studies (Gerardi et al. 2020c; Hsu et al. 2009; Jin 2018; Zhang 2019a; Zhao et al. 2017). They may be attributed to the direct and indirect interaction of wine pomace compounds with the adipose tissue (Gerardi 2020c). Among the various mechanisms that have been proposed are: suppression of dietary fat absorption; enhancing fat oxidation in adipose tissue and skeletal muscle; increasing glucose utilization; decreasing de novo lipogenesis; inhibition of adipocyte differentiation by C/EBPβ and PPARγ downregulation; stimulation of adipocyte apoptosis and cell cycle arrest; and reduction of RONS levels and inhibition of the inflammatory process. Some polyphenols present in the wine pomace, such as flavonoids, catechins and resveratrol, reduce oxidative markers associated with obesity and diabetes in obese adults (De Groote 2012). Diet supplementation with 100-300 mg of seed

527 extract reduced postprandial glucose levels in healthy adults (Kalli 2018; Sapwarobol et al. 2012).
528 Furthermore, wine pomace reduced food intake in rats and energy intake in humans (Gerardi
529 2020c; Vogels and Plantenga 2004). The incorporation of wine pomace product in the diet of
530 high-fat diet-obese rats, reduced weight gain through amelioration of abdominal fat and
531 improving lipid profile. Moreover, the wine pomace product reduced the obesity-related
532 complications, by regulating oxidative stress, inflammatory processes, and intestinal microbiota
533 (Gerardi 2020c). Supplementation of diet-induced obese mice with grape seed flour ameliorates
534 hepatic steatosis and insulin resistance through downregulation of genes involved in triglyceride
535 and ceramide synthesis, the immune response, oxidative stress and inflammation, and
536 upregulation of genes associated with fatty acid oxidation, and cholesterol and bile synthesis
537 (Seo et al. 2016).

538 **6. Conclusion**

539 There are many cellular mechanisms involved in the antioxidant and anti-inflammatory actions
540 of the wine pomace products obtained from winemaking industry. Several molecules and
541 intracellular pathways are modulated (Nrf2, NF-κB, MAPK, Akt, SIRT1, eNOS, NOX, etc), which
542 could explain the protective effects of these compounds in the vascular endothelium and other
543 epitheliums. Furthermore, the wine pomace products can improve epithelium integrity through
544 the regulation of the expression of cell-cell interaction proteins. Therefore, these by-products
545 from winemaking industry could be used for the prevention of vascular injury associated with
546 oxidative stress and inflammation.

547 The findings confirmed in this systematic review indicate the health effects of wine pomace
548 products against diseases associated with oxidative stress and inflammatory processes. The
549 bioactive compounds of these products exert their antioxidant action through the modulation
550 of signaling pathways, increasing endogenous antioxidant systems, decreasing RONS
551 production, and enhancing NO bioavailability, among others. Through those mechanisms,

552 polyphenols show a capability to improve pathological states and metabolic disorders, such as

553 diabetes, hypertension, obesity, cancer, and infection and inflammatory processes.

554 **Abbreviations**

ACE	angiotensin I converting enzyme
AGE	advanced glycation end-products
Akt	protein kinase B
AMPK	AMP-activated protein kinase
Ang II	angiotensin II
AP-1	activator protein 1
ARE	antioxidant responsive element
BH4	tetrahydrobiopterin
CAT	catalase
cGMP	cyclic guanosine monophosphate
COX2	cyclooxygenase 2
DAG	diacylglycerol
DNMT	DNA methyltransferase
EC	epicatechin
EGCG	epigallocatechin gallato
EMT	epithelial mesenchymal transition
eNOS	endothelial nitric oxide synthase
ET-1	endothelin 1
GPCR	G protein-coupled receptors
HDAC	histone deacetylases enzymes
HF	high-fat
HIF-1α	hypoxia-inducible factor 1-alpha
HO-1	hemo oxigenase 1
HUVEC	human umbilical vein endothelial cell
ICAM	intercellular adhesion molecule 1
IKKα	IκB kinase alpha
IKKβ	IκB kinase beta
IL-1β	interleukin 1 beta
INF-γ	interferon gamma
iNOS	inducible nitric oxide synthase
IP3	inositol triphosphate
IκBα	inhibitor of kappa B alpha
Keap-1	Kelch-like ECH-associated protein 1
MAPK	mitogen-activated protein kinase
miRNA	micro-RNA
NADPH	reduced nicotinamide adenine dinucleotide phosphate
NF-κB	nuclear factor-kappa B
NO	nitric oxide
NOS	nitric oxide synthase
NOX	NADPH oxidase
NQO1	NAD(P)H:quinone oxidoreductase 1
Nrf2	nuclear factor erythroid 2-related factor 2
p38-MAPK	p38 mitogen-activated protein kinase
PDE	phosphodiesterase

PI3K	phosphatidylinositol kinase
PKA	protein kinase A
PKC	protein kinase C
PTEN	phosphatase and tensin homolog
RAAS	rennin angiotensin aldosterone system
RONS	reactive oxygen and nitrogen species
RTK	receptor tyrosine kinase
SIRT1	NAD-dependent deacetylase sirtuin-1
SOD	superoxide dismutase
TNF-α	tumor necrosis factor alpha
VCAM	vascular cell adhesion molecule 1
VE-cadherin	vascular endothelial cadherin
VSMC	vascular smooth muscle cell

555

556 ## Acknowledgements

557 The authors thank the financial support of the Spain Ministry of Science, Innovation and
558 Universities (Ref. PGC2018-097113-B-I00).

559

560 ## Conflicts of interest

561 The authors declare no conflict of interest.

562

563

564

565

566 ## References

567 Aditya, S., Ohh, S. J., Ahammed, M., and Lohakare, J. 2018. Supplementation of grape pomace
568 (Vitis vinifera) in broiler diets and its effect on growth performance, apparent total tract
569 digestibility of nutrients, blood profile, and meat quality. *Animal Nutrition*, *4*(2), 210–4.
570 https://doi.org/10.1016/j.aninu.2018.01.004

571 Álvarez, E., Campos-Toimil, M., Justiniano-Basaran, H., Lugnier, C., and Orallo, F. 2006. Study of
572 the mechanisms involved in the vasorelaxation induced by (-)-epigallocatechin-3-gallate

in rat aorta. *British Journal of Pharmacology*, *147*(3), 269–80. https://doi.org/10.1038/sj.bjp.0706507

Amico, V., Chillemi, R., Mangiafico, S., Spatafora, C., and Tringali, C. 2008. Polyphenol-enriched fractions from Sicilian grape pomace: HPLC–DAD analysis and antioxidant activity. *Bioresource Technology*, *99*, 5960–5966.

Appeldoorn M., Venema, D. P., Peters, T. H. F., Koenen, M. E., Arts, I. C. W., Vincken, J. P., Gruppen, H., Keijer, J., and Hollman, P. C. H. 2009. Some phenolic compounds increase the nitric oxide level in endothelial cells in vitro. *Journal of Agricultural and Food Chemistry*, *57*, 7693–9. https://doi.org/10.1021/jf901381x

Arora, I., Sharma, M., and Tollefsbol, T. O. 2019. Combinatorial epigenetics impact of polyphenols and phytochemicals in cancer prevention and therapy. *International Journal of Molecular Sciences*, *20*(18). https://doi.org/10.3390/ijms20184567

Aryaeian, N., Sedehi, S. K., and Arablou, T. 2017. Polyphenols and their effects on diabetes management: A review. *Medical Journal of the Islamic Republic of Iran*, *31*(1), 886–92. https://doi.org/10.14196/mjiri.31.134

Aykin-Burns, N., Ahmad, I. M., Zhu, Y., Oberley, L. W., and Spitz, D. R. 2009. Increased Levels of Superoxide and Hydrogen Cancer Cells Vs . Normal Cells To Glucose Deprivation. *Biochemical Journal*, *418*(1), 319–35. https://doi.org/10.1042/BJ20081258.INCREASED

Bak, M. J., Jun, M., and Jeong, W. S. 2012. Procyanidins from wild grape (Vitis amurensis) seeds regulate ARE-mediated enzyme expression via Nrf2 coupled with p38 and PI3K/Akt pathway in HepG2 cells. *International Journal of Molecular Sciences*, *13*(1), 801–18. https://doi.org/10.3390/ijms13010801

Balasuriya, B. W. N., and Rupasinghe, H. P. V. 2011. Plant flavonoids as angiotensin converting enzyme inhibitors in regulation of hypertension. *Functional Foods in Health Disease*, 5(5), 172–188. https://doi.org/10.1234/ffhd.v1i5.132

Balea, S. S., Parvu, A. E., Parvu, M., Vlase, L., Dehelean, C. A., and Pop, T. I. 2020. Antioxidant, anti-inflammatory and antiproliferative effects of the Feteasc ă neagr ă and Pinot noir grape pomace extracts. Frontiers in Pharmacology, 11, 990.

Balea, Ş. S., Pârvu, A. E., Pop, N., Marín, F. Z., and Pârvu, M. 2018. Polyphenolic Compounds, Antioxidant, and Cardioprotective Effects of Pomace Extracts from Feteasc ă Neagr ă Cultivar. *Oxidative Medicine and Cellular Longevity*, *2018*, 8194721. https://doi.org/10.1155/2018/8194721

Barber ,T.M., Kabisch, S., Pfeiffer, A.F.H., and Weickert, M.O. The Health Benefits of Dietary Fibre. Nutrients. 2020 Oct 21;12(10):3209. https://doi.org/10.3390/nu12103209.

Battino, M., Giampieri, F., Pistollato, F., Sureda, A., Roberto, M., Oliveira, D., Pittalà, V., Fallarino, F., and Fazel, S. 2018. Nrf2 as regulator of innate immunity : A molecular Swiss army knife ! *Biotechnology Advances*, *36*(2), 358–70. https://doi.org/10.1016/j.biotechadv.2017.12.012

Bellezza, I., Giambanco, I., Minelli, A., and Donato, R. 2018. Nrf2-Keap1 signaling in oxidative and reductive stress. *Biochimica et Biophysica Acta - Molecular Cell Research*, *1865*(5), 721–33. https://doi.org/10.1016/j.bbamcr.2018.02.010

Bettaieb, A., Cremonini, E., Kang, H., Kang, J., Haj, F., and Oteiza, P. 2016. Anti-inflammatory actions of (−)-epicatechin in the adipose tissue of obese mice. *International Journal of Biochemistry and Cellular Biology*, *81*, 383–92. https://doi.org/https://doi.org/

10.1016/j.biocel.2016.08.044

Biesalski, H. K., Dragsted, L. O., Elmadfa, I., Grossklaus, R., Müller, M., Schrenk, D., Walter, P., and Weber, P. 2009. Bioactive compounds: Definition and assessment of activity. *Nutrition*, *25*(11–12), 1202–5. https://doi.org/10.1016/j.nut.2009.04.023

Birkett, A. M., Jones, G. P., De Silva, A. M., Young, G. P., and Muir, J. G. 1997. Dietary intake and faecal excretion of carbohydrate by Australians: Importance of achieving stool weights greater than 150 g to improve faecal markers relevant to colon cancer risk. *European Journal of Clinical Nutrition*, *51*(9), 625–32. https://doi.org/10.1038/sj.ejcn.1600456

Bjørklund, G., and Chirumbolo, S. 2017. Role of oxidative stress and antioxidants in daily nutrition and human health. *Nutrition*, *33*, 311–21. https://doi.org/10.1016/j.nut.2016.07.018

Bode, A. M., and Dong, Z. 2013. Signal transduction and molecular targets of selected flavonoids. *Antioxidants and Redox Signaling*, *19*(2), 163–80. https://doi.org/10.1089/ars.2013.5251

Bogdan, C. 2015. Nitric oxide synthase in innate and adaptive immunity: An update. *Trends in Immunology*, *36*(3), 161–78. https://doi.org/10.1016/j.it.2015.01.003

Burnett, A. 2006. The role of nitric oxide in erectile dysfunction: implications for medical therapy. *The Journal of Clinical Hypertension*, *8*(12), 53–62.

Cani, P. D., Osto, M., Geurts, L., and Everard, A. 2012. Involvement of gut microbiota in the development of low-grade inflammation and type 2 diabetes associated with obesity. *Gut Microbes*, *3*(4), 279–88. https://doi.org/10.4161/gmic.19625

Cantos, E., Espín, J., and Tomás-Barberán, F. 2002. Varietal Differences among the Polyphenol Profiles of Seven Table Grape Cultivars Studied by LC − DAD − MS − MS. *Journal of Agricultural and Food Chemistry*, *50*, 5691–6.

Cao, S.-Y., Zhao, C.-N., Gan, R.-Y., Xu, X.-Y., Wei, X.-L., Corke, H., Atanasov, A. G., and Li, H.-B. 2019. Effects and Mechanisms of Tea and Its Bioactive Compounds for the Prevention and Treatment of Cardiovascular Diseases: An Updated Review. *Antioxidants*, *8*(6), 166. https://doi.org/10.3390/antiox8060166

Cao, Y., Zhang, Y., Qi, J., Liu, R., Zhang, H., and He, L. 2015. Ferulic acid inhibits H2O2-induced oxidative stress and inflammation in rat vascular smooth muscle cells via inhibition of the NADPH oxidase and NF-κB pathway. *International Immunopharmacology*, *28*(2), 1018–25. https://doi.org/10.1016/j.intimp.2015.07.037

Carmona-Jiménez, Y., Palma, M., Guillén-Sánchez, D. A., and García-Moreno, M. V. 2021. Study of the Cluster Thinning Grape as a Source of Phenolic Compounds and Evaluation of Its Antioxidant Potential. Biomolecules, 11(2), 227.

Cassidy, A., O'Reilly, É. J., Kay, C., Sampson, L., Franz, M., Forman, J. P., Curhan, G., and Rimm, E. B. 2011. Habitual intake of flavonoid subclasses and incident hypertension in adults. *American Journal of Clinical Nutrition*, *93*(2), 338–47. https://doi.org/10.3945/ajcn.110.006783

Castello, F., Costabile, G., Bresciani, L., Tassotti, M., Naviglio, D., Luongo, D., Ciciolab, P., Vitaleb, M,, Vetranib, C., Galavernaa, G., Brighentia, F., Giaccoe, R., Del Rio, D., and Mena, P. 2018. Bioavailability and pharmacokinetic profile of grape pomace phenolic compounds in humans. *Archives of Biochemistry and Biophysics*, 646(March), 1–9.

https://doi.org/10.1016/j.abb.2018.03.021

Castillo-Munoz, N., Fernandez-Gonzalez, M., Gomez-Alonso, S., Garcia-Romero, E., and Hermosin-Gutierrez, I. 2009. Red-color related phenolic composition of Garnacha Tintorera (Vitis vinifera L.) grapes and red wines. Journal of Agricultural and Food Chemistry, 57(17), 7883-7891.

Chambers, E. S., Preston, T., Frost, G., and Morrison, D. J. 2018. Role of gut microbiota-generated short-chain fatty acids in metabolic and cardiovascular health. Current nutrition reports, 7(4), 198-206.

Chamorro, S., Viveros, A., Alvarez, I., Vega, E., and Brenes, A. 2012. Changes in polyphenol and polysaccharide content of grape seed extract and grape pomace after enzymatic treatment. *Food Chemistry*, *133*(2), 308–14. https://doi.org/10.1016/j.foodchem.2012.01.031

Chedea, V. S., Palade, L. M., Marin, D. E., Pelmus, R. S., Habeanu, M., Rotar, M. C., Gras, M. A., Pistol, G. C., and Taranu, I. 2018. Intestinal Absorption and Antioxidant Activity of Grape Pomace Polyphenols. *Nutrients*, *10*(588), 1–24. https://doi.org/10.3390/nu10050588

Chen, Y., Wang, X. Q., Zhang, Q., Zhu, J. Y., Li, Y., Xie, C. F., Li, X. T., Wu, J. S., Geng, S. S., Zhong, C. Y., and Han, H. Y. 2017. (-)-Epigallocatechin-3-gallate inhibits colorectal cancer stem cells by suppressing Wnt/β-catenin pathway. *Nutrients*, *9*(6), 1–11. https://doi.org/10.3390/nu9060572

Chung, S., Yao, H., Caito, S., Hwang, J. woong, Arunachalam, G., and Rahman, I. 2010. Regulation of SIRT1 in cellular functions: Role of polyphenols. *Archives of Biochemistry and Biophysics*, *501*(1), 79–90. https://doi.org/10.1016/j.abb.2010.05.003

Coleman, H. R., Chan, C. C., Ferris, F., and Chew, E. Y. 2008. Age-related macular degeneration. *The Lancet*, *372*(9652), 1835–1845.

