Chapter 11
Potential of Red Winemaking Byproducts as Health-Promoting Food Ingredients

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11.1 Introduction

The winemaking industry produces huge amounts of wastes (Nunes et al. 2017) being a sustainable source of natural health-promoting compounds (Drosou et al. 2015). The winemaking waste, called grape pomace, is composed by seeds, skins and stems. It represents an environmental problem when incinerated or discarded in landfills, causing pH decrease by phenolic compounds and degradation resistance, as well as attraction of flies and pests, foul odor, pollution and oxygen depletion of water because of tannins and other compounds (Drevelegka and Goula 2020). Grape pomace is a sustainable source of antioxidants and dietary fiber (Rivera et al. 2019). Grape phytochemicals are represented by a wide variety of bioactive compounds such as flavonoids (anthocyanins and proanthocyanidins), simple phenolics mostly derivatives of hydroxybenzoic acid (p-hydroxybenzoic, gallic, gentisic, and

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protocatechuic acids) and hydroxycinnamic acid (ferulic, p-coumaric, caffeic, and sinapic acids), stilbenes, and vitamin E (Georgiev et al. 2014). The main polyphenols found in grapes are flavonoids that present numerous properties such as antioxidant, anti-inflammatory, cardioprotective, neuroprotective, antimicrobial and antiaging (Georgiev et al. 2014; Magrone and Jirillo 2010).

Red winemaking process consists of de-stemming, pressing of grapes to release the juice (must), maceration to extract anthocyanins and tannins from skin and seeds, fermentation in tanks, settling, clarification, filtration and maturation. In the case of red wines, fermentation is done in the presence of the entire grape (juice and pomace) causing anthocyanins extraction, conducted at 28–30 °C, from the skin which gives red wine its typical color, consisting of yeasts conversion of sugar into alcohol for one or two weeks. The process is followed by pressing of the skins to extract the remaining juice and wine obtaining the winemaking residue (20–26% of grape pomace are seeds), followed by a secondary bacterial fermentation (optional) that can decrease the acidity and soften the wine taste through the conversion of malic into lactic acid. Then, settling, clarification and filtration of the wine is followed, as well as maturation which varies depending on the wine (Barba et al. 2016; Beres et al. 2017; Ribereau-Gayon et al. 2006). The polyphenolic content and profile of wine depending on the grape variety, geographic localization of vineyards, viticulture practices, and the winemaking process itself (Fourment et al. 2017; Markoski et al. 2016; Pérez-Navarro et al. 2019). White wine is obtained by the fermentation of grape juice by contrast with red wine production where the fermentation occurs on grape juice in contact with berries (skin, seeds, and stem) (Markoski et al. 2016). In consequence, the polyphenolic content of red wines is higher than in white wines, also possessing different polyphenolic profiles (Magrone and Jirillo 2010; Nardini and Garaguso 2018). Red grape color, which gives the color to red wine, is confided by anthocyanins in the skin: cyanidin, petunidin, delphinidin, peonidin, glucosides [malvidin 3-glucosides, 3-(6-acetyl)-glucosides and 3-(6-p-coumaroyl)-glucosides, peonidin and malvidin 3-(6-caffeoyl)-glucoside]. During the winemaking process, anthocyanins suffer a list of reactions (oxidation, hydrolysis, cycle-addition, condensation and polymerization) where the yeasts reabsorb and fix them onto the solid parts of the grapes such as skins. Other polyphenols, such as tannins, are the compounds responsible for astringency and bitterness (Pérez-Navarro et al. 2019). Most of the polyphenols (70%) remain in the whole by-product (grape pomace) after fermentation (Beres et al. 2019; Da Porto et al. 2015), offering a great opportunity to be used as a healthy food ingredient, natural colorant and/or preservatives to extend food products shelf-life (Beres et al. 2019; Iriondo-Dehond et al. 2018). Red wine polyphenols have shown to maintain immune system homeostasis in the host by releasing pro-inflammatory and anti-inflammatory cytokines as well as nitric oxide, inhibiting atherogenesis and preventing age-related diseases as a consequence of its immunomodulation properties (Magrone and Jirillo 2010).

Non-communicable chronic diseases are the main cause of death worldwide (71% of all deaths), which include cardiovascular diseases, cancers, respiratory diseases, and diabetes, according to the World Health Organization (WHO 2019).

These diseases are the main cause of “premature” deaths between the ages of 30 and 69 years. Metabolic risk factors such as high blood glucose, pressure, and lipids as well as obesity may lead to cardiovascular disease, which is the main chronic disease. These chronic diseases could be prevented by a healthy diet and lifestyle accomplished by routine physical activity (WHO 2019). Among the main metabolic disorders, there is glucose intolerance, insulin resistance, dyslipidemia, and overweight, which may be promoted by chronic oxidative stress and inflammation. The presence of lipids excess leads to the accumulation of fat in the adipose tissue (fat storage endocrine organ composed of adipocytes) delivering chronic low-grade inflammation by other cell types such as macrophages that are promoters of inflammation and oxidative stress. Hormones and cytokines (adipokines) are produced by the adipose tissue and could lead to an overproduction of ROS (Rebollo-Hernanz et al. 2019). Thus, obesity can lead to cellular oxidative stress and insulin resistance, cytokines release, lipid-induced impairment, and dysfunctional protein tyrosine phosphatase signaling leading to the pathogenesis of type 2 diabetes. During oxidative stress, ROS production can cause DNA damage, cell dysfunction, and organelle injury. Moreover, insulin resistance and cell dysfunction can lead to partial or total insulin deficiency, with subsequent development of type 2 diabetes. Glucose and lipids uptake excess, oxidative stress, inflammation, adipokines, and altered insulin secretion could lead to insulin sensitivity (Xu et al. 2018). As already stated, dietary polyphenols possess numerous bioactive properties that may help in the prevention and/or treatment of these diseases and their complications (Xu et al. 2018). In this sense, red grape by-products (pomace, skin, seeds, and stems) are a rich source of polyphenols, especially anthocyanins that may exert several bioactive properties and cope with prevention/treatment of chronic diseases. Grape pomace in general represents approximately 20% of grapes’ fresh weight leading to the enormous accumulation of this winemaking industry by-product despite its common use as animal feed or for grape seed oil, citric acid, and anthocyanins obtaining (Martín-Carrón et al. 2000). Thus, the valorization of winemaking by-products for human nutrition and health is of great importance.

11.2 Winemaking By-product Composition

11.2.1 Polyphenols

The intake of polyphenols is associated with the reduction of risk of chronic diseases such as heart disease, atherosclerosis, cancer and diabetes (Nash et al. 2018; Toaldo et al. 2015). These bioactive compounds may exert its antioxidant activity by scavenging oxidant molecules inside (mitochondrial ROS) and outside the cell, interacting with cell membrane proteins and lipids as cell enzymes (modifying their activity because of receptor-ligand binding) and transcription factors (DNA binding site) by the uptake of phenolic compounds into the cells (Hatia et al. 2014).

During red-winemaking polyphenols are extracted from the berry into grape juice. A study on Syrah, Marselan and Tannat wines showed that p-coumaroylated anthocyanin proportions were 5% in wines, 37% in pomace, and 19% in skins, caffeoylated anthocyanins presented higher concentrations in pomace than in skins (synthesis could take place during vinification), di-methoxylated based anthocyanins increased their relative contribution in pomace and wines compared to skins, and for the first time, an anthocyanin acylated with ferulic acid was found in wine in the Tannat samples (malvidin 3-feruloyl-glucoside) (Favre et al. 2019).

Grape pomace has a total polyphenol content of 4.8–5.4% dry matter, but only 2% of them are extractable under mild conditions (Yu and Ahmedna 2013), most of which are highly polymerized condensed tannin, and others may interact with fiber being non-extractable unless strong acidic extraction is performed (Fernández-Fernández et al. 2019; Yu and Ahmedna 2013). Grape pomace is composed of anthocyanins (delphinidin, malvidin, cyanidin), flavanols (epicatechin, catechin, epigallocatechin, gallocatechin), flavonols (quercetin, kaempferol and myricetin), phenolic acids, stilbenes (resveratrol) (Beres et al. 2017), and dietary fiber (Ajila and Prasada Rao 2013; Drevelegka and Goula 2020), including extractable phenolic antioxidants such as phenolic acid, flavonoids, procyanidins and resveratrol from grape seeds, and abundant anthocyanins from grape skins (Drevelegka and Goula 2020; Yu and Ahmedna 2013). Among grape pomace anthocyanins it can be found 3-O-monoglucosides and acetyl glucosides of delphinidin, cyanidin, petunidin, peonidin and malvidin, being malvidin 3-O-glucoside the main anthocyanin (Yu and Ahmedna 2013). Extracts (ethanol: water, 40:60 v/v) of 4 grape pomaces from *Vitis vinifera* (Cabernet Sauvignon and Merlot) demonstrated the potential of grape pomace as a source of phenolic compounds with 13 different anthocyanins, presenting antioxidant activity, as well as a rich source of PUFA (Ribeiro et al. 2015). Red grape pomace extracts obtained by conventional, ultrasound-assisted and microwave-assisted extraction revealed higher phenolic recovery for the non-conventional extraction methods (conventional phenolic recovery 5.7–48.6 mg GAE/g of grape skin), presenting ultrasound-assisted extraction the best phenolic recovery. Grape pomace extracts were composed mainly of the anthocyanin malvidin-3-glucoside, followed by quercetin (Caldas et al. 2018). Syrah red grape pomace extract showed higher contents of the anthocyanins peonidin 3-O-glucoside and malvidin 3-glucoside compared to Petit Verdot pomace extract, being malvidin 3-glucoside the main anthocyanin, and also containing phenolic acids (gallic and syringic), procyanidins B1 and B2, catechin, epicatechin, and quercetin 3-β-D-glucoside (Siqueira Melo et al. 2015). A Syrah grape pomace anthocyanin-rich extract (acidified methanol, pH = 4.0) presented 21 anthocyanins being malvidin-3-O-glucoside, malvidin-3-(6″-acetylglucoside) and malvidin-3-(6-O-p-coumaroylglucoside) the main ones (Trikas et al. 2016). An extract of red grape pomace from Portugal (80% v/v ethanol) presented (−)-epicatechin, caffeic acid, and the major compounds syringic acid and (+)-catechin (Tournour et al. 2015). Also, enzymatic assisted extraction of red grape pomace has been reported. Pectinase, cellulase and tannase extraction of Syrah grape pomace was found to enhanced the extraction yield of phenolics, by the release of gallic acid by tannase and p-coumaric acid and malvidin-3-O-glucoside by cellulase (Meini et al. 2019). Another study of red grape pomace enzymatic assisted extraction with cellulase and pectinase enzymes showed an increase in phenolics extraction by cellulase as compared to pectinase (Drevelegka and Goula 2020).

Grape seeds contain oil (13–19%) with essential fatty acids, protein (~11%), non-digestible carbohydrates (60–70%), tocopherols and beta-carotene (Yu and Ahmedna 2013) as well as nutritional macroelements (K, Na, Ca, Mg and P) and nutritional essential microelements (Fe, Cu, Zn and Mn) (Lachman et al. 2013). Red varieties contain higher amounts of Fe, Cu, Zn, and comparable values of Mn (Lachman et al. 2013). Grape seeds oil contains high amounts of unsaturated fatty acids (Yilmaz et al. 2011). Besides, polyunsaturated fatty acids (PUFA) have also been detected (Ribeiro et al. 2015), mostly present in the seeds (Manna et al. 2015). Grape seeds are a source of proanthocyanidins which possess antioxidant properties and may also have cardioprotective effects (Drosou et al. 2015; Lachman et al. 2013; Yilmaz et al. 2011), cataract prevention, anti-hyperglycemic effects, anti-inflammatory effects as well as anti-cancer efficacy (Drosou et al. 2015). Grape seeds possess monomeric phenolic compounds [(+)-catechins, (−)-epicatechin and (−)-epicatechin-3-O-gallate], and procyanidins (dimeric, trimeric and tetrameric) (Yu and Ahmedna 2013). Grape seeds from red varieties grown in Serbia were found to possess flavan-3-ols as the main phenols, most of which were gallocatechin gallate and catechin (Pantelic et al. 2016). As to red grape variety "Prokupac" seed extract, among phenolic acids ellagic acid was the most abundant, followed by gallic acid, representing a high content compared to other grape varieties seed extract, and among flavonols quercetin and isorhamnetin were the most abundant (Pešić et al. 2019).

Grape skin phenols can be located in the cell wall, bound to polysaccharides through hydrogen bonds and hydrophobic interactions, and can be confined in cell plant vacuoles or associated with the cell nucleus. During red winemaking, the fermentation of grape juice in contact with grape skin and seeds grape skin phenols suffer a mild ethanolic extraction that still leaves grape pomace with a high amount of polyphenols because of skin matrix retention (Pinelo et al. 2006). Grape skin is a source of anthocyanins, flavonols, flavonol glycosides, and hydroxycinnamic acids, whereas gallic acid and flavonols were mainly present in the seed portion (Yu and Ahmedna 2013). Red grape skin shows the highest concentration of tannins (mainly catechin, epicatechin and epicatechin gallate) (Deng et al. 2011) with a greater degree of polymerization and lower quantity of gallates when comparing with seeds, as well as containing other polyphenols such as gallic acid and its glucosides, caftaric and coutaric acid, resveratrol, quercetin and kaempferol glucosides and glucuronides (Pinelo et al. 2006). Red grape skin has higher amounts of reducing sugars, total phenolics, anthocyanin, and resveratrol than pulp (Ni et al. 2017), and its color is due to anthocyanins presence, which can be extracted by an acidic medium, are stable at low pHs and possess antioxidant activity (Fernández-Fernández et al. 2019; Vatai et al. 2009). Resveratrol, also present in red grape skin, passes down to wine during maceration, but a significant amount remains in the pomace (Yu and Ahmedna 2013). Deng et al. (2011) reported a total phenolic content of red wine grape peel was of 21.4–26.7 mg GAE/g dry matter and total flavanol content resulted in 31.0–61.2 mg CE/g dry matter and proanthocyanidin contents was of 8.0–24.1 mg/g dry matter for five wine grape pomace varieties (two white and three red). Pantelic et al. (2016) found mostly flavonols (quercetin and myricetin) and regarding anthocyanins 20 derivatives of delphinidin, malvidin, cyanidin, petunidin, and peonidin were found in 7 red grapevine varieties grown in Serbia ('Cabernet Sauvignon', 'Merlot', 'Cabernet Franc', 'Shiraz', 'Sangiovese', 'Pinot Noir' and 'Prokupac') (Pantelic et al. 2016). In the case of the red grape variety "Prokupac", skin extract presented a 24.4% of phenolic acids (mainly ellagic acid), 65.9% of flavonols (mainly quercetin and isorhamnetin, and detecting glycosides of quercetin and isorhamnetin), and approximately 6% of anthocyanins of total polyphenol content. Particularly, this grape variety contains moderate amounts of anthocyanins, which after a drying process, yields malvidin-3-O-glucoside as the most abundant anthocyanin, followed by peonidin-3-O-glucoside (Pešić et al. 2019). Among red varieties, Tannat is the richest *Vitis vinifera* cultivar in tannins containing high levels of tannins in seeds, and high levels of anthocyanins in skins at maturity (Da Silva et al. 2013), and Tannat grape skin was reported for the absence of galloylated forms and prodelphinidins ranged between 30 and 35% with very low values for epigallocatechin, as well as identifying eleven phenolic acids in Tannat grape skins and wines (Boido et al. 2011). Studies at different maceration times and different winemaking technics have shown a decrease in anthocyanins post-fermentation concentration mostly by the fixation on yeasts and solids (Boido et al. 2011).

11.2.2 Dietary Fiber

The World Health Organization recommends a 25–30 g daily intake of dietary fiber (WHO 2019). Dietary fiber consists of the "carbohydrates that are resistant to digestion and absorption in the human small intestine with complete or partial fermentation in the large intestine" (AACC Report, 2001). Dietary fiber consumption is associated with reduced risks of cardiovascular disease, cancer, and diabetes (Deng et al. 2011). The ideal ratio of soluble-insoluble fiber for consumption is 1:3. Soluble fibers are known to increase viscosity, reduce the glycemic response and plasma cholesterol, protect against inflammatory bowel diseases and prebiotic effect improving host health, whereas insoluble fibers are known for having low density, high porosity, increasing fecal bulk, and reduced diabetes risk. Soluble fiber can be fermented by large intestine microbiota producing short-chain fatty acids, positively affecting major regulatory systems (blood glucose and lipid levels), colonic environment and intestinal immune functions (Yu and Ahmedna 2013).

Grape pomace has been recognized for many years now as a potential source of dietary fiber. Red grape pomace of a mix of grape varieties was found to possess an acid detergent fiber content of 42.4%, and the neutral detergent fiber content of 48.5%, with a lignin content of 31.9%, cellulose content of 10.5%, and hemicellulose of 6.1% (Gowman et al. 2019). Grape skins' and seeds' main components are insoluble fiber and polyphenolic compounds, containing little soluble fiber (20–40 g/kg) (Martín-Carrón et al. 2000). Polysaccharides can be associated to polyphenols by covalent, ionic or hydrogen bonds, being recognized as potential antioxidant dietary fiber (Beres et al. 2019). Thus, the extraction of bioactive compounds from the grape pomace constituents' matrix represents a loss of dietary fiber component that promotes health benefits. Plant cell-wall architecture is formed by a rigid network composed of cellulose (a linear polymer of β-1,4-linked glucose) and hemicelluloses (xyloglucans and xylans) that interacts with a gel-like matrix of hydrated pectins (Drevelegka and Goula 2020). Dietary fiber architecture can be visualized as a net that entraps polyphenols and so it may be non-hydrolyzable by digestive enzymes in the small intestine. Consequently, they pass to the large intestine where they can be fermented as well as dietary fiber and so leading to systemic effects because of the production of metabolites such as phenylacetic, phenyl propionic, and phenyl butyric acids, among others. Moreover, they can just create an antioxidant environment in the colonic lumen contributing to the scavenging of free radicals and the amelioration of dietary pro-oxidants effects (Ajila and Prasada Rao 2013; Dufour et al. 2018). A clear example of a polyphenolic linkage to dietary fiber is ferulic acid, which takes part in the binding between polysaccharides and the lignin constituents. Lignin is not a polysaccharide because in its composition appears some acids through enzymatic reactions: ferulic, p-coumaric, diferulic, sinapic, cinnamic and p-hydroxybenzoic. Thus, enzymatic hydrolysis could be a solution to accomplish an effective extraction of cell wall polyphenols (Pinelo et al. 2006), as in the case of pectinase, cellulase and tannase enzymatic assisted extraction from red grape pomace enhancing the release of polyphenols from dietary fiber net (Drevelegka and Goula 2020; Meini et al. 2019). Particularly, p-coumaric acid can be released from the insoluble fraction (attached by ester bonds to lignocelluloses) or the soluble fraction (bound to small molecules by ester linkages and is stored in vacuoles or is in its free form) by cellulase (Drevelegka and Goula 2020). Furthermore, special solvent mixtures (such as acidic solvents and organic solvents: ethanol, methanol) may also achieve polyphenols release as well as green and economically viable alternatives to the conventional techniques such as ultrasound-assisted extraction (Drevelegka and Goula 2020; Fernández-Fernández et al. 2019), through the cavitation phenomenon (formation of bubbles in the liquid that favors solvent penetration) (Drevelegka and Goula 2020) and microwave-assisted extraction (Caldas et al. 2018; Drevelegka and Goula 2020) penetrating the plant matrix and favoring cell rupture by generated heat within the cell (Drevelegka and Goula 2020).

Red grape pomace fiber is mainly composed of cellulose, small proportions of pectins and hemicelluloses, finding different contents depending on the grape variety. 'Tempranillo' red grape pomace possesses 36.9% (fresh weight) and 'Manto Negro' 77.2% (dry matter) (O'Shea et al. 2012). Brazilian Pinot noir grape pomace aqueous extracts obtained in hot water showed the presence of pectic- and glucose-based polysaccharides, composed of Rha:Ara:Xyl:Man:Gal:Glc:GalA in a 3:32:2:13:11:20:19 M ratio (Beres et al. 2016).

Grape skin cell walls present neutral polysaccharides (30%, including cellulose, xyloglucan, arabinan, galactan, xylan and mannan), acidic pectin substances (20% of which 62% are methyl esterified), insoluble proanthocyanidins (approximately 15%), and structural proteins (<5%) (Pinelo et al. 2006). Deng et al. (2011) reported for grape skin that 95.5% of total dietary fiber was insoluble dietary fiber. They determined grape skin insoluble dietary fiber was composed of Klason lignin (7.9–36.1% dry matter), neutral sugars (4.9–14.6% dry matter), and uronic acid (3.6–8.5% dry matter). Total dietary fiber from red grape skin resulted in 51.1–56.3%, and soluble sugars in 1.3–1.7% dry matter, respectively (Deng et al. 2011). Grape skins also contain a small amount of pectic polysaccharides (rhamnogalacturonan I and rhamnogalacturonan II), among which pectin is widely used as a gelling and stabilizing agent and as a functional food ingredient (Beres et al. 2017). Mendes et al. (2013) also reported the chemical composition of red grape skins but in this case for the Touriga Nacional variety (20.8% cellulose, 12.5% hemicelluloses, 18.8% proteins, 13.8% tannins, 5.0% extractives soluble in dichloromethane and 7.8% ash), indicating 26.4% water-soluble compounds, which are mainly monomeric sugars (glucose and fructose), and a complex mixture of hemicelluloses (pectin, the most abundant, and acetylated glucomannan). They also stated that most structural polysaccharides amount, such as cellulose, xylan, xyloglucan and others, is entrapped in the cuticular layer and so being poorly accessible to the acid hydrolysis (Mendes et al. 2013).