Crespy, V., Morand, C., Besson, C., Cotelle, N., Vézin, H., Demigne, C., and Rémésy, C. 2003. The splanchnic metabolism of flavonoids highly differed according to the nature of the compound. *American Journal of Physiology-Gastrointestinal and Liver Physiology*, 284, 980–988. https://doi.org/ 10.1152/ajpgi.00223.2002

Crimi, E., Ignarro, L. J., and Napoli, C. 2007. Microcirculation and oxidative stress. *Free Radical Research*, *4*, 12–4. https://doi.org/https://doi.org/ 10.1080/10715760701732830

Cueva, C., Gil-Sánchez, I., Ayuda-Durán, B., González-Manzano, S., González-Paramás, A. M., Santos-Buelga, C., Bartolomé, B., and Moreno-Arribas, M. V. 2017. An integrated view of the effects of wine polyphenols and their relevant metabolites on gut and host health. *Molecules*, 22(99), 1–15. https://doi.org/10.3390/molecules22010099

Dai, H., Deng, H. B., Wang, Y. H., and Guo, J. J. 2018. Resveratrol inhibits the growth of gastric cancer via the wnt/β-catenin pathway. *Oncology Letters*, *16*(2), 1579–83. https://doi.org/10.3892/ol.2018.8772

Dalle-Donne, I., Rossi, R., Colombo, R., Giustarini, D., and Milzani, A. 2006. Biomarkers of oxidative damage in human disease. *Clinical Chemistry*, *52*(4), 601–23. https://doi.org/10.1373/clinchem.2005.061408

Das, A. K., Nanda, P. K., Madane, P., Biswas, S., Das, A., Zhang, W., and Lorenzo, J. M. 2020. A comprehensive review on antioxidant dietary fibre enriched meat-based functional foods. Trends in Food Science & Technology, 99, 323-336.

De Groote, D., Van Belleghem, K., Devière, J., Van Brussel, W., Mukaneza, A., and Amininejad, L. 2012. Effect of the intake of resveratrol, resveratrol phosphate, and catechin-rich grape seed extract on markers of oxidative stress and gene expression in adult obese subjects. *Annals of Nutrition and Metabolism*, *61*(1), 15–24.

De Sales, N. F. F., Da Costa, L. S., Carneiro, T. I. A., Minuzzo, D. A., Oliveira, F. L., Cabral, L. M. C., Torres, A. G., and El-Bacha, T. 2018. Anthocyanin-rich Grape Pomace Extract (Vitis vinifera L.) from wine industry affects mitochondrial bioenergetics and glucose metabolism in human hepatocarcinoma HepG2 cells. *Molecules*, *23*(3), 1–17. https://doi.org/10.3390/molecules23030611

Del Pino-García, R., Gerardi, G., Rivero-Pérez, M. D., González-SanJosé, M. L., García-Lomillo, J., and Muñiz, P. 2016. Wine pomace seasoning attenuates hyperglycaemia-induced endothelial dysfunction and oxidative damage in endothelial cells. *Journal of Functional Foods*, *22*, 431–45. https://doi.org/10.1016/j.jff.2016.02.001

Del Pino-García, R., González-SanJosé, M. L., Rivero-Pérez, M. D., García-Lomillo, J., and Muñiz, P. 2016a. Total antioxidant capacity of new natural powdered seasonings after gastrointestinal and colonic digestion. *Food Chemistry*, *211*, 707–14. https://doi.org/10.1016/j.foodchem.2016.05.127

Del Pino-García, R., González-SanJosé, M. L., Rivero-Pérez, M. D., García-Lomillo, J., and Muñiz, P. 2017. The effects of heat treatment on the phenolic composition and antioxidant capacity of red wine pomace seasonings. *Food Chemistry*, *221*, 1723–32. https://doi.org/10.1016/j.foodchem.2016.10.113

Del Pino-García, R., Rivero-Pérez, M. D., González-Sanjosé, M. L., Castilla-Camina, P., Croft, K. D., and Muñiz, P. 2016b. Attenuation of oxidative stress in Type 1 diabetic rats supplemented with a seasoning obtained from winemaking by-products and its effect on endothelial function. *Food and Function*, *7*(10), 4410–21. https://doi.org/10.1039/c6fo01071g

Del Pino-García, R., Rivero-Pérez, M. D., González-SanJosé, M. L., Croft, K. D., and Muñiz, P. 2016c. Bioavailability of phenolic compounds and antioxidant effects of wine pomace seasoning after oral administration in rats. *Journal of Functional Foods*, *25*(2), 486–96. https://doi.org/10.1016/j.jff.2016.06.030

Del Pino-García, R., Rivero-Pérez, M. D., González-SanJosé, M. L., Croft, K. D., and Muñiz, P. 2017a. Antihypertensive and antioxidant effects of supplementation with red wine pomace in spontaneously hypertensive rats. *Food & Function*, *8*(7), 2444–54. https://doi.org/10.1039/C7FO00390K

Del Pino-García, R. Del, Rivero-Pérez, M. D., Gonzalez-Sanjosé, M. L., Ortega-Heras, M., Lomillo, J. G., and Muñiz, P. 2017b. Chemopreventive potential of powdered red wine pomace seasonings against colorectal cancer in HT-29 cells. *Journal of Agricultural and Food Chemistry*, *65*(1), 66–73. https://doi.org/10.1021/acs.jafc.6b04561

Deng, Q., Penner, M. H., and Zhao, Y. 2011. Chemical composition of dietary fiber and polyphenols of five different varieties of wine grape pomace skins. *Food Research International*, *44*(9), 2712–20. https://doi.org/10.1016/j.foodres.2011.05.026

Dikalov, S. I., Nazarewicz, R. R., Bikineyeva, A., Hilenski, L., Lassègue, B., Griendling, K. K., Harrison, D. G., and Dikalova, A. E. 2014. Nox2-Induced production of mitochondrial Superoxide in Angiotensin ii-mediated endothelial oxidative stress and hypertension. *Antioxidants and Redox Signaling*, *20*(2), 281–94. https://doi.org/10.1089/ars.2012.4918

749 Ding, Q., Hayashi, T., Packiasamy, A. J., Miyazaki, A., Fukatsu, A., Shiraishi, H., Nomura, T., and
750 Iguchi, A. 2004. The effect of high glucose on NO and O 2- through endothelial GTPCH1
751 and NADPH oxidase. *Life Sciences*, *75*(26), 3185–94.
752 https://doi.org/10.1016/j.lfs.2004.06.005

753 Domínguez-Avila, A. J., González-Aguilar, G. A., Alvarez-Parrilla, E., and de la Rosa, L. A. 2016.
754 Modulation of PPAR expression and activity in response to polyphenolic compounds in
755 high fat diets. *International Journal of Molecular Sciences*, *17*(7), 1–17.
756 https://doi.org/10.3390/ijms17071002

757 D'Oria, R., Schipani, R., Leonardini, A., Natalicchio, A., Perrini, S., Cignarelli, A., Laviola, L., and
758 Giorgino, F. 2020. The role of oxidative stress in cardiac disease: from physiological
759 response to injury factor. Oxidative medicine and cellular longevity, 2020.

760 Doshi, P., Adsule, P., Banerjee, K., and Oulkar, D. 2015. Phenolic compounds, antioxidant
761 activity and insulinotropic effect of extracts prepared from grape (Vitis vinifera L)
762 byproducts. *Journal of Food Science and Technology*, *52*(1), 181–90.
763 https://doi.org/10.1007/s13197-013-0991-1

764 Edwards, M., Czank, C., Woodward, G. M., Cassidy, A., and Kay, C. D. 2015. Phenolic
765 metabolites of anthocyanins modulate mechanisms of endothelial function. *Journal of*
766 *Agricultural and Food Chemistry*, *63*(9), 2423–31. https://doi.org/10.1021/jf5041993

767 Endemann, D. H., and Schiffrin, E. L. 2004. *Endothelial Dysfunction J Am Soc Nephrol 15: 1983–*
768 *1992, 2004*. *12*, 1983–92. https://doi.org/10.1097/01.ASN.0000132474.50966.DA

769 Esmerina Tili, Michaille, J.-J., Alder, H., Volinia, S., Delmas, D., Latruffe, N., and Croce1, C. M.
770 2013. Resveratrol modulates the levels of microRNAs targeting genes encoding tumor-
771 suppressors and effectors of TGFβ signaling pathway in SW480 cells. *Biochemical*
772 *Pharmacology*, *18*(9), 1199–216. https://doi.org/10.1016/j.micinf.2011.07.011.Innate

773 Exner, M., Hermann, M., Hofbauer, R., Kapiotis, S., Quehenberger, P., Speiser, W., Held, I., and
774 Gmeiner, B. 2001. Genistein prevents the glucose autoxidation mediated atherogenic
775 modification of low density lipoprotein. *Free Radical Research*, *34*(1), 101–12.
776 https://doi.org/10.1080/10715760100300101

777 Farooqi, A. A., Khalid, S., and Ahmad, A. 2018. Regulation of cell signaling pathways and
778 miRNAs by resveratrol in different cancers. *International Journal of Molecular Sciences*,
779 *19*(3). https://doi.org/10.3390/ijms19030652

780 Faustino, M., Veiga, M., Sousa, P., Costa, E. M., Silva, S., and Pintado, M. 2019. Agro-food
781 byproducts as a new source of natural food additives. *Molecules*, *24*(6), 1–23.
782 https://doi.org/10.3390/molecules24061056

783 Fechtner, S., Singh, A., Chourasia, M., and Ahmed, S. 2017. Molecular insights into the
784 differences in anti-inflammatory activities of green tea catechins on IL-1β signaling in
785 rheumatoid arthritis synovial fibroblasts. *Toxicolology and Applied Pharmacology*, *329*,
786 112–20. https://doi.org/Https://doi.org/10.1016/j.taap.2017.05.016

787 Fernandes, I., Pérez-Gregorio, R., Soares, S., Mateus, N., and Freitas, V. De. 2017. Wine
788 flavonoids in health and disease prevention. *Molecules*, 22(292), 1–30.
789 https://doi.org/10.3390/molecules22020292

790 Fernández-García, E., Carvajal-Lérida, I., and Pérez-Gálvez, A. 2009. In vitro bioaccessibility
791 assessment as a prediction tool of nutritional efficiency. *Nutrition Research*, *29*, 751–60.

792 Ferri, M., Vannini, M., Ehrnell, M., Eliasson, L., Xanthakis, E., Monari, S., Sisti, L., Marchese, P.,

Celli, A., and Tassoni, A. 2020. From winery waste to bioactive compounds and new polymeric biocomposites: A contribution to the circular economy concept. *Journal of Advanced Research*, *24*, 1–11. https://doi.org/10.1016/j.jare.2020.02.015

Forman, H. J., Davies, K. J. A., and Ursini, F. 2014. How Do Nutritional Antioxidants Really Work: Nucleophilic Tone and Para-Hormesis Versus Free Radical Scavenging in vivo. *Free Radical Biology and Medicine*, *66*, 1–26. https://doi.org/10.1038/jid.2014.371

Fraga, César G., Croft, K. D., Kennedy, D. O., and Tomás-Barberán, F. A. 2019. The effects of polyphenols and other bioactives on human health. *Food and Function*, *10*(2), 514–28. https://doi.org/10.1039/c8fo01997e

Fraga, Cesar G., Oteiza, P. I., and Galleano, M. 2018. Plant bioactives and redox signaling: (–)-Epicatechin as a paradigm. *Molecular Aspects of Medicine*, *61*, 31–40. https://doi.org/10.1016/j.mam.2018.01.007

Fuller, S., Beck, E., Salman, H., and Tapsell, L. 2016. New Horizons for the Study of Dietary Fiber and Health: A Review. *Plant Foods for Human Nutrition*, *71*(1). https://doi.org/10.1007/s11130-016-0529-6

Furuuchi, R., Shimizu, I., Yoshida, Y., Hayashi, Y., Ikegami, R., Suda, M., Katsuumi, G., Wakasugi, T., Nakao, M., and Minamino, T. 2018. Boysenberry polyphenol inhibits endothelial dysfunction and improves vascular health. *PLoS ONE*, *13*(8), 1–16. https://doi.org/10.1371/journal.pone.0202051

Galleano, M., Puzserova, A., and Balis, P. 2013. (–) -Epicatechin Reduces Blood Pressure and Improves Vasorelaxation in Spontaneously Hypertensive Rats by NO-mediated Mechanism. *Union of Biochemistry and Molecular Biology*, *65*(8), 710–5. https://doi.org/10.1002/iub.1185

García-Lomillo, J., González-SanJosé, M. L., Del Pino-García, R., Rivero-Pérez, M. D., and Muñiz-Rodríguez, P. 2014. Antioxidant and antimicrobial properties of wine byproducts and their potential uses in the food industry. *Journal of Agricultural and Food Chemistry*, *62*(52), 12595–602. https://doi.org/10.1021/jf5042678

Garrido, J.; Borges, F. Wine and grape polyphenols - A chemical perspective. *Food Research International*, 2013, 54, 1844–1858.

Gerardi, G., Cavia-Saiz, M., del Pino-García, R., Rivero-Pérez, M. D., González-SanJosé, M. L., and Muñiz, P. 2020. Wine pomace product ameliorates hypertensive and diabetic aorta vascular remodeling through antioxidant and anti-inflammatory actions. *Journal of Functional Foods*, *66*(September 2019), 103794. https://doi.org/10.1016/j.jff.2020.103794

Gerardi, G., Cavia-Saiz, M., Rivero-Pérez, M. D., González-SanJosé, M. L., and Muñiz, P. 2019. Modulation of Akt-p38-MAPK/Nrf2/SIRT1 and NF-κB pathways by wine pomace product in hyperglycemic endothelial cell line. *Journal of Functional Foods*, *58*(May), 255–65. https://doi.org/10.1016/j.jff.2019.05.003

Gerardi, G., Cavia-Saiz, M., Rivero-Pérez, M. D., González-SanJosé, M. L., and Muñiz, P. 2020a. The dose–response effect on polyphenol bioavailability after intake of white and red wine pomace products by Wistar rats. *Food & Function*, 1661–71. https://doi.org/10.1039/c9fo01743g

Gerardi, G., Cavia-Saiz, M., Rivero-Pérez, M. D., González-SanJosé, M. L., and Muñiz, P. 2020b. The protective effects of wine pomace products on the vascular endothelial barrier

function. *Food & Function*. https://doi.org/10.1039/d0fo01199a

Gerardi, G., Cavia-Saiz, M., Rivero-Pérez, M. D., González-SanJosé, M. L., and Muñiz, P. 2020c. Wine pomace product modulates oxidative stress and microbiota in obesity high-fat diet-fed rats. *Journal of Functional Foods*, *68*(February), 103903. https://doi.org/10.1016/j.jff.2020.103903

Gessner, D. K., Winkler, A., Koch, C., Dusel, G., Liebisch, G., Ringseis, R., and Eder, K. 2017. Analysis of hepatic transcript profile and plasma lipid profile in early lactating dairy cows fed grape seed and grape marc meal extract. BMC genomics, 18(1), 253.