11.3 Health-Promoting Properties of the Red Grape By-product

11.3.1 Antioxidant

Antioxidants are molecules that neutralize free radicals preventing the damage of biomolecules that may lead to the development of many chronic diseases. Furthermore, the normal aging process is associated with cumulative oxidative stress and low-grade inflammation (Petersen and Smith 2016). Chronic diseases such as cardiovascular disease (CVD), diabetes, metabolic syndrome, and Alzheimer's disease are associated with advanced age. Aging oxidative stress is mainly driven by reactive oxygen and nitrogen species (RONS), which include superoxide (O_2^-), hydrogen peroxide (H_2O_2), hydroxyl radical (•OH), peroxynitrite (ONO_2^-), and nitric oxide (NO). These reactive species are produced during normal body functioning (growth, repair, and immune functions) but they can also damage biomolecules. The endogenous enzymatic antioxidant system which includes superoxide dismutase (SOD), glutathione peroxidase, catalases, glutathione/TrxR, and peroxiredoxins, is often surpassed by RONS overproduction or consumption, being necessary dietary antioxidants intake (Petersen and Smith 2016). NADPH oxidase system produces ROS exerting antimicrobial mechanisms but also resulting in collateral damage to tissues such as the parenchymal cells in the brain (Glass et al. 2010). Particularly, flavonoids are good scavengers of reactive oxygen species (ROS) and up-regulate antioxidant defenses (Xu et al. 2017). Grape by-products have been recognized for having high benefit and low risk to counteract both oxidative stress and inflammation (Petersen and Smith 2016) (Fig. 11.1).

Red grape pomace antioxidant dietary fiber presented an antioxidant capacity determined by DPPH method of 153 ± 9 g of dry sample/g DPPH CE50% and FRAP 525 ± 28 μmol TE/g of dry sample) (Sánchez-Alonso et al. 2006). Red grape pomace intake (5%) has been reported for increasing the antioxidant status of piglets with increased total antioxidant status in the liver, spleen, and kidneys, through the augment of catalase activity (spleen and kidneys), superoxide dismutase activity (liver, kidneys, and spleen), and glutathione peroxidase activity (kidneys), as well as through the decrease in lipid peroxidation (liver and kidneys) (Chedea et al. 2019). Red wine grape pomace has also been reported for increasing plasma antioxidant activity in a murine model of lethal ischemic heart disease (atherogenic diet-fed

Fig. 11.1 Bioactive properties of red grape pomace

SR-B1 KO/ApoER61h/h mice), as well as reducing premature death, and changing TNF-α and IL-10 levels (Rivera et al. 2019).

As previously stated, grape pomace is a source of dietary fiber and polyphenols that interact with each other, making the extraction of grape polyphenols from the berry matrix necessary for the phenolic compounds to exert their bioactivity. Grape pomace enzymatic-assisted extraction has been studied using tannase, pectinase and cellulase enzymes to increase polyphenols release, finding an increase of antioxidant capacity with the release of caffeic acid, gallic acid, quercetin, and trans-resveratrol, mostly in the case of using tannase with 1.8 and 3.7 fold for DPPH and ORAC values as well as a mild increase of FRAP value (Martins et al. 2016). Syrah grape pomace enzymatic-assisted extraction with tannase and cellulase showed a 66% increased total polyphenol content and an 80% increased antioxidant capacity, finding tannase extraction leads to a gallic and syringic acids enriched phenolic extract while cellulase leads to a p-coumaric acid and malvidin-3-O-glucoside enriched one (Meini et al. 2019). In another study, grape pomace enzymatic-assisted extraction followed by ultrasound-assisted extraction with cellulase resulted in 48.76 ± 1.06 mg GAE/g dry pomace (Drevelegka and Goula 2020). Syrah red grape pomace extract (ethanol: water) showed 310 ± 7 μmol TE/g sample for DPPH, 653 ± 34 μmol TE/g sample for ABTS, 1363 ± 79 μmol TE/g sample for peroxyl radical (ROO·), 0.24 ± 0.01 μmol TE/g sample for superoxide radical (O_2^-) and 0.031 ± 0.001 mg/mL (EC50) for hypochlorous acid (HOCl) (Siqueira Melo et al. 2015). A Syrah grape pomace anthocyanin-rich extract (acidified methanol, pH = 4.0) presented 6.79 mM of Trolox per gram of solid wastes (IC50 = 372 ng/mL) (Trikas et al. 2016). Merlot grape pomace extracts presented the highest antioxidant capacity with 75% acetone and 50% AcN in samples, with average antioxidant activity levels of 77 g of ascorbic acid (AA) equivalents per kg of pomace DW (gAAeq/kg DW) determined by ABTS assay (Ferri et al. 2020). Grape pomace ethanol/water extracts from Portuguese grape varieties presented high antioxidant capacity determined by ORAC (906–2337 μmol TE/g residue) and chelating capacity (55–104% inhibition/mg residue) (Tournour et al. 2015). A hydroalcoholic extract of a Merlot grape pomace maintained close to normal levels several oxidative stress indicators in the plasma, liver and brain in arthritic rats (Gonçalves et al. 2017). Malbec grape pomace extract antioxidant activity determined by ORAC assay resulted in 2756 μmol TE/g extract (Antoniolli et al. 2015). Aqueous grape pomace extract obtained by ultrasound-assisted extraction presented higher phenolic content and antioxidant capacity when compared to conventional extraction and with increasing temperature (González-Centeno et al. 2015). Cabernet Sauvignon grape pomace flour presented 41.11 ± 3.01 mg GAE/g of total polyphenols, 1.49 ± 0.18 mg/g cyanidin 3-glucoside equivalents of total anthocyanin, 362.9 μmol TE/g determined by ORAC (Urquiaga et al. 2018). Red grape pomace extracts obtained by enzymatic-assisted extraction and by high hydrostatic pressure (HHP) resulted in a higher release of polyphenols (higher total polyphenols content) for the combined extraction (enzymatic complex and HPP at 200 MPa from 5 to 10 min), as well as a high proanthocyanidin extraction (Cascaes Teles et al. 2021). Grape pomace antioxidant compounds (polyphenols) have also been extracted by supercritical fluids finding catechin, procyanidin B2, epicatechin, procyanidin gallate dimer, quercetin glucuronide and syringetin glucoside and the same seven anthocyanins as the most abundant polyphenols found in Cannonau and Cabernet (Floris et al. 2010). Red grape pomace extracts from Merlot, Cabernet Sauvignon, Syrah, Petit Verdot, Tempranillo and Tintilla, obtained by two high pressure extraction techniques, supercritical fluid extraction (CO_2 + 20% ethanol) and pressurized liquid extraction (either ethanol, water or an ethanol/water mixture as the extraction solvents), demonstrated being promising techniques for the green extraction of antioxidant phenolic compounds from red grape pomace (Otero-Pareja et al. 2015).

Proanthocyanidins from grape seed extract has been found to protect antioxidant defenses, specifically, glutathione (GSH), when tested in rat primary glial cell cultures treated with LPS/IFN-γ as well as showing better tolerance against treatment with hydrogen peroxide (H_2O_2) and tert-butyl hydroperoxide when pre-treated with grape seed extract. Primary glial cells play a dual role in neuropathological processes implicating the production of nitric oxide and other radicals including their metabolites and in parallel, they produce GSH to protect other cells from oxidative stress (Roychowdhury et al. 2001). Grape seeds also contain oil with high levels of unsaturated fatty acids (90%), including linoleic (C18:2) and oleic (C18:1), as well as traces of linolenic (C18:3) and palmitoleic (C16:1). These healthy fatty acids could be extracted by supercritical fluid extraction, which represents a green alternative for grape seed oil extraction as well as to preserve its natural phytochemicals (such as antioxidant tocopherols), and has proved antioxidant capacity by DPPH (Passos et al. 2010; Prado et al. 2012). Besides, supercritical fluid extraction of grape seeds has shown to not only extract fatty acids but to also extract natural antioxidants from grape seeds such as catechin, epicatechin, gallic acid and resveratrol, where the extract was enriched in antioxidants in more than 150% concerning the starting extracts by supercritical fluid extraction (Marqués et al. 2013).

In a study conducted on two red wine grape cultivars, Pusa Navarang and Merlot, the first one showed a total phenolic content of 95.8 mg/mL, flavonoids of 30.5 mg/mL and flavan-3-ols of 21.8 mg/mL in seeds extract and its skin extract showed a total anthocyanin content of 4.9 mg/mL. Seed extract showed a better antioxidant capacity. Particularly, skin extract from Pusa Navarang showed the highest total polyphenols and anthocyanins content as well as the highest antioxidant capacity determined by ABTS, DPPH and FRAP. The study showed a correlation between antioxidant capacity and polyphenols, flavonoids and flavan-3-ols content (Doshi et al. 2015). In the case of Tannat grape skin, Fernández-Fernández et al. (2019) found an antioxidant capacity of 29.325 ± 0.897 mg/mL of dry sample by ABTS and 0.150 ± 0.011 μmol TE/mg of dry sample by ORAC-FL, while Tannat grape skin extracts presented higher antioxidant capacity by ABTS and ORAC-FL methods: hydro-alcoholic-acid (0.474 ± 0.036 mg/mL and 0.715 ± 0.063 μmol TE/mg), ethanolic (1.278 ± 0.093 mg/mL and 0.721 ± 0.077 μmol TE/mg) and ultrasound-assisted extracts (0.866 ± 0.047 mg/mL and 0.652 ± 0.031 μmol TE/mg). Hydro-alcoholic-acid extract from Tannat grape skin presented the highest antioxidant capacity which corresponds with higher total polyphenols and total monomeric anthocyanins, presenting great potential as a natural source of antioxidants useful for ROS neutralization. Deng et al. (2011) reported a total phenolic content of red wine grape peel was of 21.4–26.7 mg GAE/g dry matter and DPPH radical scavenging activity of 32.2–40.2 mg AAE/g dry matter. Total flavanol resulted in 31.0–61.2 mg CE/g dry matter and proanthocyanidin contents were of 8.0–24.1 mg/g dry matter for five wine grape pomace varieties (two white and three red). Fermented Petit Verdot grape skin (after separation of the must in the first step of fermentation) was found to possess higher total polyphenol content (185.53 ± 14.73 μg/mg DW), antioxidant capacity by DPPH (EC50 = 1.10 ± 0.14 μg of ext./μg of DPPH), a vasorelaxant-effect on small rat mesentery artery and a significant reduction on ROS production in small mesenteric artery rings when compared to basal (Albuquerque et al. 2017).

11.3.2 Anti-inflammatory

Chronic inflammation is related to many body complications that may lead to chronic diseases. As previously stated, an over-accumulation of lipids in the adipose tissue might result in the production of pro-inflammatory cytokines, nitric oxide (NO), ROS, and the up-regulation of the expression of transcription factors such as NF-κB. Moreover, other diseases involving gut inflammation such as diarrhea, irritable bowel syndrome, chronic inflammatory bowel disease and other immune-related disorders, and junction inflammation such as arthritis rheumatoid, may be prevented and/or treated by ameliorating inflammation (Chacón et al. 2009). Also, inflammatory and cytotoxic factors could cause neuronal damage in the central nervous system (Jeong et al. 2013). Inflammation is associated with several neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and multiple sclerosis (Glass et al. 2010). Chronic inflammation is also associated with obesity, diabetes and insulin resistance states, where pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF-a), interleukin 6 (IL-6), C reactive protein (CRP) and monocyte chemoattracting protein 1 (MCP-1) are secreted as well as displaying deregulation of the levels of the adipokines such as adiponectin and leptin (Chacón et al. 2009). Moreover, NF-κB pro-inflammatory transcription factor regulates the gene expression of IL-2, IL-6, IL-8, IL-1b, and T-cell surface receptors and its activation can interfere with insulin signaling (Chacón et al. 2009). Thus, the search for anti-inflammatory natural sources such as grape byproducts (Fig. 11.1) is of great interest in order to alleviate inflammation consequences.

Taking this interest into account, a lyophilized wine extract obtained from Jacquez grapes showed a decrease of IL-1β-induced nitric oxide production in a dose-dependent manner in human articular chondrocytes (Panico et al. 2006). Polysaccharides from Cabernet Franc, Cabernet Sauvignon, and Sauvignon Blanc wines have shown in vitro anti-inflammatory properties by decreasing NO production and inflammatory cytokines (TNF-α and IL-1β) (de Lacerda Bezerra et al. 2018).

Red and white grape pomace have shown to suppress chronic inflammation induced by lipopolysaccharide (LPS) and galactosamine (GalN) in Sprague–Dawley rats, when orally administered methanolic extracts. The extracts inhibited the activation of NF-κB by LPS/GalN stimulation in a dose-dependent manner, and red grape pomace effect was stronger than white grape pomace. In addition, rats fed an AIN93 M-based diet and red grape pomace-supplemented (5%) for 7 days, was found to suppress the LPS/GalN-induced activation of NF-κB and to inhibit the expression of iNOS and COX-2 proteins. Thus, red grape pomace may have anti-inflammatory potential (Nishiumi et al. 2012). Merlot grape pomace treatment of adjuvant-induced arthritic rats showed to delay the development of the paw edema as well as diminishing the infiltration of polymorphonuclear leukocytes (neutrophils) in the femoro-tibial joint cavities of the legs (Gonçalves et al. 2017). An ethanolic extract from Petit Verdot red grape pomace was found to reduce paw edema and neutrophil migration when compared with control groups as well as reducing TNF-α and IL1-β levels in the peritoneal fluid, representing an interesting source of anti-inflammatory bioactive compounds (Denny et al. 2014). Red wine grape pomace has been reported for preventing the increase of TNF-α and IL-10 levels in a murine model of lethal ischemic heart disease (atherogenic diet-fed SR-B1 KO/ApoER61h/h mice), which is an inflammatory condition, after 7 days of 20% of grape pomace flour intake (Rivera et al. 2019). Red grape pomace extract rich in anthocyanins exhibited anti-inflammatory activity against COX-1 and COX-2 (Trikas et al. 2016). Petit Verdot pomace suppressed TNF-α liberation at the concentration of 10 μg/mL in LPS-induced RAW264.7 macrophages (Siqueira Melo et al. 2015). Tannase-biotransformed grape pomace extracts were found to reduce ROS formation in Caco-2 cells before and after biotransformation at 100 and 200 μg/mL (dry extract w/v), being more potent after biotransformation in the amelioration of inflammation induced by IL-1β in Caco-2 cells, finding great potential as a functional ingredient with anti-inflammatory activity (Martins et al. 2020).

It has been studied the anti-inflammatory potential of procyanidins from grapeseed extract on human adipocytes (SGBS) and macrophage-like (THP-1) cell lines showing a reduction of IL-6 and MCP-1 expression after an inflammatory stimulus when pre-treated with grape seed procyanidin extract. In addition, grape seed procyanidin extract stimuli alone demonstrated to modulate the gene expression of adipokines (APM1 and LEP) and cytokines (IL-6 and MCP-1) as well as partially inhibit NF-κB translocation to the nucleus (Chacón et al. 2009). Grape seed extract supplementation in IL-10-deficient mice (model for human Crohn's disease), showed to down-regulate NF-κB signaling and reduce the expression of TNF-α and IFN-γ (Unusan 2020). Proanthocyanidins from grape seed extract exert no effect on LPS/IFN-γ-induced NO production or iNOS expression but enhance low-level NO intracellular production by primary rat astroglial cultures, as well as protecting GSH pool in microglial cells during high output NO production and better tolerance against H_2O_2 in astroglial cells when pre-treated (Roychowdhury et al. 2001). Furthermore, procyanidins from wild grape (Vitis amurensis) seeds significantly reduced the production of NO, PGE2, and ROS as well as inhibiting pro-inflammatory mediators' protein expression (iNOS and COX-2) and pro-inflammatory cytokines (TNF-α and IL-1β) in LPS-Induced RAW 264.7 macrophages. Moreover, procyanidins extract prevented nuclear translocation of NF-κB by diminishing inhibitory IκBα, NF-κB and MAPK phosphorylation, representing a potent anti-inflammatory (Bak et al. 2013).

Anthocyanins have shown anti-inflammatory activity as well in murine BV2 microglial cells by inhibiting LPS-induced pro-inflammatory mediators (nitric oxide and prostaglandin E2), pro-inflammatory cytokines (TNF-α and IL-1β), without significant cytotoxicity, and inhibiting the nuclear translocation of NF-κB by diminishing the degradation of NF-κB inhibitor and the phosphorylation of cellular proteins (extracellular signal-regulated kinase, c-Jun N-terminal kinase, p38 mitogen-activated protein kinase, and Akt). Also, anthocyanins downregulated the excessive expression of iNOS, COX-2, TNF-α, and IL-1β in BV2 cells stimulated with LPS (Jeong et al. 2013).

Specifically, Tannat grape skin extract (hydro-alcoholic-acid extract) has shown to reduce LPS-induced nitric oxide production on RAW264.7 macrophages when pre-treated with the extract for 24 h (prevention assay) as well as pre-treated and treated with the extract for 24 h, without displaying cytotoxic effects (Fernández-Fernández et al. 2019). In the same study, cyanidin chloride (5, 10, and 20 μg/mL) anti-inflammatory effect was reported implying this compound is the main responsible for Tannat grape skin extract anti-inflammatory activity (Fernández-Fernández et al. 2019).

11.3.3 Anti-diabetic

Type 2 diabetes is a non-communicable chronic disease that is characterized by prolonged hyperglycemia, where insulin secretion can be partially or completely inhibited, or insulin resistance. Long-term high level of blood glucose causes chronic complications, which involves microvascular lesions that can cause diabetic nephropathy, diabetic retinopathy, and diabetic neuropathy, as well as macrovascular complications which include cardiovascular and cerebrovascular diseases (Xu et al. 2018). Type 2 diabetes is also related to Alzheimer's disease which shows similar symptoms, including insulin resistance and impaired glucose metabolism, causing an insulin transport reduction to the brain with the subsequent aberrant activation of protein kinases in the insulin signaling pathway (PI3K and ERK). When glucose metabolism in the brain is abnormal, glucose autoxidation and advances glycation end products (AGEs) formation increases, which were found to be related to amyloidogenesis. AGEs interaction with its receptor (RAGE) promotes ROS production leading to oxidative stress with the subsequent degradation of the oxidative stress cellular sensor, erythroid 2-related factor 2 (Nrf2). Insulin resistance can cause the hyperphosphorylation of tau, which is a neurodegenerative disease marker such as Alzheimer’s disease, and the antioxidant system downregulation leads to neurodegenerative disorders (Liao et al. 2017). Many antidiabetic drugs (biguanides, sulfonylureas, meglitinides, thiazolidinediones, α-glucosidase and dipeptidyl peptidase-IV inhibitors, incretin mimetics, and insulin) present serious side/adverse effects (Arulselvan et al. 2014), making the search for antidiabetic natural sources of great importance such as red grape by products (Fig. 11.1).

Chronic eye diseases such as cataracts, age-related macular degeneration, diabetic retinopathy and glaucoma have become the leading cause of irreversible vision loss in the elderly population and prevention is vital because of treatment infectiveness. These chronic eye diseases are caused by oxidative stress and chronic inflammation. In the case of cataracts, the disruption of the lens protein architecture is the cause of blindness which can be caused by oxidative stress-inducing lens protein aggregation, thus flavonoids have great potential for common cataract and diabetic cataract prevention. Some grape skin flavonoids such as myricetin, cyanidin, rutin, among others, have been found to potentially inhibit diabetes-induced cataracts. Moreover, polyphenols have been related to the inhibition effects of age-related macular degeneration (AMD), more precisely, anthocyanins have been found to help reverse oxidative stress and have an ocular protective effect. Diabetic retinopathy is a microvascular complication that involves the breakdown of the blood-retinal barrier which in early stages swelling of blood vessels cause leaks and edema. Prolonged hyperglycemia induces oxidative stress by the formation of advanced glycation end products (AGEs) and cellular inflammation, leading to the damage of the retina. Polyphenols have been found to help in the prevention and/or retardation of diabetic retinopathy progression. Glaucoma is a progressive neurodegeneration that involves oxidative stress, inflammation, mitochondrial dysfunction, glial cell dysfunction and activation of apoptotic pathways. Polyphenols have been found to ameliorate the damage by positively influence inner retinal functional. Specifically, grape polyphenols have been found to reduce the expression of inflammatory cytokines and the accumulation of leukocytes in eyes and retinal leakage in C57BL/6 mice (Xu et al. 2017). An anthocyanin extract from blueberry showed protective effects against oxidative injuries induced by H_2O_2 in human retinal pigment epithelial cells through decreasing ROS and malondialdehyde levels and increasing superoxide dismutase, catalase, and glutathione peroxidase levels. Anthocyanins activated Akt-signal pathways and decreased vascular-endothelial-cell-growth-factor levels. Thus, blueberry anthocyanins could prevent and stop the progression of age-related macular degeneration by antioxidant mechanisms (Huang et al. 2018).