Gil-Sánchez, I., Ayuda-Durán, B., González-Manzano, S., Santos-Buelga, C., Cueva, C., Martín-Cabrejas, M. A., Sanz-Buenhombre, M., Guadarrama, A., Moreno-Arribas, M. V., and Bartolomé, B. 2017. Chemical characterization and in vitro colonic fermentation of grape pomace extracts. *Journal of the Science of Food and Agriculture*, *97*(10), 3433–44. https://doi.org/10.1002/jsfa.8197

Gil-Sánchez, I., Esteban-Fernández, A., de Llano, D. G., Sanz-Buenhombre, M., Guadarrana, A., Salazar, N., Gueimondec, M., de los Reyes-Gavilánce, C. G., Martín Gómez, L., García Bermejo, M. L., Bartolomé, B., and Moreno-Arribas, M. V. (2018). Supplementation with grape pomace in healthy women: Changes in biochemical parameters, gut microbiota and related metabolic biomarkers. Journal of Functional Foods, 45, 34-46.

Gómez-Guzmán, M., Jiménez, R., Sánchez, M., Zarzuelo, M. J., Galindo, P., Quintela, A. M., López-Sepúlveda, R., Romero, M., Tamargo, J., Vargas, F., Pérez-Vizcaíno, F., and Duarte, J. 2012. Epicatechin lowers blood pressure, restores endothelial function, and decreases oxidative stress and endothelin-1 and NADPH oxidase activity in DOCA-salt hypertension. *Free Radical Biology and Medicine*, *52*(1), 70–9. https://doi.org/10.1016/j.freeradbiomed.2011.09.015

Goñi, I., Martín, N., and Saura-Calixto, F. 2005. In vitro digestibility and intestinal fermentation of grape seed and peel. *Food Chemistry*, *90*(1–2), 281–6. https://doi.org/10.1016/j.foodchem.2004.03.057

Gonzales, G. B., Smagghe, G., Grootaert, C., Zotti, M., Raes, K., and Camp, J. Van. 2015. Flavonoid interactions during digestion, absorption, distribution and metabolism: A sequential structure-activity/property relationship-based approach in the study of bioavailability and bioactivity. *Drug Metabolism Reviews*, *47*(2), 175–90. https://doi.org/10.3109/03602532.2014.1003649

González-Paramás, A. M., Esteban-Ruano, S., Santos-Buelga, C., De Pascual-Teresa, S., and Rivas-Gonzalo, J. C. 2004. Flavanol Content and Antioxidant Activity in Winery Byproducts. *Journal of Agricultural and Food Chemistry*, *52*(2), 234–8. https://doi.org/10.1021/jf0348727

Goutzourelas, N., Stagos, D., Housmekeridou, A., Karapouliou, C., Kerasioti, E., Aligiannis, N., Skaltsounis, A.L., Spandidos, D.A., Tsatsakis, A. M., and Kouretas, D. 2015. Grape pomace extract exerts antioxidant effects through an increase in GCS levels and GST activity in muscle and endothelial cells. *International Journal of Molecular Medicine*, 36(2), 433–441. https://doi.org/10.3892/ijmm.2015.2246

Groh, I. A. M., Bakuradze, T., Pahlke, G., Richling, E., and Marko, D. 2020. Consumption of anthocyanin-rich beverages affects Nrf2 and Nrf2-dependent gene transcription in peripheral lymphocytes and DNA integrity of healthy volunteers. BMC chemistry, 14, 1-10.

Guaita, M., and Bosso, A. 2019. Polyphenolic Characterization of Grape Skins and Seeds of Four Italian Red Cultivars at Harvest and after Fermentative Maceration. *Foods*, *8*(9), 395. https://doi.org/10.3390/foods8090395

Guzik, T. J., and Touyz, R. M. 2017. Oxidative stress, inflammation, and vascular aging in hypertension. *Hypertension*, *70*(4), 660–7. https://doi.org/10.1161/HYPERTENSIONAHA.117.07802

Haegeman, G., Goya, L., Bravo, L., Ramos, S., and Novais, A. 2010. *Epicatechin induces NF- k B , activator protein-1 (AP-1) and nuclear via phosphatidylinositol-3-kinase / protein kinase B (PI3K / AKT) and extracellular regulated kinase (ERK) signalling in HepG2 cells*. *1*, 168–79. https://doi.org/10.1017/S0007114509991747

He, J. 2017. Bioactivity-Guided Fractionation of Pine Needle Reveals Catechin as an Anti-hypertension Agent via Inhibiting Angiotensin-Converting Enzyme. *Scientific Reports*, *7*(1), 1–9. https://doi.org/10.1038/s41598-017-07748-x

Hegazy, A. M., El-Sayed, E. M., Ibrahim, K. S., and Abdel-Azeem, A. S. 2019. Dietary antioxidant for disease prevention corroborated by the Nrf2 pathway. *Journal of Complementary and Integrative Medicine*, 1–11. https://doi.org/10.1515/jcim-2018-0161

Higashi, Y., Noma, K., Yoshizumi, M., and Kihara, Y. 2009. Endothelial function and oxidative stress in cardiovascular diseases. *Circulation Journal : Official Journal of the Japanese Circulation Society*, *73*(3), 411–8. http://www.ncbi.nlm.nih.gov/pubmed/19194043

Hsu, C. L., Wu, C. H., Huang, S. L., and Yeng, G. C. 2009. Phenolic compounds rutin and o-coumaric acid ameliorate obesity induced by high-fat diet in rats. *Journal of Agricultural and Food Chemistry*, *57*(2), 425–31. https://doi.org/https://doi.org/10.1021/jf802715t

Huang, K., Gao, X., and Wei, W. 2017. The crosstalk between Sirt1 and Keap1/Nrf2/ARE anti-oxidative pathway forms a positive feedback loop to inhibit FN and TGF-β1 expressions in rat glomerular mesangial cells. *Experimental Cell Research*, *361*(1), 63–72. https://doi.org/10.1016/j.yexcr.2017.09.042

Hunt, J. V., Dean, R. T., and Wolff, S. P. 1988. Hydroxyl radical production and autoxidative glycosylation. Glucose autoxidation as the cause of protein damage in the experimental glycation model of diabetes mellitus and ageing. *Biochemical Journal*, *256*(1), 205–12. https://doi.org/10.1042/bj2560205

Hunyadi, A. 2019. The mechanism(s) of action of antioxidants: From scavenging reactive oxygen/nitrogen species to redox signaling and the generation of bioactive secondary metabolites. *Medicinal Research Reviews*, *February*, 1–29. https://doi.org/10.1002/med.21592

Hussain, T., Tan, B., Yin, Y., Blachier, F., Tossou, M. C. B., and Rahu, N. 2016. Oxidative Stress and Inflammation: What Polyphenols Can Do for Us? *Oxidative Medicine and Cellular Longevity*, *2016*. https://doi.org/10.1155/2016/7432797

Jara-Palacios, M., Hernanz, D., Cifuentes-Gomez, T., Escudero-Gilete, M. L., Heredia, F. J., and Spencer, J. P. E. 2015. Assessment of white grape pomace from winemaking as source of bioactive compounds , and its antiproliferative activity. *Food Chemistry*, *183*, 78–82. https://doi.org/10.1016/j.foodchem.2015.03.022

Jara-Palacios, M., Hernanz, D., Escudero-Gilete, M. L., and Heredia, F. J. 2014. Antioxidant potential of white grape pomaces: Phenolic composition and antioxidant capacity measured by spectrophotometric and cyclic voltammetry methods. *Food Research*

926 *International*, *66*, 150–7. https://doi.org/10.1016/j.foodres.2014.09.009

927 Jara-Palacios, M., Hernanz, D., Escudero-Gilete, M. L., and Heredia, F. J. 2016. The use of grape
928 seed byproducts rich in flavonoids to improve the antioxidant potential of red wines.
929 *Molecules*, *21*(11). https://doi.org/10.3390/molecules21111526

930 Javkhedkar, A. A., Quiroz, Y., Rodriguez-Iturbe, B., Vaziri, N. D., Lokhandwala, M. F., and
931 Banday, A. A. 2015. Resveratrol restored Nrf2 function, reduced renal inflammation, and
932 mitigated hypertension in spontaneously hypertensive rats. *American Journal of*
933 *Physiology - Regulatory Integrative and Comparative Physiology*, *308*(10), R840–6.
934 https://doi.org/10.1152/ajpregu.00308.2014

935 Jin, Q., O'Hair, J., Stewart, A. C., O'Keefe, S. F., Neilson, A. P., Kim, Y. T., McGuire, M., Lee, A.,
936 Wilder, G., and Huang, H. 2019. Compositional characterization of different industrial
937 white and red grape pomaces in Virginia and the potential valorization of the major
938 components. Foods, 8(12), 667.

939 Jin, T., Song, Z., Weng, J., and Fantus, I. G. 2018. Curcumin and other dietary polyphenols:
940 potential mechanisms of metabolic actions and therapy for diabetes and obesity.
941 *American Journal of Physiology-Endocrinology and Metabolism*, *314*(3), E201–5.
942 https://doi.org/10.1152/ajpendo.00285.2017

943 Kabir, F., Sultana, M. S., and Kurnianta, H. 2015. Polyphenolic contents and antioxidant
944 activities of underutilized grape (Vitis vinifera L.) pomace extracts. *Preventive Nutrition*
945 *and Food Science*, *20*(3), 210–4. https://doi.org/10.3746/pnf.2015.20.3.210

946 Kadouh, H. C., Sun, S., Zhu, W., and Zhou, K. 2016. α-Glucosidase inhibiting activity and
947 bioactive compounds of six red wine grape pomace extracts. *Journal of Functional Foods*,
948 *26*, 577–84. https://doi.org/10.1016/j.jff.2016.08.022

949 Kalli, E., Lappa, I., Bouchagier, P., Tarantilis, P. A., and Skotti, E. 2018. Novel application and
950 industrial exploitation of winery by-products. *Bioresources and Bioprocessing*, *5*(1).
951 https://doi.org/10.1186/s40643-018-0232-6

952 Kammerer, D., Claus, A., Carle, R., and Schieber, A. 2004. Polyphenol screening of pomace from
953 red and white grape varieties (Vitis vinifera L.) by HPLC-DAD-MS/MS. *Journal of*
954 *Agricultural and Food Chemistry*, *52*(14), 4360–7. https://doi.org/10.1021/jf049613b

955

956 Karbach, S., Wenzel, P., Waisman, A., Munzel, T., and Daiber, A. 2014. eNOS uncoupling in
957 cardiovascular diseases - the role of oxidative stress and inflammation. *Current Phar-*
958 *Maceutical Design*, *20*(22), 3579–3594.

959 Kårlund, A., Reinisalo, M., Kårlund, A., Koskela, A., Kaarniranta, K., and Karjalainen, R. O. 2015.
960 *Polyphenol Stilbenes : Molecular Mechanisms of Defence against Oxidative Stress and*
961 *Aging- Related Diseases Polyphenol Stilbenes : Molecular Mechanisms of Defence against*
962 *Oxidative Stress and Aging-Related Diseases*. *2015*(April).
963 https://doi.org/10.1155/2015/340520

964 Katalinić, V., Možina, S. S., Skroza, D., Generalić, I., Abramovič, H., Miloš, M., Ljubenkov, I.,
965 Piskernik, S., Pezo, I., Terpinc, P., and Boban, M. 2010. Polyphenolic profile, antioxidant
966 properties and antimicrobial activity of grape skin extracts of 14 Vitis vinifera varieties
967 grown in Dalmatia (Croatia). *Food Chemistry*, *119*(2), 715–23.
968 https://doi.org/10.1016/j.foodchem.2009.07.019

969 Kim, D. H., Khan, H., Ullah, H., Hassan, S. T. S., Šmejkal, K., Efferth, T., Mahomoodally, M. F., Xu,

S., Habtemariam, S., Filosa, R., Lagoa, R., and Rengasamy, K. R. 2019. MicroRNA targeting by quercetin in cancer treatment and chemoprotection. *Pharmacological Research*, *147*(July). https://doi.org/10.1016/j.phrs.2019.104346

Kuo, K. L., Hung, S. C., Lee, T. S., and Tarng, D. C. 2014. Iron sucrose accelerates early atherogenesis by increasing superoxide production and upregulating adhesion molecules in CKD. *Journal of the American Society of Nephrology*, *25*(11), 2596–606. https://doi.org/10.1681/ASN.2013080838

Ky, I., Lorrain, B., Kolbas, N., Crozier, A., and Teissedre, P. L. 2014. Wine by-Products: Phenolic characterization and antioxidant activity evaluation of grapes and grape pomaces from six different French grape varieties. *Molecules*, *19*(1), 482–506. https://doi.org/10.3390/molecules19010482

Larivie`re, L., Thibault, G., and Schiffrin, E. 1993. Increased endothelin-1 content in blood vessels of deoxycorticosterone acetate-salt hypertensive but not in spontaneously hypertensive rats. *Hypertension*, *21*, 294–300.

Lavelli, V., Torri, L., Zeppa, G., Fiori, L., and Spigno, G. 2016. Recovery of Winemaking By-Products. *Italian Journal of Food Science*, *28*(4), 542–64.

Lecumberri, E., Sc, B., Goya, L., Ph, D., Mateos, R., Ph, D., Alía, M., Ph, D., Ramos, S., Ph, D., Izquierdo-pulido, M., Ph, D., Bravo, L., and Ph, D. 2007. *A diet rich in dietary fiber from cocoa improves lipid profile and reduces malondialdehyde in hypercholesterolemic rats*. *23*, 332–41. https://doi.org/10.1016/j.nut.2007.01.013

Lee, H. J., Lee, J. J., Jung, M. O., Choi, J. S., Jung, J. T., Choi, Y. Il, and Lee, J. K. 2017. Meat quality and storage characteristics of pork loin marinated in grape pomace. *Korean Journal for Food Science of Animal Resources*, *37*(5), 726–34. https://doi.org/10.5851/kosfa.2017.37.5.726

Llobera, A., and Cañellas, J. 2007. Dietary fibre content and antioxidant activity of Manto Negro red grape (Vitis vinifera): pomace and stem. *Food Chemistry*, *101*(2), 659–66. https://doi.org/10.1016/j.foodchem.2006.02.025

Loft, S., Danielsen, P. H., Mikkelsen, L., Risom, L., Forchhammer, L., and Møller, P. 2008. Biomarkers of oxidative damage to DNA and repair. *Biochemical Society Transactions*, *36*(5), 1071–6. https://doi.org/10.1042/BST0361071

Lubecka, K., Kaufman-Szymczyk, A., Cebula-Obrzut, B., Smolewski, P., Szemraj, J., and Fabianowska-Majewska, K. 2018. Novel clofarabine-based combinations with polyphenols epigenetically reactivate retinoic acid receptor beta, inhibit cell growth, and induce apoptosis of breast cancer cells. *International Journal of Molecular Sciences*, *19*(12), 1–23. https://doi.org/10.3390/ijms19123970

Lugrin, J., Rosenblatt-Velin, N., Parapanov, R., and Liaudet, L. 2014. The role of oxidative stress during inflammatory processes. *Biological Chemistry*, *395*(2), 203–30. https://doi.org/10.1515/hsz-2013-0241

Maaliki, D., Shaito, A. A., Pintus, G., El-Yazbi, A., and Eid, A. H. 2019. Flavonoids in hypertension: a brief review of the underlying mechanisms. *Current Opinion in Pharmacology*, *45*, 57–65. https://doi.org/10.1016/j.coph.2019.04.014

Machado, N. F. L., and Domínguez-Perles, R. 2017. Addressing Facts and Gaps in the Phenolics Chemistry of Winery By-Products. *Molecules*, *22*(286), 1–48. https://doi.org/10.3390/molecules22020286

1014 Makris, D. P., Boskou, G., and Andrikopoulos, N. K. 2007. Recovery of antioxidant phenolics
1015 from white vinification solid by-products employing water/ethanol mixtures. *Bioresource*
1016 *Technology*, *98*(15), 2963–7. https://doi.org/10.1016/j.biortech.2006.10.003