Risk factors comprise overweight/obesity, physical inactivity and an unhealthy diet. An important strategy for prevention and/or treatment of type 2 diabetes is the inhibition or retardation of enzymatic activities of the carbohydrases α-amylase (Sun et al. 2019) and α-glucosidase (Fernández-Fernández et al. 2019), in order to avoid post-prandial blood glucose pick, and the inhibition of advanced glycation end products (AGEs) formation (Bastos and Gugliucci 2015). Another strategy is the inhibition of glucose transporters such as GLUT-2, GLUT-4, and SGLT-1 at the level of the intestinal cell (Wang et al. 2018a). Also, the improvement of insulin receptors sensitivity by the enhancement of Akt/PI3K pathway contributes to diminish insulin resistance and to promote glucose transporters translocation to cells lipid bilayers as well as the up-regulation of glucose transporters expression. Also, type

2 diabetes involves a pro-inflammatory state as well as an overproduction of ROS which influences insulin sensitivity through insulin receptor phosphorylation and ectopic fat deposits related to the development of obesity-related cardiovascular diseases. These strategies can be approached by natural bioactive compounds such as polyphenols (Arulselvan et al. 2014; Hatia et al. 2014) with the potential of delaying diabetic complications and altering metabolic abnormalities through cellular and molecular mechanisms (Arulselvan et al. 2014). Dietary antioxidants that inhibit peroxidation chain reactions have been associated with type II diabetes risk reduction, regulating weight control, and blood glucose in diabetic patients (Doshi et al. 2015).

Intestinal glucose absorption is carried out by sodium-dependent glucose transporter-1 (SGLT1) and glucose transporter 2 (GLUT2). Free glucose concentration in the intestine lumen varies depending on the meal: before the meal, the concentration is <5 mM (low) and SGLT1 in the apical side of the enterocyte actively transports available glucose into the intestinal cell, GLUT2 in the basolateral membrane is also active postprandial to maintain cellular metabolism transporting glucose from the blood into the cell, and during the meal glucose concentration starts increasing (5–10 mM) and is transported by SGLT1 from the intestinal lumen and subsequently into the systemic circulation via GLUT2 (Wang et al. 2018a). After the meal, very high glucose concentrations (25–100 mM) are detected because of food carbohydrates hydrolysis by α-glucosidase located on the apical enterocyte membrane, producing monosaccharides that are absorbed by SGLT1 and GLUT2 in the apical side. There has been evidence of inhibition of GLUT2 by flavonoids such as quercetin and myricetin (Wang et al. 2018a) that are present in red grape pomace. Anthocyanins have shown several antidiabetic activities. These may decrease glucose levels, activate insulin receptor phosphorylation, increase GLUT-4 expression, and prevent pancreatic apoptosis in STZ-induced diabetic rats. They might also activate AMPK, up-regulate GLUT4 to improve insulin sensitivity, suppress glucose production and inactivate acetyl-CoA carboxylase in T2DM mice. Also, anthocyanins could enhance the secretion of adipokine (adiponectin and leptin), as well as increasing the mRNA levels of PPARγ in isolated rat adipocytes. Among anthocyanins, cyanidin 3-glucoside has shown to ameliorate insulin sensitivity and hyperglycemia, up-regulate GLUT-4 levels, reduce the levels of fasting glucose, and to reduce the secretion of inflammatory cytokines via JNK/FoxO1 signaling pathway (Xu et al. 2018). Anthocyanins from purple corn have shown antidiabetic (insulin secretion activity, anti-hyperglycemic activity, and HbA1c-decreasing activity) and beta cell-protection activities from cell death in HIT-T15 cell culture (pancreatic beta cell culture) and db/db mice (Hong et al. 2013). Proanthocyanidins have been reported for inhibiting digestive enzymes such as α-amylase and α-glucosidase, decreasing hyperinsulinemia (enhance adiponectin secretion in white adipocytes and promote GLUT-4 expression in skeletal muscle), reducing postprandial glycemia, improving insulin sensitivity, inhibiting insulin and β-cell mass secretion, and reducing anti-inflammatory activity (Unusan 2020).

Bioactive polysaccharides have shown to restore the body and fat mass weight, improve glucose tolerance ability, reduce fasting blood glucose levels, increase hepatic glycogen level, ameliorate insulin resistance, increase HDL-C levels and decrease TC, TG and LDL-C levels, when tested on a high-fat diet and STZ-induced type 2 diabetic mice compared to the control diabetic mice. It also showed to alleviate lesioned organ tissues such as liver, kidney, and pancreas, and to be involved in activating PI3K and Akt phosphorylation as well as the translocation of GLUT4 in diabetic mice (Wang et al. 2017b).

Pusa Navarang and Merlot grapes by-products (seeds, skin and berry stems) have shown to stimulate insulin secretion on mice pancreatic islets at basal glucose level (5.5 mM) and at enhanced glucose level (16.5 mM) compared to mice without extracts supplementation (insulinotropic effects). Pusa Navarang grape skin and stems presented the highest insulin stimulation in both conditions with a better stimulation of secretion by the berry stems' extract. In the case of grape skin, anthocyanins could be responsible for the insulinotropic effect. Grape pomace extracts exert an anti-postprandial hyperglycemic effect, which could be a source of antioxidants and anti-hyperglycemic compounds to regulate blood glucose levels and oxidative stress associated with Type 2 diabetes (Doshi et al. 2015). Red wine grape pomace flour has shown to improve fasting glucose and postprandial insulin levels in a randomized controlled trial of 16-week conducted on 38 human males (30–65 years of age) with at least one component of metabolic syndrome (Urquiaga et al. 2015).

Altered glucose metabolism in the brain is associated with cognitive decline, and powder from Taiwan grapes was found to reduce RAGE expression and tau hyperphosphorylation in the brain tissues of aged Wistar rats fed with high-fructose–high-fat diet and 6% of grape powder. In contrast, grape powder upregulated the expression of Nrf2 and BDNF, and the phosphorylation of PI3K and ERK. Thus, grape powder demonstrated the potential to ameliorate changes in proteins associated with neurodegeneration in the brain of aged rats fed a high-fructose–high-fat diet (Liao et al. 2017).

Red grape pomace extracts obtained by enzymatic-assisted extraction and by high hydrostatic pressure (HHP) were found to inhibit α-amylase in a 92.31% (IC50 = 0.054 g/mL) for the combined extraction (enzymatic complex and HPP at 200 MPa from 5 to 10 min) (Cascaes Teles et al. 2021). Tannat grape skin has demonstrated α-glucosidase inhibition capacity for several extracts. IC50 values for α-glucosidase inhibition capacity were reported for hydro-alcoholic-acid, ethanolic and ultrasound-assisted extractions (888.5 ± 79.3, 2584.1 ± 211.1, and 1966.1 ± 109.4 μg/mL, respectively), compared to acarbose, chlorogenic acid, and cyanidin chloride standard (4.0 ± 0.3 μg/mL, 69.1 ± 1.6 μg/mL, and 95.5 ± 1.8 μg/mL, respectively). Hydro-alcoholic-acid Tannat grape skin extract rich in anthocyanins, showed the best inhibition capacity among the extracts, suggesting its potential in helping with the regulation of type II diabetes by retarding post-prandial blood glucose increase (Fernández-Fernández et al. 2019). Berry extracts from black currant and rowanberry showed inhibition of α-glucosidase with IC50 values of 20 and 30 μg GAE/mL respectively, being as effective as acarbose (pharmaceutical inhibitor) (Boath et al. 2012).

11.3.4 Anti-obesity

The abnormal or excessive accumulation of fat in the body is called overweight and obesity, respectively, which are associated with the development of metabolic diseases such as metabolic syndrome, hypertension, cardiovascular diseases and type 2 diabetes (Hatia et al. 2014). At the cellular level, obesity characterizes by an augment in the number (hyperplasia) and size of adipocytes (hypertrophy). Adipocytes TAG synthesis may be a body mechanism to counteract the large number of other molecules present in the blood, mainly fat and glucose, implying a risk increment of hyperlipidemia and hyperglycemia due to its inhibition, to lipotoxicity and glucotoxicity, respectively. Lipotoxicity is associated with diabetes pathogenesis as a consequence of lipid overloaded pancreatic β-cells leading to a reduction in β-cell mass (Torabi and DiMarco 2016).

Higher consumption of nutrients (carbohydrates and fat) than needed leads to overweight and obesity. Thus, the inhibition of fat absorption involving pancreatic lipase enzyme may prevent/treat obesity. Accumulation of fat induces an augment on preadipocytes' proliferation and differentiation into adipocytes. In consequence, adipocytes present intracellular dysfunction involving endoplasmic reticulum and mitochondrial stress. Free fatty acids cause reticulum stress leading to oxidative stress in the mitochondria, generating an imbalance on reactive oxygen species (ROS). Cell overproduction of ROS in adipocytes induce insulin resistance, contributing to diabetes caused by obesity. ROS reduce antioxidant endogenous system leading to the damage of free radicals and peroxides on biomolecules (DNA, lipids, and proteins) as well as the dysregulation of adipokine secretion. Consequently, it causes the production of pro-inflammatory cytokines (interleukin-6, tumor necrosis factor-α, monocyte chemoattractant protein-1) and the reduction in anti-inflammatory molecules (adiponectin) by preadipocytes, macrophages and adipose stem cells. Adipose tissue chronic inflammation caused by cytokines secretion seems to play an important role in desensitizing cells to insulin (Hatia et al. 2014). Thus, obesity is related to oxidative stress and inflammation (Gerardi et al. 2020).

Polyphenols, particularly proanthocyanidins (condensed type tannin bonded by condensation or polymerization such as flavan-3-ols and flavan-3,4-diols) have been found to inhibit pancreatic lipase (Shihui Wang et al. 2014). Polyphenols (epicatechin gallate, chlorogenic acid, 3,4-dihydroxy-benzaldehyde, naringenin, quercetin and the microbial metabolite 3,4-dihydroxyphenylacetic acid) have shown to reverse the detrimental effect of H_2O_2 and cytotoxicity on 3T3-L1 preadipocytes. Besides, epicatechin gallate, epicatechin, genistein, naringenin, curcumin and 3,4-dihydroxyphenylacetic acid reduced basal IL-6 secretion as well as H_2O_2 co-exposition (Hatia et al. 2014). Proanthocyanidins stimulate glucagon-like peptide 1 (GLP-1)/dipeptidylpeptidase 4 (DPP4) activity that inhibits the neuropeptides associated with food consumption and satiety, as well as inhibiting fat absorption through lipase inhibition, reducing adipocyte hypertrophy, decreasing hyperinsulinemia (enhance adiponectin secretion in white adipocytes and promote GLUT-4 expression in skeletal muscle), inhibiting insulin and β-cell mass secretion, and decreasing obesity-mediated chronic inflammation (Unusan 2020).