1017 Maleki, S. J., Crespo, J. F., and Cabanillas, B. 2019. Anti-inflammatory effects of flavonoids.
1018 *Food Chemistry*, *299*, 125124. https://doi.org/10.1016/j.foodchem.2019.125124

1019 Manach, C., Scalbert, A., Morand, C., Rémésy, C., and Jiménez, L. 2004. Polyphenols: food
1020 sources and bioavailability. *The American Journal of Clinical Nutrition*, 79, 727–747.
1021 https://doi.org/ 10.1093/ajcn/79.5.727

1022 Manna, P., and Jain, S. K. 2015. Obesity, Oxidative Stress, Adipose Tissue Dysfunction, and the
1023 Associated Health Risks: Causes and Therapeutic Strategies. *Metabolic Syndrome and*
1024 *Related Disorders*, *13*(10), 423–44. https://doi.org/10.1089/met.2015.0095

1025 Marín, L., Miguélez, E. M., Villar, C. J., and Lombó, F. 2015. Bioavailability of dietary
1026 polyphenols and gut microbiota metabolism: Antimicrobial properties. *BioMed Research*
1027 *International*, *2015*. https://doi.org/10.1155/2015/905215

1028 Martín Ortega, A. M., and Segura Campos, M. R. 2019. Bioactive Compounds as Therapeutic
1029 Alternatives. In *Bioactive Compounds*. Elsevier Inc. https://doi.org/10.1016/b978-0-12-
1030 814774-0.00013-x

1031 Martins, I. M., Roberto, B. S., Blumberg, J. B., Chen, C. O., and Macedo, G. A. 2016. Enzymatic
1032 biotransformation of polyphenolics increases antioxidant activity of red and white grape
1033 pomace. *Food Research International*, 89, 533–539.
1034 https://doi.org/10.1016/j.foodres.2016.09.009

1035 Mateen, S., Moin, S., Zafar, A., and Khan, A. Q. 2016. Redox signaling in rheumatoid arthritis
1036 and the preventive role of polyphenols. *Clinica Chimica Acta*, *463*, 4–10.
1037 https://doi.org/10.1016/j.cca.2016.10.007

1038 Medina-Remón, A., Tresserra-Rimbau, A., Pons, A., Tur, J. A., Martorell, M., Ros, E., Buil-
1039 Cosiales, P., Sacanella, E., Covas, M. I., Corella, D., Salas-Salvadó, J., Gómez-Gracia, E.,
1040 Ruiz-Gutiérrez, V., Ortega-Calvo, M., García-Valdueza, M., Arós, F., Saez, G. T., Serra-
1041 Majem, L., Pinto, X., Vinyoles, E., Estruch, R., and Lamuela-Raventos, R. M. 2015. Effects
1042 of total dietary polyphenols on plasma nitric oxide and blood pressure in a high
1043 cardiovascular risk cohort. The PREDIMED randomized trial. *Nutrition, Metabolism and*
1044 *Cardiovascular Diseases*, *25*(1), 60–7. https://doi.org/10.1016/j.numecd.2014.09.001

1045 Milenkovic, D., Deval, C., and Gouranton, E. 2012. *Modulation of miRNA Expression by Dietary*
1046 *Polyphenols in apoE Deficient Mice : A New Mechanism of the Action of Polyphenols*. *7*(1).
1047 https://doi.org/10.1371/journal.pone.0029837

1048 Moldogazieva, N. T., Mokhosoev, I. M., Feldman, N. B., and Lutsenko, S. V. 2018. ROS and RNS
1049 signalling: adaptive redox switches through oxidative/nitrosative protein modifications.
1050 *Free Radical Research*, *52*(5), 507–43. https://doi.org/10.1080/10715762.2018.1457217

1051 Moreno, A.D., Ballesteros, M., and Negro, M. J. 2020. Biorefineries for the valorization of food
1052 processing waste. The Interaction of Food Industry and Environment. Academic Press,
1053 155-190.

1054 Negro, C., Tommasi, L., and Miceli, A. 2003. Phenolic compounds and antioxidant activity from
1055 red grape marc extracts. *Bioresource Technology*, *87*(1), 41–4.
1056 https://doi.org/10.1016/S0960-8524(02)00202-X

1057 Neilson, A. P., and Ferruzzi, M. G. 2011. Influence of Formulation and Processing on Absorption

and Metabolism of Flavan-3-Ols from Tea and Cocoa. *Annual Review of Food Science and Technology*, *2*(1), 125–51. https://doi.org/10.1146/annurev-food-022510-133725

Niki, E. 2016. Oxidative stress and antioxidants: Distress or eustress? *Archives of Biochemistry and Biophysics*, *595*, 19–24. https://doi.org/10.1016/j.abb.2015.11.017

Nishizuka, T., Fujita, Y., Sato, Y., Nakano, A., Kakino, A., Ohshima, S., Kanda, T., Yoshimoto, R., and Sawamura, T. 2011. Procyanidins are potent inhibitors of LOX-1: A new player in the French Paradox. *Proceedings of the Japan Academy Series B: Physical and Biological Sciences*, *87*(3), 104–13. https://doi.org/10.2183/pjab.87.104

Oh, H., Kim, H., Lee, D., Lee, A., Giovannucci, E., Kang, S., and Keum, N. 2019. Different dietary fibre sources and risks of colorectal cancer and adenoma: a dose–response meta-analysis of prospective studies. *The British Journal of Nutrition*, *2*, 1:11. https://doi.org/10.1017/S0007114519001454.

O'Rourke, M. F., and Hashimoto, J. 2007. Mechanical factors in arte- rial aging: a clinical perspective. *Journal of the American College of Cardiology*, 50, 1–13.

Otsuka, K., Yamamoto, Y., and Ochiya, T. 2018. Regulatory role of resveratrol, a microRNA-controlling compound, in HNRNPA1 expression, which is associated with poor prognosis in breast cancer. *Oncotarget*, *9*(37), 24718–30. https://doi.org/10.18632/oncotarget.25339

Ozdal, T., Sela, D. A., Xiao, J., Boyacioglu, D., Chen, F., and Capanoglu, E. 2016. The reciprocal interactions between polyphenols and gut microbiota and effects on bioaccessibility. *Nutrients*, *8*(2), 1–36. https://doi.org/10.3390/nu8020078

Pal, S., Naissides, M., and Mamo, J. 2004. Polyphenolics and fat absorption. *International Journal of Obesity*, *28*(2), 324–6. https://doi.org/10.1038/sj.ijo.0802577

Palafox-Carlos, H., Ayala-Zavala, J. F., and González-Aguilar, G. A. 2011. The Role of Dietary Fiber in the Bioaccessibility and Bioavailability of Fruit and Vegetable Antioxidants. *Journal of Food Science*, *76*(1), 6–15. https://doi.org/10.1111/j.1750-3841.2010.01957.x

Paredes, M. D., Romecín, P., Atucha, N. M., O'Valle, F., Castillo, J., Ortiz, M. C., and García-Estañ, J. 2018. Beneficial effects of different flavonoids on vascular and renal function in L-NAME hypertensive rats. *Nutrients*, *10*(4), 1–15. https://doi.org/10.3390/nu10040484

Patel, H., Chen, J., Das, K. C., and Kavdia, M. 2013. Hyperglycemia induces differential change in oxidative stress at gene expression and functional levels in HUVEC and HMVEC. *Cardiovascular Diabetology*, *12*(1), 1–14. https://doi.org/10.1186/1475-2840-12-142

Peixoto, C. M., Dias, M. I., Alves, M. J., Calhelha, R. C., Barros, L., Pinho, S. P., and Ferreira, I. C. F. R. 2018. Grape pomace as a source of phenolic compounds and diverse bioactive properties. *Food Chemistry*, *253*(January), 132–8. https://doi.org/10.1016/j.foodchem.2018.01.163

Pérez-Navarro, J., Cazals, G., Enjalbal, C., Izquierdo-Cañas, P. M., Gómez-Alonso, S., and Saucier, C. 2019. Flavanol glycoside content of grape seeds and skins of vitis vinifera varieties grown in Castilla-la Mancha, Spain. *Molecules*, *24*(21). https://doi.org/10.3390/molecules24214001

Price, J. M., Hellermann, A., Hellermann, G., and Sutton, E. T. 2004. Aging enhances vascular dysfunction induced by the Alzheimer's peptide β-amyloid. *Neurological Research*, *26*(3), 305–11.

Rahman, I., Biswas, S. K., and Kirkham, P. A. 2006. Regulation of inflammation and redox signaling by dietary polyphenols. *Biochemical Pharmacology*, *72*(11), 1439–52. https://doi.org/10.1016/j.bcp.2006.07.004

Ramos-Romero, S., Léniz, A., Martínez-Maqueda, D., Amézqueta, S., Fernández-Quintela, A., Hereu, M., Torres, J. L., Portillo, M. P., and Pérez-Jiménez, J. (2021). Inter-Individual Variability in Insulin Response after Grape Pomace Supplementation in Subjects at High Cardiometabolic Risk: Role of Microbiota and miRNA. Molecular Nutrition & Food Research, 65(2), 2000113.

Rasines-Perea, Z., Ky, I., Cros, G., and Crozier, A. 2018. *Against Hypertension and Metabolites Characterization after Intake*. *Cvd*. https://doi.org/10.3390/diseases6030060

Ratovitski, E. 2017. Anticancer Natural Compounds as Epigenetic Modulators of Gene Expression. In *Current Genomics* (Vol. 18, Issue 2). https://doi.org/10.2174/1389202917666160803165229

Reho, J. J., and Rahmouni, K. 2017. Oxidative and inflammatory signals in obesity-associated vascular abnormalities. *Clinical Science*, *131*(14), 1689–700. https://doi.org/10.1042/CS20170219

Rein, M. J., Renouf, M., Cruz-Hernandez, C., Actis-Goretta, L., Thakkar, S. K., and da Silva Pinto, M. 2013. Bioavailability of bioactive food compounds: A challenging journey to bioefficacy. *British Journal of Clinical Pharmacology*, *75*(3), 588–602. https://doi.org/10.1111/j.1365-2125.2012.04425.x

Rivera, K., Salas-Pérez, F., Echeverría, G., Urquiaga, I., Dicenta, S., Pérez, D., de la Cerda, P., González, L., Andia, M.E., Uribe, S., Tejos, C., Martínez, G., Busso, D., Irarrázabal, P., Rigotti, A. 2019. Red Wine Grape Pomace Attenuates Atherosclerosis and Myocardial Damage and Increases Survival in Association with Improved Plasma Antioxidant Activity in a Murine Model of Lethal Ischemic Heart Disease. *Nutrients*, 11(9):2135. Published 2019 Sep 6. doi:10.3390/nu11092135

Rockenbach, I. I., Rodrigues, E., Gonzaga, L. V., Caliari, V., Genovese, M. I., Gonalves, A. E. D. S. S., and Fett, R. 2011. Phenolic compounds content and antioxidant activity in pomace from selected red grapes (Vitis vinifera L. and Vitis labrusca L.) widely produced in Brazil. *Food Chemistry*, *127*(1), 174–9. https://doi.org/10.1016/j.foodchem.2010.12.137

Rodriguez Lanzi, C., Perdicaro, D. J., Antoniolli, A., Piccoli, P., Vazquez Prieto, M. A., and Fontana, A. 2018. Phenolic metabolites in plasma and tissues of rats fed with a grape pomace extract as assessed by liquid chromatography-tandem mass spectrometry. *Archives of Biochemistry and Biophysics*, *651*(April), 28–33. https://doi.org/10.1016/j.abb.2018.05.021

Rodríguez-Morgado, B., Candiracci, M., Santa-María, C., Revilla, E., Gordillo, B., Parrado, J., Castaño, A. 2015. Obtaining from grape pomace an enzymatic extract with anti-inflammatory properties. *Plant Foods for Human Nutrition*, 70, 42–49.

Rodriguez-Rodriguez, R., Justo, M. L., Claro, C. M., Vila, E., Parrado, J., Herrera, M. D., and Alvarez De Sotomayor, M. 2012. Endothelium-dependent vasodilator and antioxidant properties of a novel enzymatic extract of grape pomace from wine industrial waste. *Food Chemistry*, 135(3), 1044–1051. https://doi.org/10.1016/j. foodchem.2012.05.089

Romano, M. R., and Lograno, M. D. 2009. Epigallocatechin-3-gallate relaxes the isolated bovine ophthalmic artery: Involvement of phosphoinositide 3-kinase-Akt-nitric oxide/cGMP signalling pathway. *European Journal of Pharmacology*, *608*(1–3), 48–53.

https://doi.org/10.1016/j.ejphar.2009.02.034

Ruberto, G., Renda, A., Daquino, C., Amico, V., Spatafora, C., Tringali, C., and Tommasi, N. De. 2007. Polyphenol constituents and antioxidant activity of grape pomace extracts from five Sicilian red grape cultivars. *Food Chemistry*, *100*(1), 203–10. https://doi.org/10.1016/j.foodchem.2005.09.041

Sandoval-Acuña, C., Ferreira, J., and Speisky, H. 2014. Polyphenols and mitochondria: An update on their increasingly emerging ROS-scavenging independent actions. *Archives of Biochemistry and Biophysics*, *559*, 75–90. https://doi.org/10.1016/j.abb.2014.05.017

Sapwarobol, S., Adisakwattana, S., Changpeng, S., Ratanawachirin, W., Tanruttana- wong, K., and Boonyarit, W. 2012. Postprandial blood glucose response to grape seed extract in healthy participants: a pilot study. *Pharmacognosy Magazine*, *8*(31), 192.

Sarsour, E. H., Kalen, A. L., and Goswami, P. C. 2014. Manganese superoxide dismutase regulates a redox cycle within the cell cycle. *Antioxidants and Redox Signaling*, *20*(10), 1618–27. https://doi.org/10.1089/ars.2013.5303

Saura-Calixto, F. 2011. Dietary fiber as a carrier of dietary antioxidants: An essential physiological function. Journal of Agricultural and Food Chemistry, 59, 43–49. https://doi.org/10.1021/jf1036596.

Saura-Calixto, F., Serrano, J., and Goñi, I. 2007. Intake and bioaccessibility of total polyphenols in a whole diet. *Food Chemistry*, *101*(2), 492–501. https://doi.org/10.1016/j.foodchem.2006.02.006

Saura-Calixto, F., Pérez-Jiménez, J., Touriño, S., Serrano, J., Fuguet, E., Torres, J. L., and Goñi, I. 2010. Proanthocyanidin metabolites associated with dietary fibre from in vitro colonic fermentation and proanthocyanidin metabolites in human plasma. Molecular nutrition & food research, 54(7), 939-946.

Scalbert, A., Morand, C., Manach, C., and Rémésy, C. 2002. Absorption and metabolism of polyphenols in the gut and impact on health. *Biomedicine & Pharmacotherapy*, *56*, 276–82. https://doi.org/10.1109/CCST.2012.6393568

Schieber, M., and Chander, N. S. 2014. ROS Function in Redox Signaling and Oxidative Stress. *Current Biology*, *24*(10), 453–62. https://doi.org/10.1016/j.pestbp.2011.02.012.Investigations

Schiffrin, E. L. 2012. Vascular remodeling in hypertension: Mechanisms and treatment. *Hypertension*, *59*(2 SUPPL. 1), 367–74. https://doi.org/10.1161/HYPERTENSIONAHA.111.187021

Seo, K. H., Bartley, G. E., Tam, C., Kim, H. S., Kim, D. H., Chon, J. W., Kim, H., and Yokoyama, W. 2016. Chardonnay grape seed flour ameliorates hepatic steatosis and insulin resistance via altered hepatic gene expression for oxidative stress, inflammation, and lipid and ceramide synthesis in diet-induced obese mice. *PLoS ONE*, *11*(12), 1–20. https://doi.org/10.1371/journal.pone.0167680

Serino, A., and Salazar, G. 2019. Protective Role of Polyphenols against Vascular Inflammation, Aging and Cardiovascular Disease. *Nutrients*, 11(53), 1–23. https://doi.org/10.3390/nu11010053

Shanmugam, M. K., Kannaiyan, R., and Sethi, G. 2011. Targeting cell signaling and apoptotic pathways by dietary agents: Role in the prevention and treatment of cancer. *Nutrition and Cancer*, *63*(2), 161–73. https://doi.org/10.1080/01635581.2011.523502

1190 Sheng, K., Qu, H., Liu, C., Yan, L., You, J., Shui, S., and Zheng, L. 2017. A comparative assess of
1191 high hydrostatic pressure and superfine grinding on physicochemical and antioxidant
1192 properties of grape pomace. International Journal of Food Science & Technology, 52(9),
1193 2106-2114.

1194 Sheng, J., Shi, W., Guo, H., Long, W., Wang, Y., Qi, J., Liu, J., and Xu, Y. 2019. The inhibitory
1195 effect of (-)-Epigallocatechin-3 -gallate on breast cancer progression via reducing SCUBE2
1196 Methylation and DNMT Activity. *Molecules*, *24*(16), 1–15.
1197 https://doi.org/10.3390/molecules24162899

1198 Sies, H. 2018. On the history of oxidative stress: Concept and some aspects of current
1199 development. *Current Opinion in Toxicology*, *7*, 122–6.
1200 https://doi.org/10.1016/j.cotox.2018.01.002

1201 Son, P. S., Park, S. A., Na, H. K., Jue, D. M., Kim, S., and Surh, Y. J. 2010. Piceatannol, a catechol-
1202 type polyphenol, inhibits phorbol ester-induced NF-κB activation and cyclooxygenase-2
1203 expression in human breast epithelial cells: Cysteine 179 of IKKβ as a potential target.
1204 *Carcinogenesis*, *31*(8), 1442–9. https://doi.org/10.1093/carcin/bgq099

1205 Spinetti, G., Kraenkel, N., Emanueli, C., and Madeddu, P. 2010. Diabetes and vessel wall
1206 remodelling : from mechanistic insights to regenerative therapies. *Cardiovascular*
1207 *Research*, 78(2), 1–19. https://doi.org/10.1093/cvr/cvn039

1208 Stangl, V., Dreger, H., Stangl, K., and Lorenz, M. 2007. Molecular targets of tea polyphenols in
1209 the cardiovascular system. *Cardiovascular Research*, 73(2), 348–358.
1210 https://doi.org/10.1016/j.cardiores.2006.08.022

1211 Steven, S., Frenis, K., Oelze, M., Kalinovic, S., Kuntic, M., Bayo Jimenez, M. T., Vujacic-Mirski, K.,
1212 Helmstädter, J., Kröller-Schön, S., Münzel, T., and Daiber, A. 2019. Vascular Inflammation
1213 and Oxidative Stress: Major Triggers for Cardiovascular Disease. *Oxidative Medicine and*
1214 *Cellular Longevity*, *2019*, 1–26. https://doi.org/10.1155/2019/7092151

1215 Stewart, M. L., Nikhanj, S. D., Timm, D. A., Thomas, W., and Slavin, J. L. 2010. Evaluation of the
1216 effect of four fibers on laxation, gastrointestinal tolerance and serum markers in healthy
1217 humans. *Annals of Nutrition and Metabolism*, *56*(2), 91–8.
1218 https://doi.org/10.1159/000275962

1219 Su, X., Zhang, J., Wang, H., Xu, J., He, J., Liu, L., Zhang, T., Chen, R., and Kang, J. 2017. Phenolic
1220 acid profiling, antioxidant, and anti-inflammatory activities, and miRNA regulation in the
1221 polyphenols of 16 blueberry samples from China. *Molecules*, *22*(2).
1222 https://doi.org/10.3390/molecules22020312

1223 Takada, Y., Mukhopadhyay, A., Kundu, G. C., Mahabeleshwar, G. H., Singh, S., and Aggarwal, B.
1224 B. 2003. Hydrogen peroxide activates NF-κB through tyrosine phosphorylation of IκBα
1225 and serine phosphorylation of p65. *Journal of Biological Chemistry*, *278*(26), 24233–41.
1226 https://doi.org/10.1074/jbc.M212389200

1227 Tang, J., Du, Y., Petrash, J. M., Sheibani, N., and Kern, T. S. 2013. Deletion of Aldose Reductase
1228 from Mice Inhibits Diabetes-Induced Retinal Capillary Degeneration and Superoxide
1229 Generation. *PLoS ONE*, *8*(4), 5–10. https://doi.org/10.1371/journal.pone.0062081

1230 Tang, Y., Chen, Y., Jiang, H., and

1231 Nie, D. 2011. The role of short-chain fatty acids in orchestrating two types of programmed cell
1232 death in colon cancer. Autophagy, 7(2), 235-237.

1233 Teixeira, A., Baenas, N., Dominguez-Perles, R., Barros, A., Rosa, E., Moreno, D. A., and Garcia-

Viguera, C. 2014. Natural bioactive compounds from winery by-products as health promoters: A review. *International Journal of Molecular Sciences*, *15*(9), 15638–78. https://doi.org/10.3390/ijms150915638

Teng, H., and Chen, L. 2019. Polyphenols and bioavailability: an update. *Critical Reviews in Food Science and Nutrition*, *59*(13), 2040–51. https://doi.org/https://doi.org/10.1080/10408398.2018.1437023

Touyz, R., and Schiffrin, E. L. 2004. Reactive oxygen species in vascular biology: implications in hypertension. *Histochemistry Cell Biology*, *122*, 339–52.

Tu, W., Wang, H., Li, S., Liu, Q., and Sha, H. 2019. The Anti-Inflammatory and Anti-Oxidant Mechanisms of the Keap1/Nrf2/ARE Signaling Pathway in Chronic Diseases. *Aging and Disease*, *10*(3), 637–51. https://doi.org/10.14336/ad.2018.0513

Urquiaga, I., D'Acuña, S., Pérez, D., Dicenta, S., Echeverría, G., Rigotti, A., and Leighton, F. 2015. Wine grape pomace flour improves blood pressure, fasting glucose and protein damage in humans: A randomized controlled trial. Biological Research, 48(1), 1-10.

U.S.Department of Health and Human Services, Food and Drug Administration (FaDA). Guidance for industry: bioavailability and bioequivalence studies for orally administrated drug products – general considerations. Rockville, MD: Center for Drug Evaluation. 2002

Valko, M., Leibfritz, D., Moncol, J., Cronin, M. T. D., Mazur, M., and Telser, J. 2007. Free radicals and antioxidants in normal physiological functions and human disease. *International Journal of Biochemistry and Cell Biology*, *39*(1), 44–84. https://doi.org/10.1016/j.biocel.2006.07.001

Van Varik, B. J., Rennenberg, R. J. M. W., Reutelingsperger, C. P., Kroon, A. A., De Leeuw, P. W., and Schurgers, L. J. 2012. Mechanisms of arterial remodeling: Lessons from genetic diseases. *Frontiers in Genetics*, 3, 1–10. https://doi.org/10.3389/fgene.2012.00290

Vargas, F., Romecín, P., García-guillén, A. I., Wangesteen, R., Vargas-tendero, P., Paredes, M. D., Atucha, N. M., Lambert, E., and Morris, B. J. 2018. Flavonoids in Kidney Health and Disease. *Frontiers in Physiology*, *9*(April), 1–12. https://doi.org/10.3389/fphys.2018.00394

Verstraeten, S. V., Mackenzie, G. G., Oteiza, P. I., and Fraga, C. G. 2008. (-)-Epicatechin and related procyanidins modulate intracellular calcium and prevent oxidation in Jurkat T cells. *Free Radical Research*, *42*(10), 864–72. https://doi.org/10.1080/10715760802471452

Vezza, T., Rodríguez-Nogales, A., Algieri, F., Utrilla, M. P., Rodriguez-Cabezas, M. E., and Galvez, J. 2016. Flavonoids in inflammatory bowel disease: A review. *Nutrients*, *8*(4). https://doi.org/10.3390/nu8040211

Vogels, N., and Plantenga, M. S. . 2004. The effect of grape-seed extract on 24h energy intake in humans. *European Journal of Clini- Cal Nutrition*, *58*, 667–73.

Wang, Z.-M., Zhong, C.-Y., and Zhao, G.-J. 2017. Polyphenol epigallocatechin-3-gallate alleviates high glucose-induced H9C2 cell damage through PI3K/Akt pathway. *European Review for Medical and Pharmacological Sciences*, *21*(18), 4236–42.

Wardyn, J. D., Ponsford, A. H., and Sanderson, C. M. 2015. Dissecting molecular cross-talk between Nrf2 and NF-κB response pathways. *Biochemical Society Transactions*, *43*(4), 621–6. https://doi.org/10.1042/BST20150014

Wei, Z., Luo, J., Huang, Y., Guo, W., Zhang, Y., Guan, H., Xu, C., and Lu, J. 2017. Profile of polyphenol compounds of five muscadine grapes cultivated in the United States and in newly adapted locations in China. *International Journal of Molecular Sciences*, *18*(3), 1–18. https://doi.org/10.3390/ijms18030631

Welch, W. J. 2008. Angiotensin II-dependent superoxide: Effects on hypertension and vascular dysfunction. *Hypertension*, *52*(1), 51–6. https://doi.org/10.1161/HYPERTENSIONAHA.107.090472

Weng, C. J., and Yen, G. C. 2012. Chemopreventive effects of dietary phytochemicals against cancer invasion and metastasis: Phenolic acids, monophenol, polyphenol, and their derivatives. *Cancer Treatment Reviews*, *38*(1), 76–87. https://doi.org/10.1016/j.ctrv.2011.03.001

Williamson, G., and Clifford, M. N. 2010. Colonic metabolites of berry polyphenols: The missing link to biological activity? *British Journal of Nutrition*, *104*(SUPPL.3), 48–66. https://doi.org/10.1017/S0007114510003946

Wolff, S. P., and Dean, R. T. 1987. Glucose autoxidation and protein modification. The potential role of "autoxidative glycosylation" in diabetes. *Biochemical Journal*, *245*(1), 243–50. https://doi.org/10.1042/bj2450243

Xu, S., and Touyz, R. M. 2006. Reactive oxygen species and vascular remodelling in hypertension: Still alive. *Canadian Journal of Cardiology*, *22*(11), 947–51.

Yahfoufi, N., Alsadi, N., Jambi, M., and Matar, C. 2018. The Immunomodulatory and Anti-Inflammatory Role of Polyphenols. *Nutrients*, *10*(1618), 1–23. https://doi.org/10.3390/nu10111618

Yang, X. Z., Chang, Y., and Wei, W. 2016. Endothelial Dysfunction and Inflammation: Immunity in Rheumatoid Arthritis. *Mediators of Inflammation*, *2016*. https://doi.org/10.1155/2016/6813016

Yin, Z., Machius, M., Nestler, E. J., and Rudenko, G. 2017. Activator protein-1: Redox switch controlling structure and DNA-binding. *Nucleic Acids Research*, *45*(19), 11425–36. https://doi.org/10.1093/nar/gkx795

Yu, J., and Ahmedna, M. 2013a. Functional components of grape pomace: Their composition, biological properties and potential applications. *International Journal of Food Science and Technology*, *48*(2), 221–37. https://doi.org/10.1111/j.1365-2621.2012.03197.x

Zhang, A., Fang, Y., Wang, H., Li, H., and Zhang, Z. 2011. Free-radical scavenging properties and reducing power of grape cane extracts from 11 selected grape cultivars widely grown in China. *Molecules*, *16*(12), 10104–22. https://doi.org/10.3390/molecules161210104

Zhang, H., and Tsao, R. 2016. Dietary polyphenols, oxidative stress and antioxidant and anti-inflammatory effects. *Current Opinion in Food Science*, *8*, 33–42. https://doi.org/https://doi.org/ 10.1016/j.cofs.2016.02.002

Zhang, H. Z., Chen, D. W., He, J., Zheng, P., Yu, J., Mao, X. B., Huang, Z. Q., Luo, Y. H., Luo, J. Q., and Yu, B. 2019a. Long-term dietary resveratrol supplementation decreased serum lipids levels, improved intramuscular fat content, and changed the expression of several lipid metabolism-related miRNAs and genes in growing-finishing pigs. *Journal of Animal Science*, *97*(4), 1745–56. https://doi.org/10.1093/jas/skz057

Zhang, Liang, Wang, Y., Li, D., Ho, C. T., Li, J., and Wan, X. 2016. The absorption, distribution, metabolism and excretion of procyanidins. *Food and Function*, *7*(3), 1273–81.

https://doi.org/10.1039/c5fo01244a

Zhang, Lixiao, Wang, X., Cueto, R., Effi, C., Zhang, Y., Tan, H., Qin, X., Ji, Y., Yang, X., and Wang, H. 2019b. Biochemical basis and metabolic interplay of redox regulation. *Redox Biology*, *26*(July), 101284. https://doi.org/10.1016/j.redox.2019.101284

Zhang, Y. J., Gan, R. Y., Li, S., Zhou, Y., Li, A. N., Xu, D. P., Li, H. Bin, and Kitts, D. D. 2015. Antioxidant phytochemicals for the prevention and treatment of chronic diseases. *Molecules*, *20*(12), 21138–56. https://doi.org/10.3390/molecules201219753

Zhao, Y., Chen, B., Shen, J., Wan, L., Zhu, Y., Yi, T., and Xiao, Z. 2017. The Beneficial Effects of Quercetin, Curcumin, and Resveratrol in Obesity. *Oxidative Medicine and Cellular Longevity*, *2017*, 1–8. https://doi.org/10.1155/2017/1459497

Zhou, J., Lei, Y., Chen, J., and Zhou, X. 2018. Potential ameliorative effects of epigallocatechin-3-gallate against testosterone-induced benign prostatic hyperplasia and fibrosis in rats. *International Immunopharmacology*, *64*(August), 162–9. https://doi.org/10.1016/j.intimp.2018.08.038

Zhu, F., Du, B., Zheng, L., and Li, J. 2015. Advance on the bioactivity and potential applications of dietary fibre from grape pomace. *Food Chemistry*, *186*, 207–12. https://doi.org/10.1016/j.foodchem.2014.07.057

Zhu, L., Zhang, Y., Deng, J., Li, H., and Lu, J. 2012. Phenolic concentrations and antioxidant properties of wines made from North American grapes grown in China. *Molecules*, *17*(3), 3304–23. https://doi.org/10.3390/molecules17033304

Figure Captions

Figure 1. Overview of the steps involved in the bioavailability and metabolism of bioactive compounds. After ingestion, bioactive compounds are first released from the food matrix in the gastrointestinal tract and modified to be then absorbed. Some bioactive compounds are absorbed in the small intestine, but a significant amount enters the large intestine where the colonic microbiota further transform them into readily absorbable molecules. After absorption,

the bioactive compounds are metabolized, and the metabolites enter the blood circulation to finally reach the target tissues and improve their biological activities.

Figure 2. Main metabolites of wine pomace polyphenols after *in vitro* and *in vivo* (Wistar rats) bioavailability studies. The bioavailability process produces large amounts of new metabolites as consequence of the digestion and metabolism of the original bioactive compounds. These new metabolites can be responsible of different biological activities.

Figure 3. Physiopathological Effect of RONS. (A) Physiological effects of redox signaling**. (B)** Pathological implications of oxidative stress.

Figure 4. Role of polyphenols in the redox signaling pathways. Polyphenols can exert their biological activities by interaction whit several intracellular molecules such as enzymes, signaling kinases/phosphatases, transcriptional factors, regulatory proteins, among others. Straight arrow: stimulatory effect; Dotted arrow: inhibitory effect.

Figure 5. Different levels affected in disorders associated with oxidative stress. Oxidative stress lead to the generation of a pro-oxidant and proinflammatory state that produces cell alteration and damage, and finally affects tissue and organ functions.

Figure 6. Mechanism involved in endothelial dysfunction. The increased levels of RONS in the endothelium can improve cell infiltration and atherosclerotic plaque formation by induction of adhesion and chemotactic molecules, platelet aggregation and alteration of nitric oxide bioavailability.