In another study conducted on 3T3-L1 and 3T3-F442A fibroblasts or preadipocytes (common in vitro models for studying adipocyte differentiation), authors showed that grape pomace extracted polyphenols upregulated protein level of glucose transport protein 4 (GLUT4), p-PKB/Akt, and p-AMPK in 3T3-F442A. Adipocytes also showed increased mRNA expression of fatty acid synthase, lipoprotein lipase, adiponectin, GLUT4, and peroxisome proliferator-activated receptor γ, while it decreased mRNA expression of leptin and Insig-1. The authors stated grape pomace extracted polyphenols may induce adipocyte differentiation by the upregulation of adipogenic genes, GLUT4, and PI3K (Torabi and DiMarco 2016). Red wine pomace (*Vitis vinifera L.* cv. Tempranillo) intake in Wistar rats (100 mg/kg body weight) was found to reduce body weight, abdominal fat area, liver weight and lipids deposition with increased antioxidant status, blood glucose levels, adipocyte size and increased Lactobacillus spp./Bacteroides spp. ratio (Gerardi et al. 2020).

In particular, Tannat grape skin has shown pancreatic lipase inhibition capacity for hydro-alcoholic-acid (IC50 = 2431.0 ± 79.9 μg/mL), ethanolic and ultrasound-assisted extracts, compared to chlorogenic acid, cyanidin chloride, gallic acid, caffeine, and rutin IC50 values (11.9 ± 1.4 μg/mL, 56.9 ± 6.6 μg/mL, 332.5 ± 32.1 μg/mL, 241.1 ± 0.8 μg/mL, and 290.0 ± 20.6 μg/mL, respectively). The hydro-alcoholic-acid extract showed the best pancreatic lipase inhibition capacity of the studied extracts, suggesting a great potential for obesity treatment (Fernández-Fernández et al. 2019).

11.3.5 Cardiovascular Health Properties

Cardiovascular diseases are associated with modified fatty acid metabolism and LDL's excessive lipid peroxidation, which implicates the formation of thromboxane, leading to enhanced platelet aggregation, with the consequent artery blockage and thrombosis (Yu and Ahmedna 2013). The accumulation of lipid oxidation products from LDL could be prevented by the presence of plasma antioxidants. ROS overproduction is associated to several disorders such as hypertension, which comprises an augment on superoxide anion and hydrogen peroxide formation, the reduction of nitric oxide synthesis, as well as decreased antioxidant bioavailability (Albuquerque et al. 2017). It is known that high concentrations of serum cholesterol, in particular LDL-cholesterol, represents a risk factor for atherosclerosis (accumulation of cholesterol deposits at the arterial wall that triggers an inflammatory response which contributes to the development of ischemic cardiovascular disease) and coronary heart disease, which can be reduced by lowering plasma lipid concentrations, especially LDL, and by increasing plasma HDL concentrations (protective against coronary heart disease) (Martín-Carrón et al. 2000; Rivera et al.

2019). Some polyphenols are known to reduce the absorption of cholesterol at the intestine of rats by diminishing the solubility of cholesterol in micelles. Consequently, bile acids return to the liver is lowered, leading to an augment on their hepatic synthesis from cholesterol, which causes a higher expression of hepatic LDL receptors that involves a reduction of LDL lipoproteins and serum cholesterol (Martín-Carrón et al. 2000). Fruit and fiber increase intake is associated with a risk reduction of cardiovascular disease (Zhu et al. 2015). In addition, soluble dietary fiber possesses hypocholesterolemic activity by forming gels in the gastrointestinal tract that decrease the absorption of cholesterol in the intestinal lumen (Pérez-Chabela and Hernández-Alcántara 2018).

Red wine grape pomace has been reported for attenuating atherosclerosis and myocardial damage in a murine model of lethal ischemic heart disease (atherogenic diet-fed SR-B1 KO/ApoER61h/h mice fed with 20% of grape pomace flour), as well as to increase the survival by improving plasma antioxidant activity (increased HDL-containing plasma antioxidant activity) and modulating inflammation by decreasing pro-inflammatory cytokine (TNF-α and IL-10) levels, having the potential to decrease the progression of atherosclerosis, reduce coronary heart disease, and improve cardiovascular outcomes (Rivera et al. 2019). Red grape pomace intake (20 g/day) in a 16-week longitudinal intervention study with 38 males (30–65 years of age) significantly decreased systolic and diastolic blood pressure (Urquiaga et al. 2015). Grape products have shown a reduction of atherogenic markers, cardioprotection and reduction of the effects in lipid profile and blood pressure. Moreover, grape pomace intake in Wistar rats have shown to reduce HMG-CoA reductase activity in the liver (the enzyme that participates in cholesterol synthesis) and increase the fractional plasma cholesterol catabolic rate (Zhu et al. 2015). Martín-Carrón et al. (2000) conducted a study on adult Wistar rats, finding that the intake of grape products increased stool weight and the amount of fat and protein excreted in feces as well as lowered serum total cholesterol and LDL cholesterol concentrations in hypercholesterolemic rats. Cholesterol-free diet rats were fed with red grape peel obtaining an increment on HDL-cholesterol compared to rats fed with cellulose, but on changes were found on triglyceride concentrations. On the cholesterol-added diet, rats decreased total cholesterol and LDL-cholesterol concentrations compared to the control group, not finding changes on HDL cholesterol and triglyceride concentrations. Grape skin effect on cholesterol and lipoprotein concentrations could be attributed to fiber characteristics or to the polyphenolic fraction (Martín-Carrón et al. 2000).

Procyanidins have shown to inhibit human endothelial NADPH oxidase, which is responsible for ROS overproduction and resveratrol alone has shown anti-atherogenic and anti-inflammatory effects in hypercholesterolemic-diet rabbits (1% cholesterol) (Yu and Ahmedna 2013). Moreover, the main vasoactive polyphenols in red wine are proanthocyanidins, which induce the endothelium-dependent dilatation of blood vessels and inhibit vasoconstrictive peptide endothelin-1 synthesis (Da Silva et al. 2013). Proanthocyanidins contribute to cardiovascular health by diminishing lipid peroxidation, contributing to lipid homeostasis by enhancing the opposite transport and removal of cholesterol in bile, decreasing plasma triglycerides and apolipoprotein B, reducing atherosclerotic risk, reducing dyslipidemia, inhibiting lipoprotein secretion, antihypertensive properties (e.g. by delayed endothelial aging), reducing blood pressure, plasma homocysteine concentrations, and serum C-reactive protein (Unusan 2020).

Petit Verdot grape skin extract from pomace, fermented and unfermented (fresh) grape skins were found to elicit vasorelaxation as well as in vitro free radical scavenger activity confirmed by determining ROS production in small mesenteric artery rings of rats. The vasorelaxation induced by fermented grape skin was about 10 times more potent than that induced by the unfermented. The results suggested that the mechanism of action is dependent on endothelium-derivative relaxant factors such as NO and EDHF. ROS formation in treated vessels (fermented and unfermented) was significantly reduced when compared to basal conditions, but fermented grape skin showed a marked antioxidant effect on the tissue (Albuquerque et al. 2017). Anthocyanins seem to have a positive role in preserving cardiovascular health, lowering the risk of myocardial infarction and mortality related to cardiovascular diseases, but the underlying molecular mechanisms of action are not entirely clear (Krga and Milenkovic 2019).

11.3.6 Anti-carcinogenic

Cancer development is associated with abnormal cell cycle progression, abnormal cell proliferation, oxidative stress damage, and inhibition of cancer cells' apoptosis (programmed cell death), acting on intracellular molecular signaling related to the initiation and/or promotion of cancer. Dietary polyphenols may have a positive effect on fighting the onset of cancer by antioxidant properties, protein kinases' inhibition, reduction of protease activities, altering phase-I and phase-II drug-metabolizing enzymes, blocking of receptor-mediated functions, alteration of cell cycle checkpoint controls, transcription factor expression and apoptosis, epigenetic changes in promoter methylation and chromatin remodeling, inhibition of angiogenesis, invasion and metastasis (Yu and Ahmedna 2013). The most important bioactive compounds with anti-cancer activity are flavonoids (Georgiev et al. 2014), such as the ones present in red grape byproduct (Fig. 11.1).

Procyanidins present in grape seeds have shown to exert cytotoxicity on human breast, lung, gastric adenocarcinoma cells while enhancing the growth and viability of gastric mucosal cells. Furthermore, grape seed extract has shown to protect skin from UV-radiation-induced oxidative stress (which may lead to skin cancer) and to activate the signals mediated by mitogen-activated protein kinase and NF-κB in human epidermal keratinocytes. It may also be helpful in the treatment of colorectal cancer by growth inhibitory and apoptosis-inducing effect as well as in the inhibition of MOLT-4 leukemia cell growth. On the other hand, resveratrol has shown to inhibit tumor initiation, promotion and progression as well as enhancing apoptotic effects of cytokines, chemotherapeutic agents and gamma-radiation (Yu and Ahmedna 2013). Proanthocyanidins present antiproliferative and antiangiogenic effects, induce apoptosis, cell cycle arrest, and inhibit metastatic processes in the lung, liver, pancreas, colorectal, prostate, breast, and skin (Unusan 2020). Lyophilized red grape pomace also shows a chemopreventive effect on spontaneous intestinal tumorigenesis in the ApcMin/+ mouse model and grape powder seems to have a beneficial in the prevention of colon cancer (Zhu et al. 2015). *Vitis vinifera* "Currant" and "Sultana" extracts exhibited anti-cancer activity by the prevention of colon cancer for their antioxidant and anti-inflammatory properties, and grape seed proanthocyanidins reduced cell viability and induced apoptosis in a dose- and time-dependent manner in human pancreatic cancer cells (migration inhibition by inactivation of NF-κB) (Georgiev et al. 2014).

11.3.7 Gut Microbiota Health Improvement

Beneficial gut microbiota (genera Lactobacillus and Bifidobacterium) is associated with health improvements through vitamin synthesis (B-group and K), conversion of non-digestible food components (dietary fiber) into short-chain fatty acids, pathogens degradation, modulation of the immune system of the host, influence on brain development and as a modulator of host behavior ('microbiota-gut-brain-axis'). On the other hand, Clostridium, Eubacterium and Bacteroides involve negative effects on health such as diarrhea, irritable bowel syndrome, chronic inflammatory bowel disease and other immune-related disorders, as a consequence of the disruption or dysbiosis of gut microbiota (Nash et al. 2018). A higher Firmicutes/Bacteroidetes ratio is associated with obese and metabolic syndrome subjects (Espín et al. 2017).