Figure 7. Clinical implications of endothelial dysfunction. Endothelial dysfunction plays a key role in the development of several chronic diseases.

Figure 8. Role of oxidative stress in inflammatory process. RONS can affect the four components of the inflammation (inductors, sensors, mediators and effectors).

Figure 9. Inflammation and oxidative stress. RONS contribute to inflammation by modulation of different inflammatory mediators.

Figure 10. Mechanisms of oxidative stress and inflammation mediated hypertension. Many vascular alterations are associated to oxidative stress including endothelial dysfunction, vascular remodeling, and atherosclerotic plaque formation.

Figure 11. Participation of hyperglycemia in multiples pathways. Hyperglycemia contribute to the development of oxidative stress by increasing RONS formation and protein damage.

Figure 12. Mechanisms implicated in the obesity. Obesity is a complex and multifactorial disease with several pathological metabolic and vascular alterations such as hyperglycemia, inflammation, lipid accumulation, endothelial dysfunction, among others, that contribute to the development of oxidative stress.

Table 1. Different wine pomaces and wine pomace by-products compositions

Composition % dry matter (dm)			By-product	References
Water	**(50-85%)**	50-70%	Grape Pomace (seeds)	(Teixeira et al., 2014)
		55-80%	Grape Pomace (stems)	(González-Centeno et al., 2010)
		73-85%	Grape	(González-Centeno et al., 2010)
Dietary Fiber	**(>70% dm)**	49-59%	Red wine pomaces	(García-Lomillo et al, 2014)
		80%	Grape pomace	(Valiente et al. , 1995)
		75%	Red grape pomace	(Llobera et al., 2007)

		77%	White grape peel	(Goñi, et al., 2005)
		73%	Grape skins	(Alí et al., 2003)
Proteins	**(2-15% dm)**	12-14%	Red wine pomaces	(García-Lomillo et al., 2014)
		11-12%	Red wine pomace (skins)	(Deng et al., 2011)
		12-14%	Red wine pomace	(Llobera et al., 2007)
		5-6%	White wine pomace (skins)	(Deng et al., 2011)
		11%	Grape pomace (seeds)	(Teixeira et al., 2014)
Fat	**(3-17% dm)**	4-17%	Red wine pomaces	(García-Lomillo et al., 2014)
		14-17%	Wine pomace (seeds)	(García-Lomillo et al., 2017b)
		3-6%	Red grape pomace	(Deng et al., 2011)
Essential Oil	*(13-16% dm)*	13%	Red grape pomace	(Llobera et al., 2007)
		16%	Grape pomace (seeds)	(Teixeira et al., 2014)
Minerals	**(6-9% dm)**	6-9%	White and red grape pomace	(Bravoet al., 1998)
		5%	Red pomace	(Llobera et al., 2007)
		6-8%	Red pomace (skins)	(Deng et al., 2011)
		2-3%	White pomace (skins)	(Deng et al., 2011)
Soluble sugars	**(1-3% Red 55-78% White)**	55-78%	White grape pomace	(Zhu et al., 2015)
		1-3%	Red grape pomace	(Deng et al., 2011)
		3%	White and red pomace (skin)	(Bravo et al., 1998)
Polyphenols	**(1-5%)**	4-5%	White and red pomace	(Bravo et al., 1998)
		2-3%	Red pomace	(Deng et al., 2011)
		3%	Red wine pomace (skins)	(García-Lomillo et al., 2014)
		1-2%	White pomace	(Deng et al., 2011)

1411

1412

1413

1414

Table 2. Major polyphenols of red and white wine pomaces from seeds or skins

			Seeds	Skins
Phenolic Families	%		mg/g	
Total Phenols (TP)	30 (r)	96 (w)	12.5 - 85.8 (r) 76.6 – 122 (w)	11.8 – 33.3 (r) 9.50 (w)
Total Flavonoids (TF)	70 (r)	4 (w)	83.6-162.8 (r) 0.77-7.98 (w)	31.2 -47.5 (r) 0.03-0.92 (w)
• *Total Flavanols*	*21 (r)*	*23 (w)*	*17.5 – 152 (r)* *4.3 - 34.8 (w)*	*0.18 – 64.2 (r)* *0.3 - 7.56 (w)*
• *Total Flavonols*	*0.6 (r)*	*5 (w)*	*0.27 – 1.22 (r)* *0.58 (w)*	*0.29 – 4.0 (r)* *0.28 - 8.41 (w)*
• *Total Anthocyanins (TA)*	*2.4 (r)*	*n.d. (w)*	*n.d.*	*1.94 – 21.5 (r)* *0.09 (w)*
• *Total Tannins*	*76 (r)*	*72 (w)*	*39.1 – 455 (r)* *4.3-8.3 (w)*	*7.1 – 345 (r)* *50.2 – 90.3 (w)*
Individual Phenolic Compounds (g/100g)	%		mg/100 g	
Gallic acid	**2.8** (r)	**5.4** (w)	2.4 – 336 (r) 10.7 – 35.8 (w)	0.31 – 2.01 (r) 0.41 – 2.01 (w)
Caftaric acid	0.5 (r)	**8.9** (w)	1.58 (r) 0.93 (w)	1.63 – 62.4 (r) 2.98 – 61.0 (w)
Coutaric acid	0.2 (r)	**2.3** (w)	0.23 – 10.5 (r) 3.02 – 10.6 (w)	0.69 – 18.3 (r) 0.98 – 5.45 (w)
Fertaric acid	<0.01 (r)	0.3 (w)	0.26 (r) 0.3 (w)	0.44 – 1.59 (r) 0.44 – 1.73 (w)
Protocatechuic acid	0.1 (r)	**2.1** (w)	3.3 – 8-7 (r) 9.3 - 10.3 (w)	1.81 – 2.13 (r) 0.78 - 4.28 (w)
Caffeic acid	0.1 (r)	0.5 (w)	7.6 (r) 0.19 (w)	0.34 - 1.07 (r) 0.17 – 3.57 (w)
Syringic acid	0.1 (r)	<0.01(w)	4.4 (r) 0.11 (w)	0.3 – 7.44 (r) 0.10 (w)
p-coumaric acid	0.1 (r)	1.5 (w)	10.0 (r) 0.72 – 10.0 (w)	0.19 – 0.59 (r) 0.21 (w)
Ferulic acid	<0.01 (r)	0.1 (w)	0.19 (r) 0.39 (w)	0.12 - 0.37 (r) 0.26 - 0.58 (w)
Vanillic acid	<0.01 (r)	0.2 (w)	0.34 (r)	0.32 – 3.04 (r) 1.15 (w)
Gentisic acid	<0.01 (r)	0.4 (w)		2.79 (r) 2.94 (w)
Catechin	**3.5** (r)	**16** (w)	10 – 280 (r) 79.0 – 87.6 (w)	1.15 - 130 (r) 6.87 – 22.7 (w)
Epicatechin	**3.2** (r)	**14** (w)	10.1 -270 (r) 67.5 – 85.0 (w)	1.56 – 110 (r) 4.45 – 13.4 (w)
Epigallocatechin gallate	0.1 (r)	1.1 (w)	n.d.	2.33 - 14.6 (r) 7.62 (w)
Epicatechin gallate	0.1 (r)	**7.5** (w)	5.29-12.5 (r) 45.8- 48.9(w)	2.05-3.41 (r) 3.55 (w)
Procyanidin B1	**4.8** (r)	**18** (w)	74.6 – 306 (r) 105 (w)	1.33 – 259 (r) 5.46 - 19.2 (w)
Procyanidin B2	**3.0** (r)	**8.5** (w)	61.5 – 223 (r) 50.6 (w)	3.35 - 128 (r) 3.28 - 9.10 (w)
Quercetin	0.1 (r)	**7.8** (w)	6.89 (r) 3.80 (w)	2.31 (r) 2.66 - 50.9 (w)
Kaempferol	0.3 (r)	**3.8** (w)	14.9 (r) 2.00 (w)	3.28 - 21.1 (r) 2.98 - 24.8 (w)
Myricetin	0.3 (r)	0.4 (w)	11.9 (r)	5.09 - 26 (r) 2.79 (w)
Delphinidin-3-O-glucoside	**7.3** (r)	n.d. (w)	3.00 – 311 (r)	6.80 -555 (r)
Cyanidin-3-O-glucoside	1.8 (r)	n.d. (w)	2.00 – 23.0 (r)	1.49 – 190 (r)
Petunidin-3-O-glucoside	**8.3** (r)	n.d. (w)	5.00 – 318 (r)	6.50 – 668 (r)
Peonidin-3-O-glucoside	**11** (r)	n.d. (w)	11.0 – 111 (r)	4.16 – 1245 (r)
Malvidin-3-O-glucoside	**52** (r)	n.d. (w)	39.0 – 1052 (r)	95.4 – 5098 (r)
t-resveratrol	0.01 (r)	1.4 (w)	0.74 (r) 1.42 (w)	0.46 – 3.45 (r) 0.12 - 8.64 (w)

TP = Total Phenols expressed as mg Gallic Acid Equivalent/g of wine pomace. TF = Total Flavonoids expressed as mg Catechin Equivalent/g of wine pomace. TA = Total Anthocyanins expressed as mg Malvidin-3-glucoside Equivalent/g of wine pomace. Total Tannins are expressed as mg Catechin Equivalent/g of wine pomace. Individual Phenolic Compounds are expressed as mg/100g of wine pomace. % = percentage of each compound/family respect to the total phenolic composition of the wine pomace. (r) = red wine pomace. (w) = white wine pomace. n.d. = not detected.

Figure 1

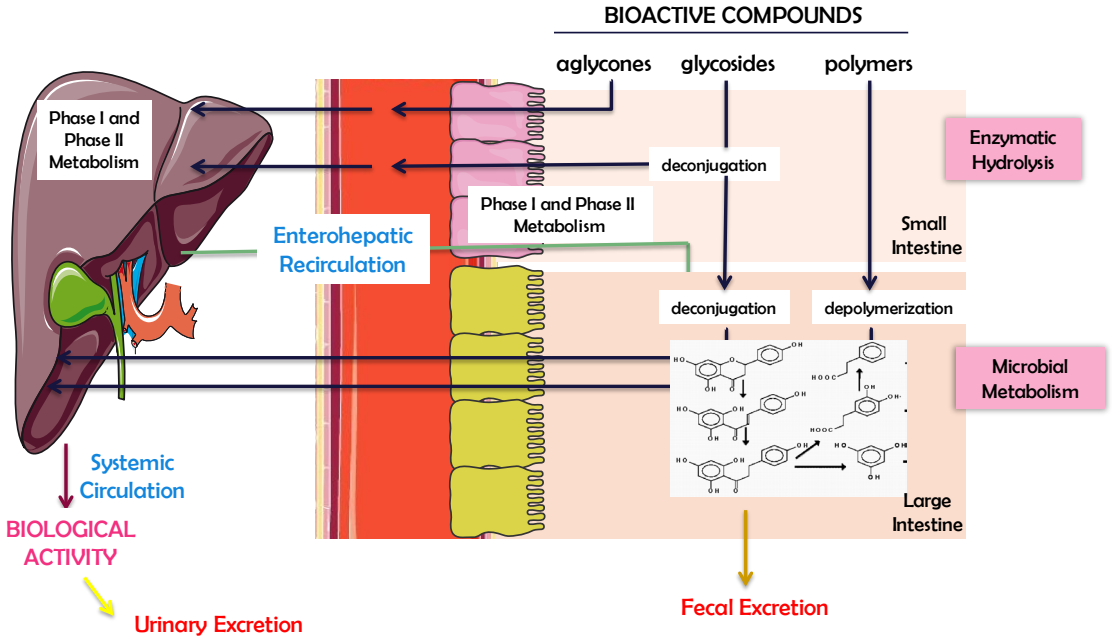

BIOACTIVE COMPOUNDS
aglycones
glycosides
polymers
Phase I and Phase II Metabolism
deconjugation
Enzymatic Hydrolysis
Phase I and Phase II Metabolism
Enterohepatic Recirculation
Small Intestine
deconjugation
depolymerization
Microbial Metabolism
Large Intestine
Systemic Circulation
BIOLOGICAL ACTIVITY
Urinary Excretion
Fecal Excretion

Figure 2

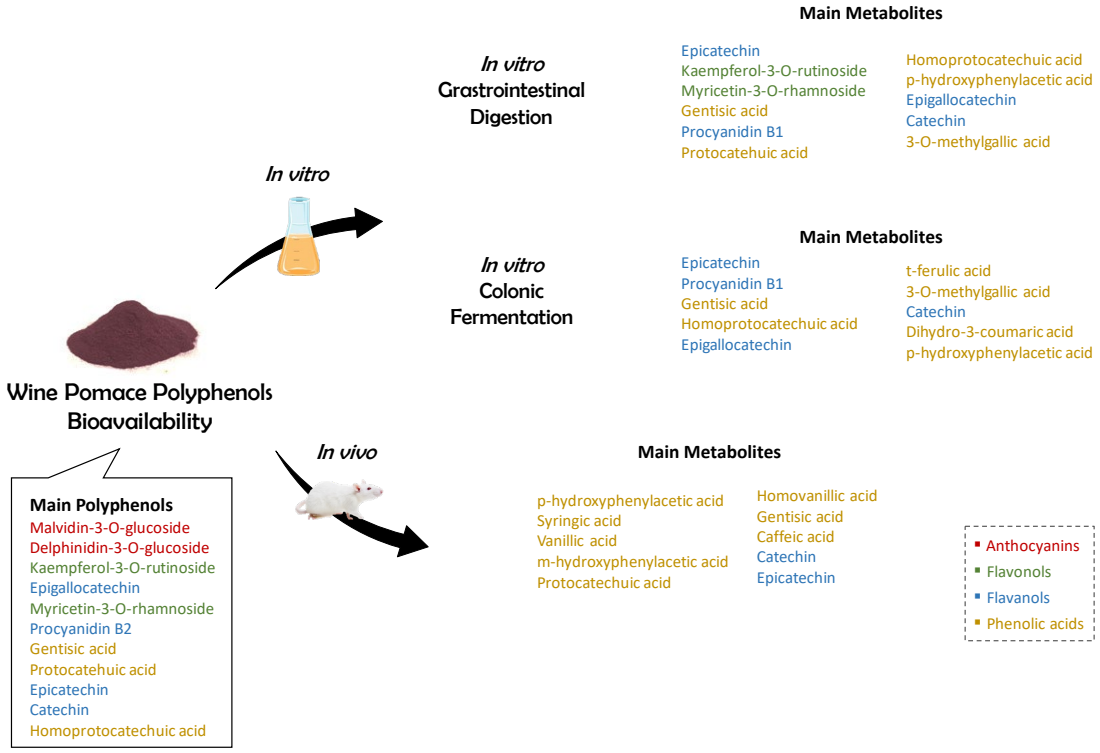

Main Metabolites
In vitro
Grastrointestinal
Digestion
Epicatechin
Kaempferol-3-O-rutinoside
Myricetin-3-O-rhamnoside
Gentisic acid
Procyanidin B1
Protocatehuic acid
Homoprotocatechuic acid
p-hydroxyphenylacetic acid
Epigallocatechin
Catechin
3-O-methylgallic acid
In vitro
Main Metabolites
In vitro
Colonic
Fermentation
Epicatechin
Procyanidin B1
Gentisic acid
Homoprotocatechuic acid
Epigallocatechin
t-ferulic acid
3-O-methylgallic acid
Catechin
Dihydro-3-coumaric acid
p-hydroxyphenylacetic acid
Wine Pomace Polyphenols
Bioavailability
In vivo
Main Metabolites
p-hydroxyphenylacetic acid
Syringic acid
Vanillic acid
m-hydroxyphenylacetic acid
Protocatechuic acid
Homovanillic acid
Gentisic acid
Caffeic acid
Catechin
Epicatechin
Anthocyanins
Flavonols
Flavanols
Phenolic acids
Main Polyphenols
Malvidin-3-O-glucoside
Delphinidin-3-O-glucoside
Kaempferol-3-O-rutinoside
Epigallocatechin
Myricetin-3-O-rhamnoside
Procyanidin B2
Gentisic acid
Protocatehuic acid
Epicatechin
Catechin
Homoprotocatechuic acid