Soluble dietary fiber has shown to reduce body weight gain and excessive accumulation of white fat tissue in a high fat diet-induced obese mouse model, and gut microbiota was characterized by a decreased ratio of Firmicutes/Bacteroidetes (phylum level), and an increased abundance of the genera Roseburia (genus level). Also, it was observed an increase in energy expenditure, but not a change energy intake. Thus, the increment of gut microbiota diversity and the colonization of beneficial bacteria by soluble dietary fiber intake improves energy homeostasis and prevents obesity (Wang et al. 2018b). There is also evidence of polyphenols with prebiotic effect promoting gut health, such as ellagitannins, lignans, isoflavones and flavanones that are substrates for the gut microbiota and may exert health benefits in the gastrointestinal tract by their gut microbiota-derived metabolites involving systemic effects (Espín et al. 2017). Randomized controlled trials have stated a significant modulation of intestinal microbes affecting mainly cardiovascular disease markers by polyphenols as prebiotics, with negative correlations between Bacteroides with triacylglycerides, high-density lipoprotein, diastolic blood pressure, and systolic blood pressure; Lactobacillus and triacylglycerides, C-reactive protein; Bifidobacterium with cholesterol and C-reactive protein (Moorthy et al. 2020). The impact of probiotic supplementation in the microbial metabolism of red grape pomace polyphenols on the Dynamic Gastrointestinal Simulator (simgi®) was assessed finding that the inclusion of *Lactobacillus plantarum* CLC 17 in the colon compartments leads to the formation of more phenolic metabolites (benzoic acids), which may be because of high-molecular-weight procyanidin polymers breakdown (Gil-Sánchez et al. 2020). Red grape pomace and seed polyphenol extracts from Kyoho grape (*Vitis vinifera* "Kyoho") have been reported for improving the recovery of gut microbiota after antibiotic cocktail treatment in high-fat diet-fed C57BL/6J mice supplemented for 7 days after withdrawal of antibiotics compared to the spontaneous recovery group, as well as changing gut microbiota diversity (changes of Verrucomicrobia and Akkermansia in feces) (Lu et al. 2019).

Among grape polyphenols, particularly proanthocyanidins present in grape seeds, have shown to reach the colon via the small intestine (initial site for glucuronidation), where small amounts are absorbed, thus the microbiota form metabolites including benzoic acid, 2-phenylacetic acid, 2-(3′-hydroxypenyl) acetic acid, 3-(3′-hydroxyphenyl) propionic acid, 3-phenylpropionic acid, 2-(4′-hydro- xyphenyl) acetic acid, and hydroxyphenylvaleric acid, increasing bacteria such as Bifidobacterium and Lactobacillus spp. (Unusan 2020). A source of anthocyanins (cranberry) was studied for its impact on gut health (Rodríguez-Morató et al. 2018). Cranberry intake for 5 days in 11 healthy adults was found to attenuate animal-based diet-induced changes in microbiota composition and functionality. The study characteristics were: randomized, double-blind, cross-over, control group was given an animal-based diet plus 30 g/day placebo powder and the rest was given a cranberry diet which included an animal-based diet plus 30 g/day freeze-dried whole cranberry powder (Rodríguez-Morató et al. 2018). The control diet implied 46 taxonomic clades modifications taking pre-diet into account, with the characteristic of Firmicutes increase and Bacteroidetes decrease, compared to cranberry diet that 9 taxonomic clades were modified, showing the opposite tendency for Firmicutes and Bacteroidetes, increasing secondary bile acids, urinary anthocyanins, and bacterially derived phenolic acids by contrast short-chain fatty acids decrease (Rodríguez-Morató et al. 2018).

11.3.8 Anti-bacterial Activity

Among polyphenols properties, defense against biotic stress relates with antimicrobial, anti-fungal, and anti-herbivore properties (Da Silva et al. 2013). Grape pomace extracts have been recognized by their antibacterial capacity against *Bacillus cereus*, *Staphylococcus aureus*, *Campylobacter coli*, *Escherichia coli* O157:H7, *Salmonella infantis*, and *Listeria monocytogenes* ATCC 7644, as well as showing bactericidal effects against total aerobic mesophilic bacteria, lactic-acid and Enterobacteriaceae (Beres et al. 2017). A study conducted on three hydro-ethanolic extracts from Merlot grape pomace showed higher antibacterial activity for Gram-positive bacteria than for Gram-negative bacteria, exhibiting highest inhibitory activities against *Enterococcus faecalis* and *Listeria monocytogenes*, being compromised the activity by simulated in vitro digestion (2-fold reduction) and simulated colonic fermentation (Corrêa et al. 2017). Syrah red grape pomace and wine extracts exhibited a dose-dependent antibacterial activity against *Escherichia coli*, *Staphylococcus aureus*, *Bacillus subtilis* and *Bacillus cereus* that cause several human infections, being more effective against E. coli and S. aureus (Trikas et al. 2016). Pinot Noir and Merlot wine grape pomace extracts showed antibacterial activity against *Listeria innocua* ATCC 51142 and *Escherichia coli* ATCC 25922, being lower for the latter, as well as the antibacterial activity against both E. coli and L. innocua displayed by films based on Merlot wine grape pomace extract (Zhu et al. 2015). Among grape seeds polyphenols, proanthocyanidins have shown to inhibit bacterial adhesion and coaggregation, with the concomitant reduction of biofilm formation and decreased inflammation: *Bacillus cereus*, *Bacillus coagulans*, *Bacillus subtilis*, *Pseudomonas aeruginosa*, *Escherichia coli*, Micrococcus luteus, S. aureus, *Listeria monocytogenes* (Unusan 2020).

11.4 Bioaccessibility and Bioavailability of Bioactive Compounds of Grape By-products: Simulation of Digestion, Cell Studies and In Vivo Studies

The biological activity of bioactive compounds such as polyphenols is subjected to their bioaccessibility and bioavailability. Bioaccessibility implies the release of polyphenols from the food matrix during digestion to be absorbed and metabolized to exert their health-promoting effects (Pešić et al. 2019). Bioaccessibility of grape pomace polyphenols is related to the proportion of non-extractable polyphenols, which are bound to grape fiber, and the portion of the intestine. Furthermore, non-extractable polyphenols are not bioaccessible in the small intestine but they can be at least partially released by large intestinal microbiota from fiber matrix (Yu and Ahmedna 2013). The main reason for bioaccessibility impairment of grape polyphenols is their tightly bound to cellulose and pectin, thus enzymatic hydrolysis could enhance the release of monomeric and oligomeric polyphenolic compounds from their conjugates, facilitating their upper gastrointestinal tract absorption (Martins et al. 2016). Thus, grape pomace fiber may be used as polyphenols carriers to be destined for large intestine (Yu and Ahmedna 2013), or polyphenols may be extracted from grape by-products matrix by ultrasound-assisted extraction, acidic extraction (Fernández-Fernández et al. 2019; González-Centeno et al. 2014), supercritical fluids extraction (Da Porto et al. 2015; Yilmaz et al. 2011), biotransformation by using enzymes (e.g., pectinases, cellulases, and glucanases) (Albuquerque et al. 2017; Martins et al. 2016). Another important reason is the instability and/or degradation of polyphenols during digestion (Pešić et al. 2019). Figure 11.2 exemplifies the steps for polyphenols evaluation of effective bioactivity through bioaccessibility and bioavailability studies. To exert their biological activities, bioactive compounds must be bioavailable, which implies being effectively absorbed from the gut into the circulation and to achieve target tissue. In the case of anthocyanidin

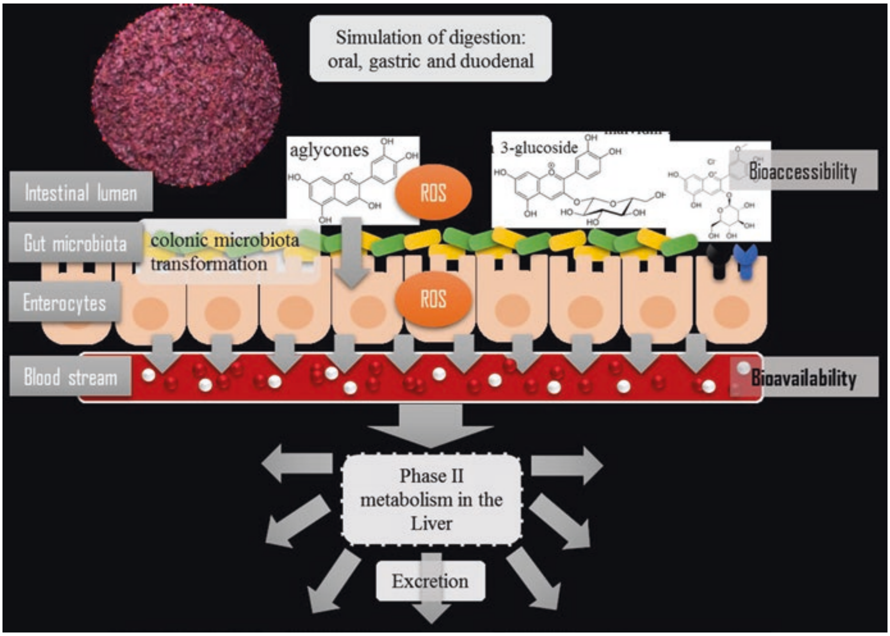

Fig. 11.2 Scheme of red grape pomace bioaccessibility and bioavailability studies, starting with in vitro simulation of digestion to state polyphenols stability/degradation, then small intestine and colon cell lines to study polyphenols bioactivity and absorption ending in the systemic circulation, followed by bioavailability studies including polyphenols metabolism, biodistribution with bioactivity analysis and excretion

aglycones, their absorption is through passive diffusion across the membrane of the gut epithelial cells because of having greater hydrophobicity. In contrast, anthocyanin glycosides are more hydrophilic with high molecular weight, which are supposed to have difficulty in being absorbed in the digestive tract by intestinal microbiota hydrolysis into aglycone form or degradation to phenolic acids. Still, anthocyanins have been reported to have an in vivo role and can be absorbed directly from the stomach (Liang et al. 2012). Even though grape polyphenols present low absorption capacity because only aglycones can effectively pass through the gut wall, they may have a direct positive impact on gut mucosa or can be hydrolyzed by the gut microbiota into aglycones or be degraded (Georgiev et al. 2014). In some food matrixes (mushrooms), polysaccharides bioactivities are affected by digestion conditions, finding negative effects (decreased antioxidant capacity) after intestinal digestion. However, some bioactivities such as α-amylase and α-glucosidase inhibitory activities are significantly increased after digestion meaning bioactive polysaccharides could be a post-prandial hyperglycemia controller (Wang et al. 2018c).