Figure 3

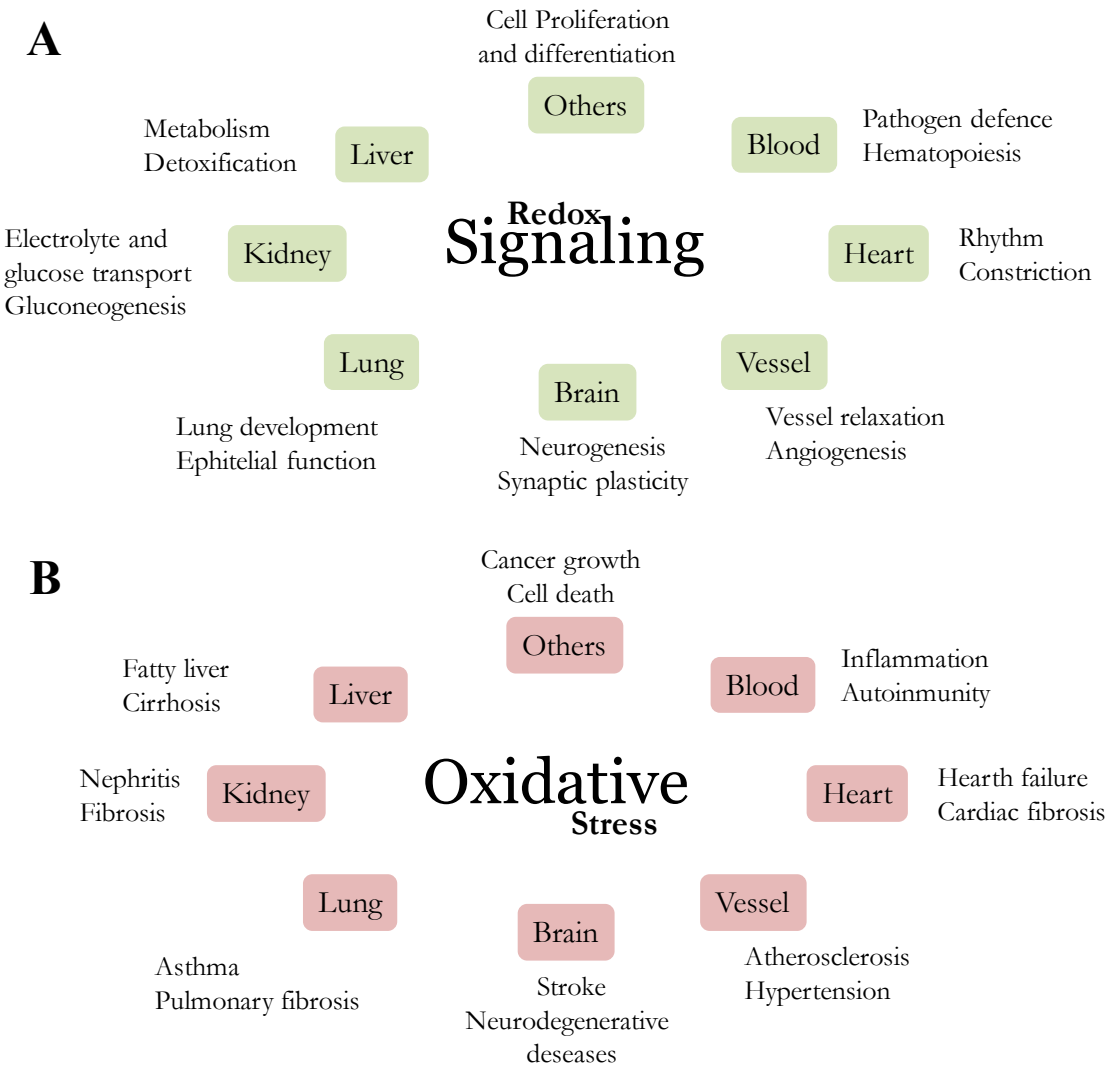

A
Cell Proliferation
and differentiation
Others
Metabolism
Detoxification
Liver
Blood
Pathogen defence
Hematopoiesis
Redox
Signaling
Electrolyte and
glucose transport
Gluconeogenesis
Kidney
Heart
Rhythm
Constriction
Lung
Vessel
Brain
Lung development
Ephitelial function
Vessel relaxation
Angiogenesis
Neurogenesis
Synaptic plasticity
B
Cancer growth
Cell death
Others
Fatty liver
Cirrhosis
Liver
Blood
Inflammation
Autoinmunity
Nephritis
Fibrosis
Kidney
Oxidative
Stress
Heart
Hearth failure
Cardiac fibrosis
Lung
Vessel
Brain
Asthma
Pulmonary fibrosis
Stroke
Neurodegenerative
deseases
Atherosclerosis
Hypertension

Figure 4

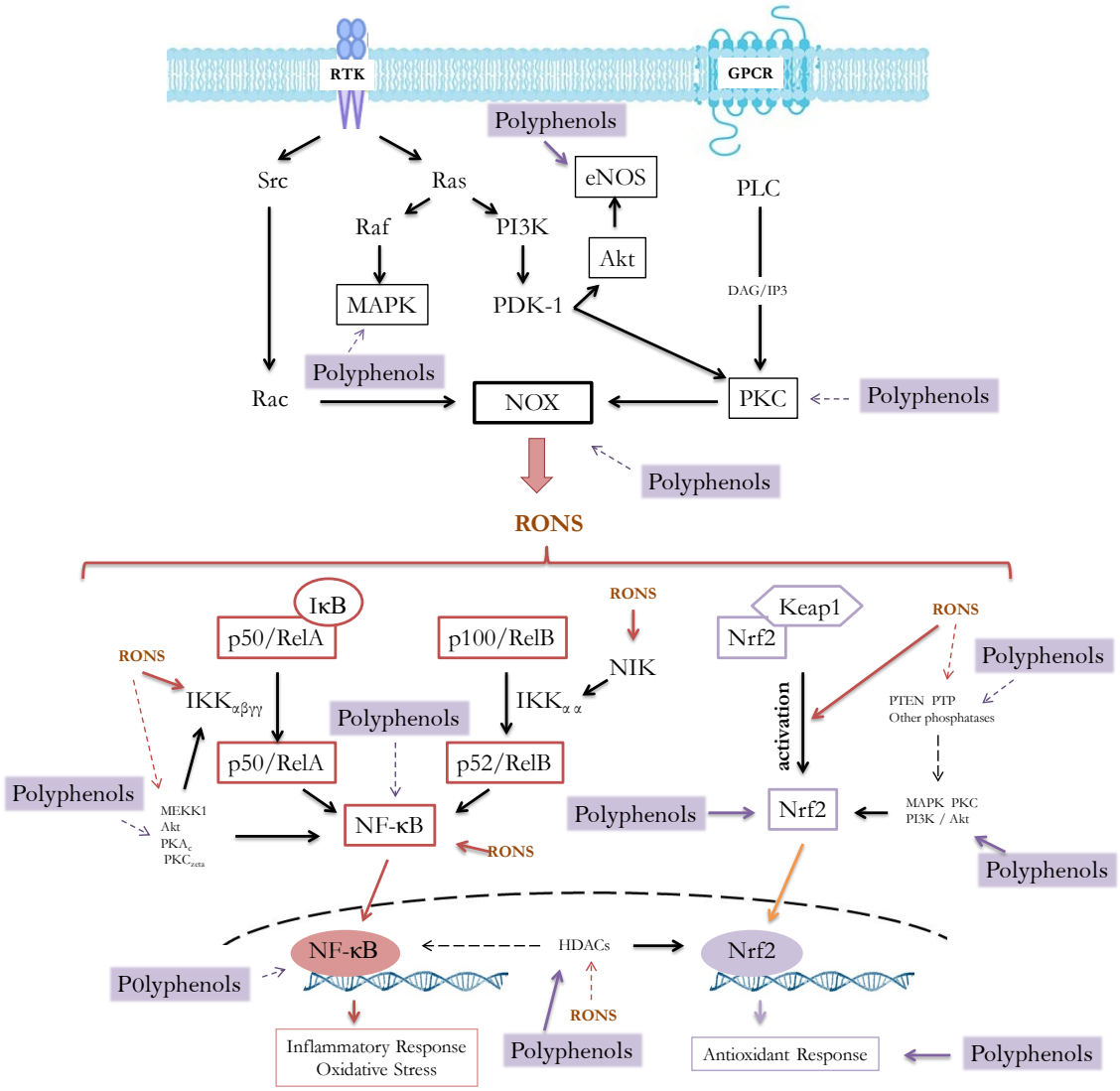

RTK
GPCR
Polyphenols
Src
Ras
eNOS
PLC
Raf
PI3K
Akt
MAPK
PDK-1
DAG/IP3
Polyphenols
Rac
NOX
PKC
Polyphenols
Polyphenols
RONS
IκB
p50/RelA
p100/RelB
RONS
NIK
Keap1
Nrf2
RONS
Polyphenols
RONS
IKK$_{\alpha\beta\gamma\gamma}$
IKK$_{\alpha\,\alpha}$
activation
PTEN PTP
Other phosphatases
Polyphenols
p50/RelA
p52/RelB
Polyphenols
Polyphenols
MEKK1
Akt
PKA$_c$
PKC$_{zeta}$
NF-κB
RONS
Polyphenols
Nrf2
MAPK PKC
PI3K / Akt
Polyphenols
NF-κB
HDACs
Nrf2
POlyphenols
RONS
Inflammatory Response
Oxidative Stress
Polyphenols
Antioxidant Response
Polyphenols

Figure 5

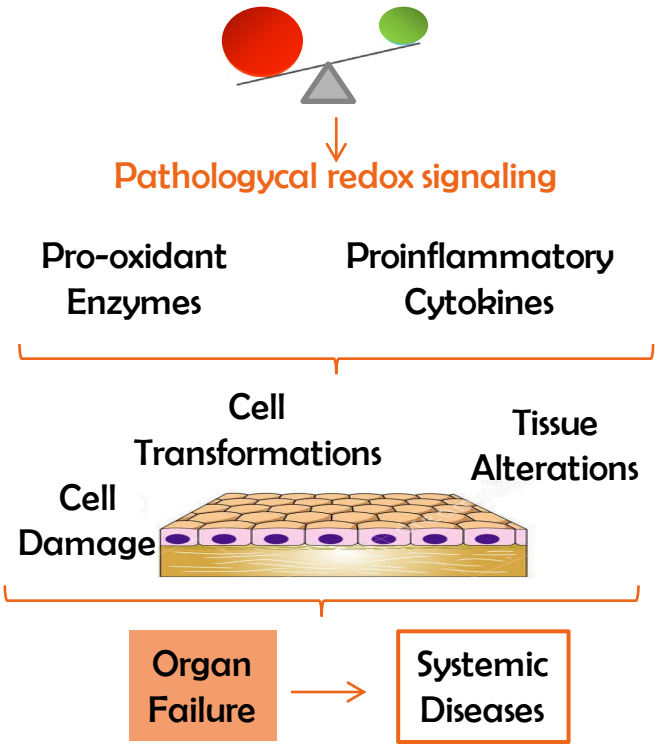

Pathologycal redox signaling
Pro-oxidant Enzymes
Proinflammatory Cytokines
Cell Transformations
Tissue Alterations
Cell Damage
Organ Failure
Systemic Diseases

Figure 6

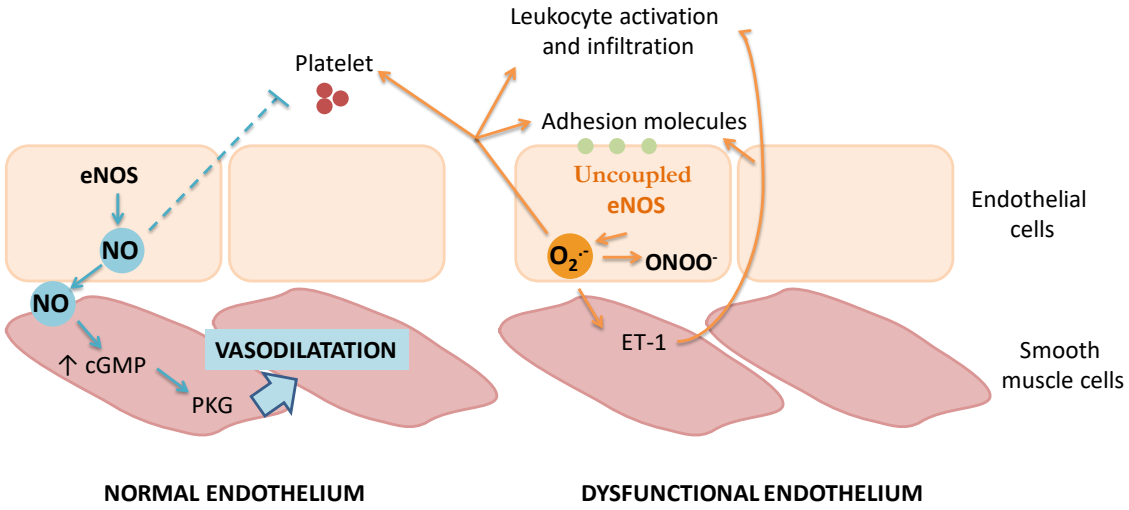


Figure 7

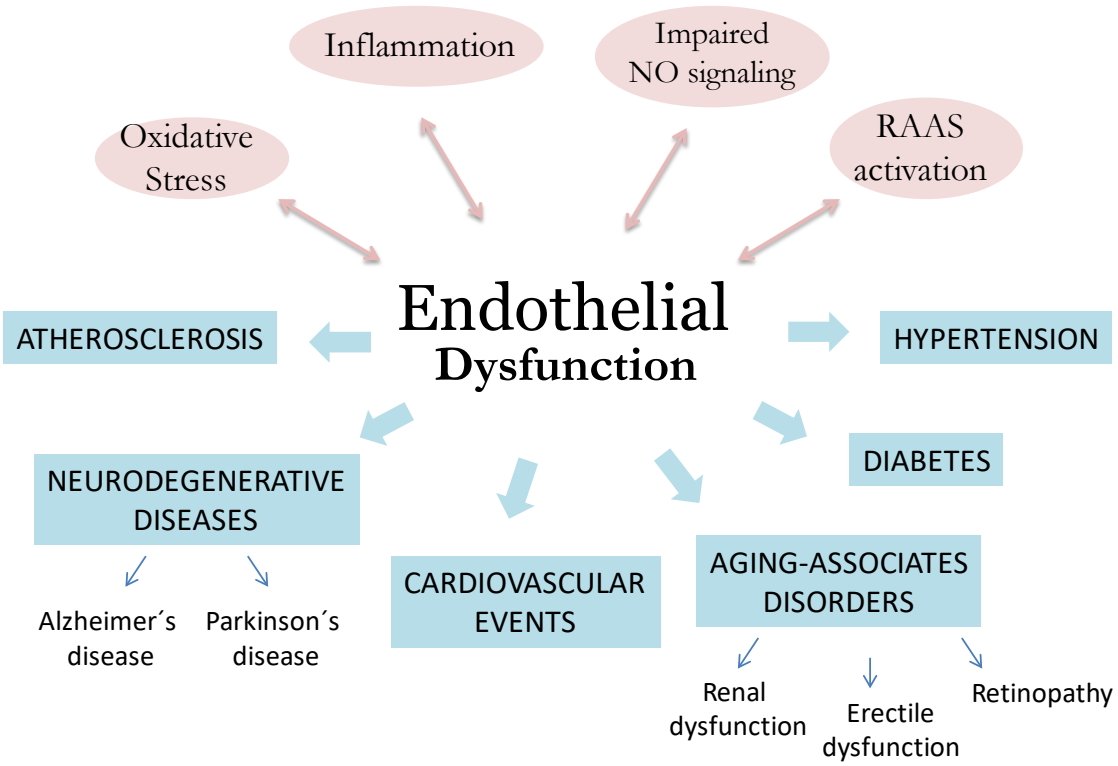
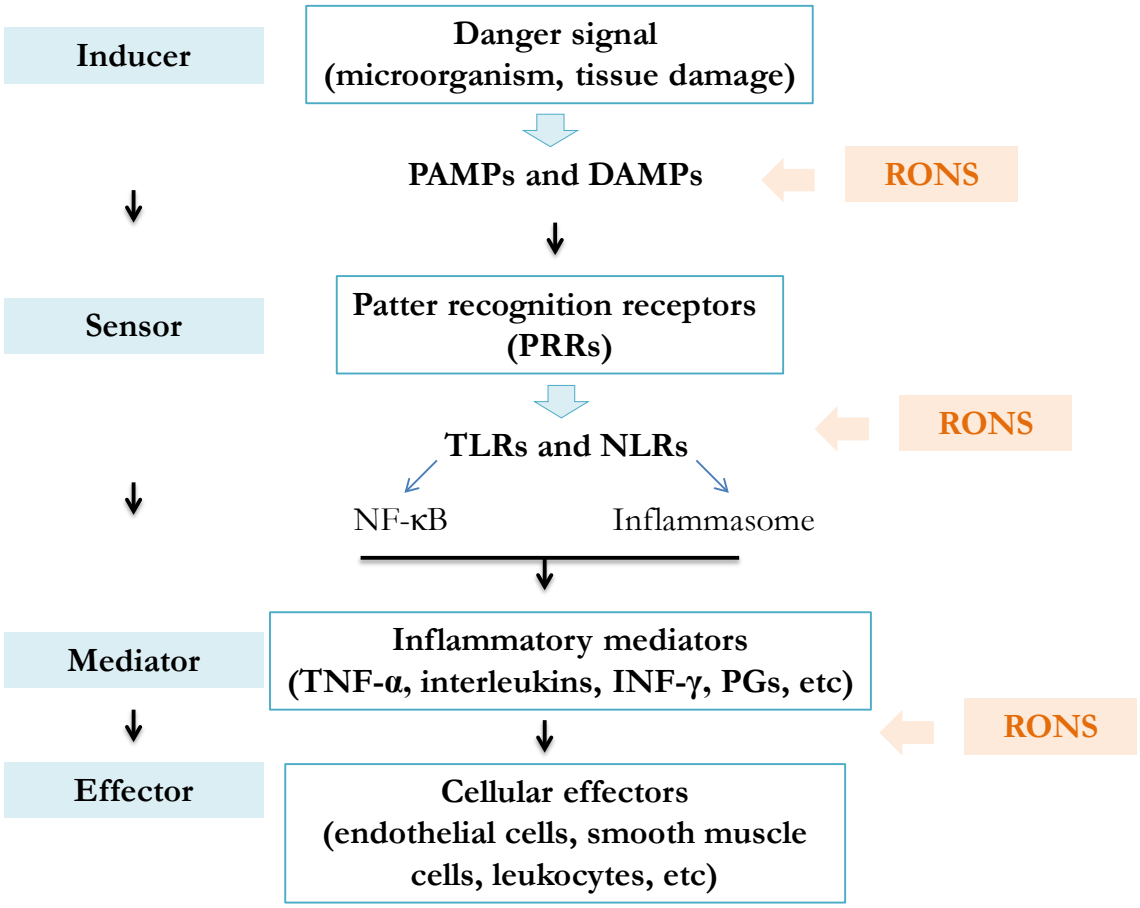
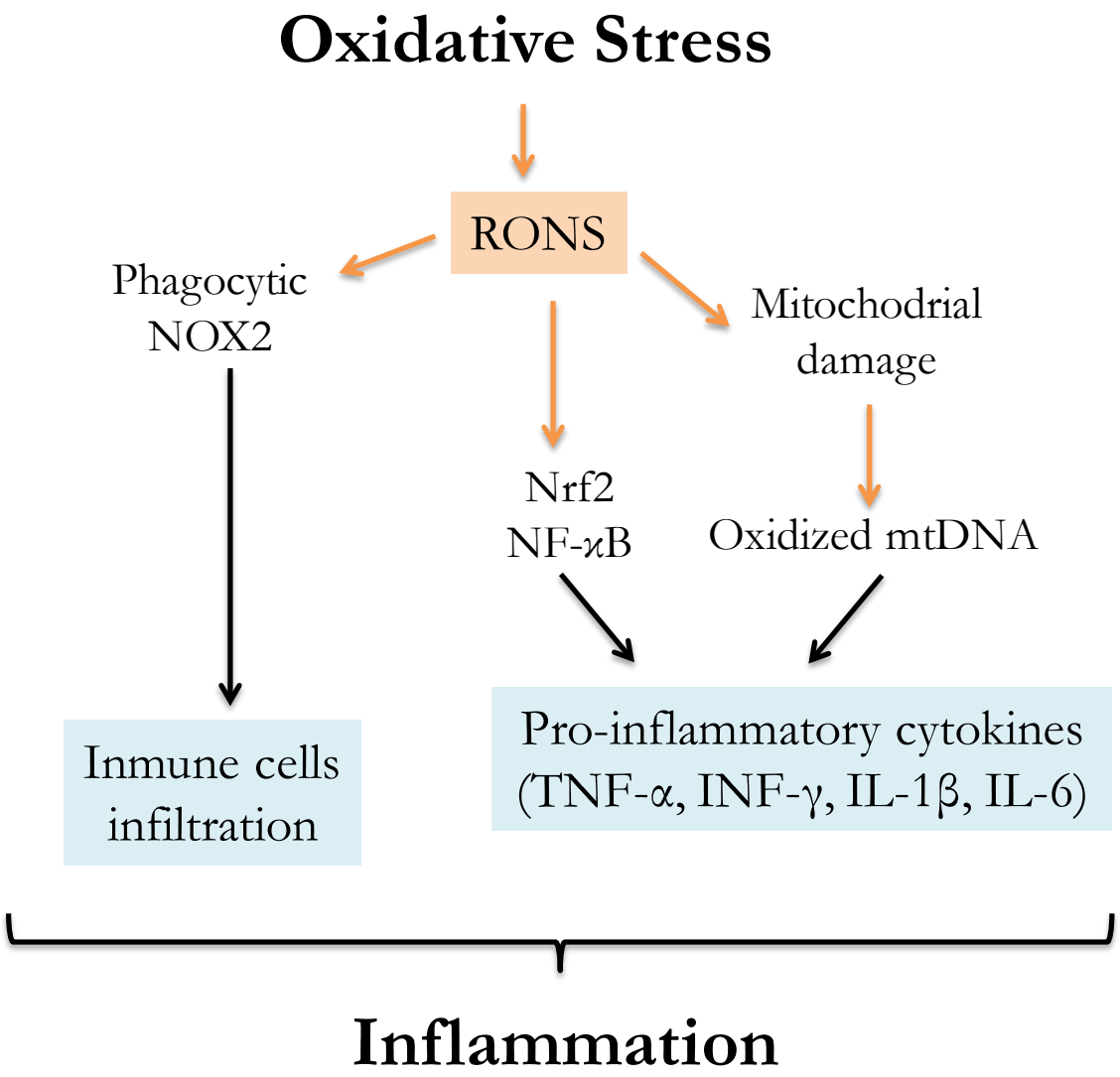


Figure 8


Inducer
Danger signal
(microorganism, tissue damage)
PAMPs and DAMPs
RONS
Sensor
Patter recognition receptors
(PRRs)
RONS
TLRs and NLRs
NF-κB
Inflammasome
Mediator
Inflammatory mediators
(TNF-α, interleukins, INF-γ, PGs, etc)
RONS
Effector
Cellular effectors
(endothelial cells, smooth muscle
cells, leukocytes, etc)

1601 **Figure 9**



1602
1603
1604
1605
1606
1607
1608
1609
1610
1611
1612

Figure 10

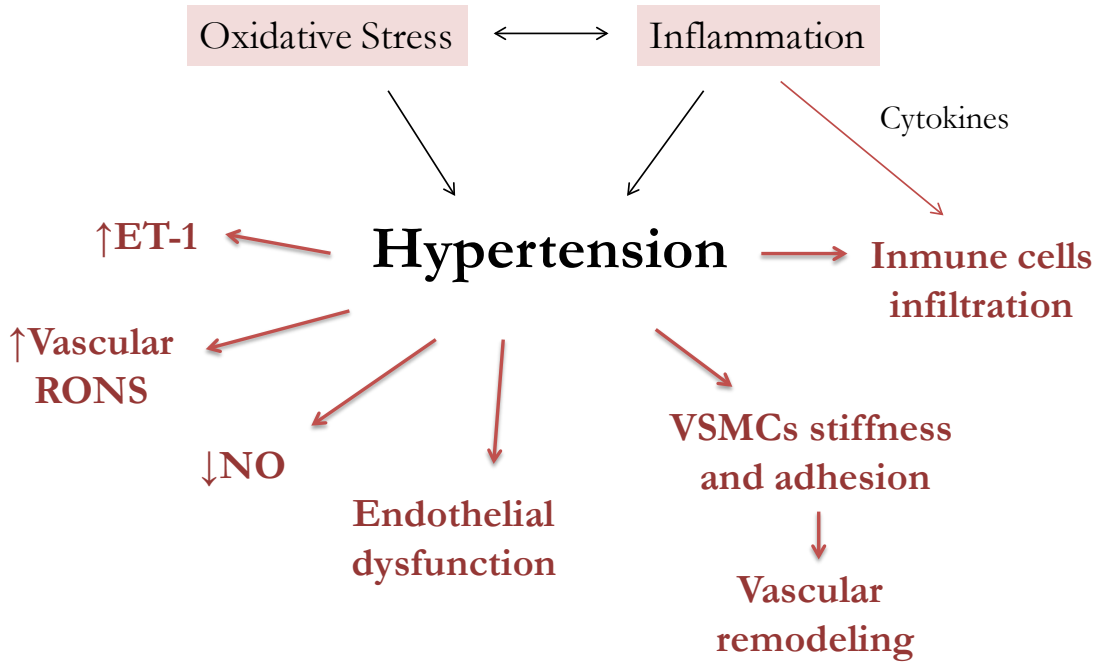


Figure 11

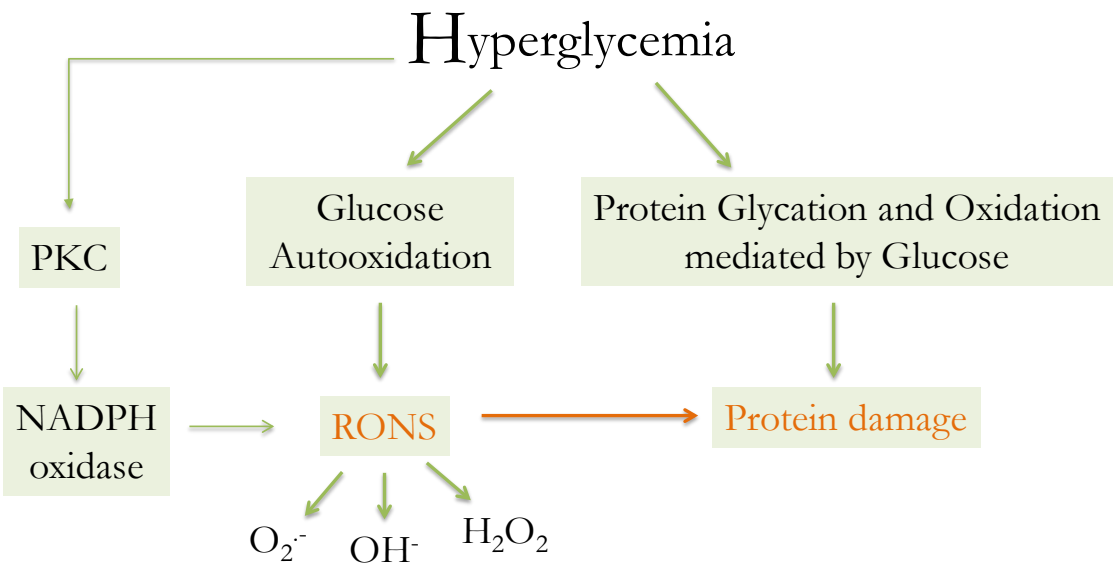
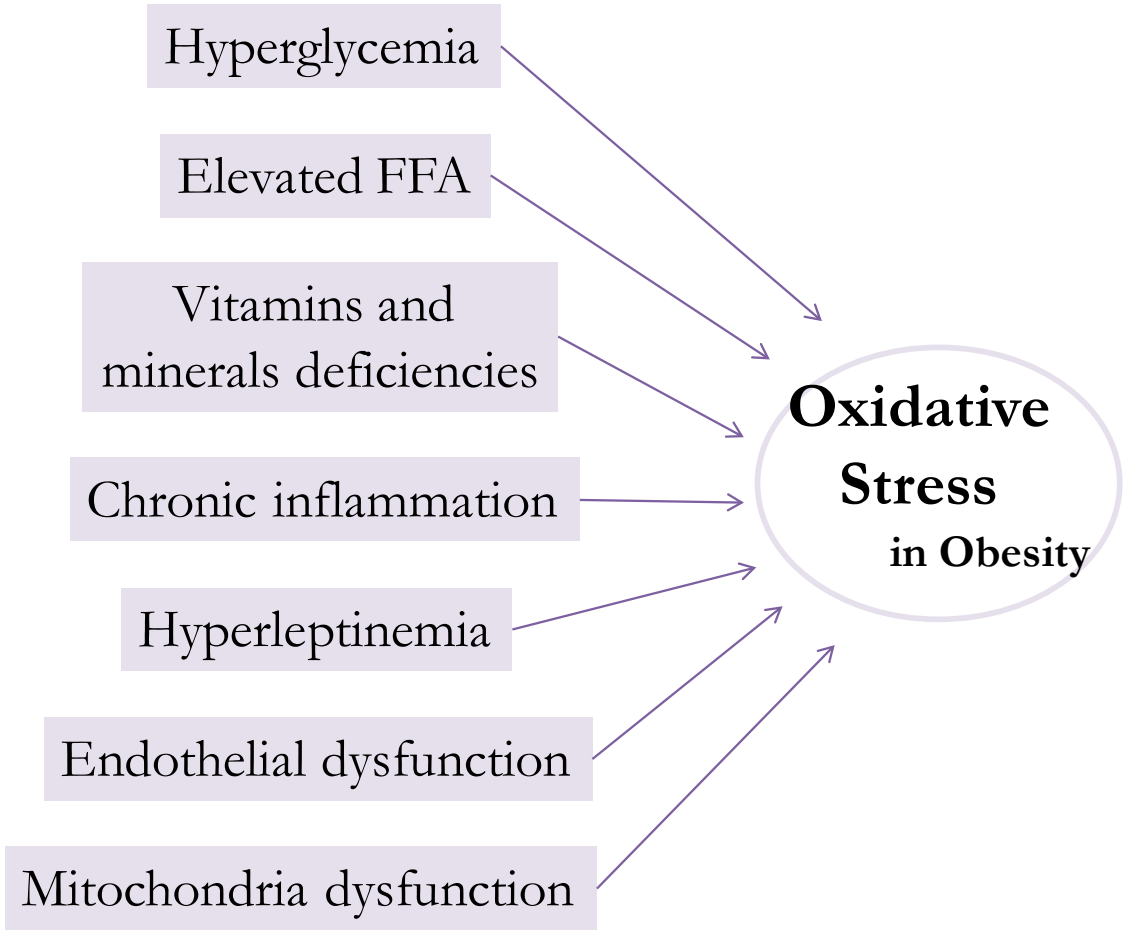


Figure 12


Hyperglycemia
Elevated FFA
Vitamins and minerals deficiencies
Chronic inflammation
Hyperleptinemia
Endothelial dysfunction
Mitochondria dysfunction
Oxidative Stress in Obesity