Bioavailability implies the arrival of bioactive compounds into the systemic circulation and their maintenance of availability to be used by cells or tissues. In general, it is considered that polyphenols must be absorbed, metabolized and bioavailable in order to exert their beneficial effects, but in some cases health effects may be exerted before their absorption through the gut barrier. This is the case of anthocyanins that may protect against the oxidative damage in the gastrointestinal tract which is implicated in degenerative diseases such as colorectal cancer or inflammatory bowel disease. In general, monomeric and low molecular weight polyphenols are absorbed in the upper small intestine in contrast with higher molecular-weight polymers that are first metabolized by colonic microbiota and then absorbed in the large intestine (Pineda-Vadillo et al. 2016). Polyphenols bioavailability and absorption rate into the circulatory system determines their bioactivity as well as the foods with which are consumed. After enzymatic deglycosylation, only 5–10% of ingested dietary polyphenols are absorbed in the small intestine. Mostly, reach the colon intact (90–95%) to be degraded into simpler phenolic acids by gut microbiota, with the consequent absorption into the systemic circulation (Nash et al. 2018). Most polyphenols cannot be absorbed in their native form because of their common form (esters, glycosides, or polymers) usually present in food, being necessary their hydrolysis by endogenous enzymes or microbiota. Their bioavailability is compromised by xenobiotics metabolism, in comparison to micro- and macronutrients (Chedea et al. 2018).

To state polyphenols biological effects, bioaccessibility and bioavailability studies are needed. For this purpose, a global approach including in vitro and in vivo studies is needed. The rate of absorption and bioavailability of bioactive compounds are generally addressed in vivo, which present limitations such as high costs and huge variability (Chedea et al. 2018). However, cell models may represent a suitable alternative for in vivo studies because of its lower cost and bigger screening capacity (Chedea et al. 2018).

Bioaccessibility studies on anthocyanins from pinto beans, black beans and black lentils (delphinidin 3,5-diglucoside, cyanidin 3-glucoside and cyanidin 3,5-diglucoside) showed their absence in the intestinal phase because of pH instability (Giusti et al. 2019). Moreover, cyanidin 3-glucoside degradation to protocatechuic acid has been reported during gastrointestinal digestion (Giusti et al. 2019). In another study, the bioaccessibility of mulberry (Morus atropurpurea Roxb.) anthocyanins showed a decrement after the intestinal digestion, however, the digest showed good antioxidant activity due to anthocyanins degradation with the subsequent generation of phenolics under intestinal conditions (Liang et al. 2012). Polyphenols from wild blueberry (*Vaccinium angustifolium*) have shown high stability (total polyphenols and anthocyanins) during gastric digestion phase (approximately 93% and 99% of recovery, respectively), but decreased during intestinal phase (49% and 15%, respectively) compared to non-digested samples. Also, the complex polyphenol mixture was degraded to a few polyphenols (syringic, cinnamic, caffeic, and protocatechuic acids) during chemostat fermentation that simulates colonic digestion, and after chemostat fermentation acetylated anthocyanins were detected in low amounts. Colonic fermentation might affect blueberry polyphenols bioactivity because of catabolites showing lowered antioxidant activity and cell growth inhibition potential (Correa-Betanzo et al. 2014). Another source of anthocyanins, chokeberry (Aronia melanocarpa) pomace powder, was found to reduce the initial content of total polyphenols by 40% when temperatures up to

140 °C were applied, not altering dietary fiber structure or content, and after in vitro digestion the retained polyphenols were fully bioaccessible, with antioxidant capacity remaining unchanged and with slight reduction of glucose bioaccessibility (Schmid et al. 2020). To improve anthocyanin stability and residence time in the upper digestive tract, which causes a partial absorption (Gadioli Tarone et al. 2020), different blends and/or encapsulation techniques may be used. Polyphenols from blueberry (Vaccinium angustifolium Aiton) and muscadine grape (Vitis rotundifolia) pomaces with a rice-pea protein isolate blend (protein-polyphenol aggregate particles) showed better stability during gastrointestinal transit (in vitro gastrointestinal model) through the protection of polyphenols allowing them to reach gut microbiota and preserve their bioactivity (Xiong et al. 2020). Colloidal carrier systems such as cyclodextrin, polymeric particles, liposomes, and emulsions, could be suitable for encapsulating anthocyanins. Among "top-down" colloidal systems, liposomes represent a promising carrier because of protecting, entrapping hydrophilic bioactive compounds and enabling intestinal absorption, as well as emulsions for protecting from the environment and gastrointestinal conditions, and regarding "bottom-up" colloidal systems spray-drying has been successfully used for anthocyanin protection (Gadioli Tarone et al. 2020). Micro-encapsulation of grape skin anthocyanin-rich extract using emulsification/internal gelation associated with spray/freeze-drying techniques showed favored anthocyanin retention in the microcapsules by spray-drying as well as improving the prolonged release of anthocyanins in simulated gastrointestinal digestion (Zhang et al. 2020).

However, anthocyanins may interact with some of the other food ingredients affecting their bioaccessibility. In a newly developed functional beverage based on exotic fruits (mango juice, papaya juice and açaí) mixed with orange juice and oat with the addition of *Stevia rebaudiana*, no substantial effect was detected during salivary and gastric phases on any of the main polyphenols, total antioxidant capacity, ascorbic acid, and steviol glycosides, in contrast with carotenoids and anthocyanins that diminished significantly during the gastric phase. All analyzed compounds were significantly affected during the pancreatic-bile digestion being more marked for carotenoids and total anthocyanins, but polyphenols, anthocyanins, total antioxidant capacity and steviol glycosides bioaccessibility increased as did Stevia concentration, whereas ascorbic acid's was negatively affected by Stevia addition (Carbonell-Capella et al. 2015).

Red grape pomace polyphenols (red grape pomace aqueous extract) have also been studied by in vitro and in vivo analyses in IPEC cells (intestinal porcine epithelial cells) and in the duodenum and colon of piglets fed, respectively, to check the correlation between in vitro and in vivo absorption of polyphenols. O-quinones and dimers were found in the cellular and extracellular medium as grape pomace polyphenols oxidation products. Major polyphenols were procyanidin trimer and a procyanidin dimer. As to in vivo studies, in duodenum and colon grape pomace piglet's diet (5%) showed an augment in the antioxidant status and decreased lipid peroxidation (TBARS), and increased SOD activity in duodenum and CAT and GPx activity in the colon (Chedea et al. 2018). Oxidative stress can display negative effects on the intestinal tract through the exposure to luminal ROS from oxidized food debris, saliva oxidants, toxins, high levels of iron ions, bacteria and bile acids, being of extreme importance for the colon, where residence time is prolonged. Endogenous cellular defense (including the antioxidant enzymes, such as SOD, GPx and CAT) is often exceeded by ROS production needing the contribution of polyphenols (Chedea et al. 2018). In a study conducted on piglets fed with red grape pomace (5%) polyphenols absorption was reported, showing a structural modification of polyphenols by metabolization, and the absorption in the liver, spleen and kidneys in this form, accompanied by the increase in the antioxidant status (Chedea et al. 2019). There has been evidence of a reduction in the phenolic compounds profile of the Merlot grape pomace extract by in vitro digestion process, whereas simulated colonic fermentation had a positive effect over the extract's antiproliferative potential tested on MCF-7 (breast adenocarcinoma), NCI-H460 (non-small cell lung cancer), and HepG2 (hepatocellular carcinoma) cells (Corrêa et al. 2017). Red grape pomace (Tempranillo grapes) has been fund to be stable at the stomach and to reduce anthocyanins and flavonols at the small intestine, preserving high antioxidant capacity (evaluated by FRAP, ABTS, and ORAC assays) after storage and in vitro digestion (Wang et al. 2017a). Bioaccessibility studies on different varieties of red grapes showed a reduction in antioxidant capacity after the digestion process because of an important loss of polymeric compounds, being lower for the Tannat variety, which could be related to its higher content of phenolic compounds after digestion. The effect of digestion was critical for anthocyanins, although it was also pronounced in flavanols, regardless of the grape variety of origin. As to flavonols, the changes were generally less pronounced, with high amounts of quercetin-3-O-glucuronide and quercetin-3-O-glucoside after digestion and phenolic acids underwent important changes in their composition. Tannat extract showed a marked decrease in caftaric acid. On the contrary, vanillic acid and syringic acid showed significant increases (Nieto Fuentes 2015). The bioaccessibility of grape pomace and its aqueous extract from white Pinot noir wine was studied by determining polyphenols content, antioxidant capacity and polyphenolic profile after a human digestion simulation, finding higher phenolic content and antioxidant capacities in the extract. The main bioaccessible phenolic compounds were gallic, vanillic and siringic acids, showing the extract higher bioactive value (Beres et al. 2019).

Red grape bioaccessibility has shown increased bioaccessibility of total polyphenols that are already bioaccessible in wine in mouth and stomach digestion while intestinal digestion reduced polyphenol bioaccessibility, being anthocyanins the less affected, along with antioxidant capacity reduction (Lingua et al. 2018). The bioaccessibility of peel, pulp, and seeds of *Vitis labrusca L.* grapes has been studied through in vitro simulation of gastrointestinal digestion showing variations in the bioaccessibility of bioactive compounds between the different digestion phases, with maintained concentrations of hydroxybenzoic and hydroxycinnamic acids, anthocyanins, flavanols, and flavonols, as well as the antioxidant potential, suggesting high bioaccessibility of most phenolic compounds (Gomes et al. 2019). The bioaccessibility of red grape skin and seeds extracts has been studied by Pešić et al. (2019) finding almost two times lower recovery after digestion of total non-flavan-3-ol phenolics extracted from red grape seed compared to red grape skin extract, probably because of the release of hydroxycinnamic acids (caffeic and p-coumaric) from the grape skin extract. It was detected a considerable loss of flavan-3-ols total recovery and a significant reduction of proanthocyanidin content during digestion of red grape seed extract. The deacylation of anthocyanidin mono- and diglucosides was also detected generating p-coumaric and caffeic acids as well as malvidin-3,5-di-O-glucoside during digestion of red grape skin extract (Pešić et al. 2019).

Anthocyanins bioavailability is subjected to intestinal epithelium physical and physiological barrier (composed of a mucus barrier and cell layer), mainly entering the enterocytes by passive diffusion, or via active transport in a lesser extent, when arriving at their surface in the cell layer for further absorption, enterocyte biotransformation and transportation to the liver for metabolization, or degradation by microbiota when not absorbed in the small intestine (Gadioli Tarone et al. 2020). Regarding polyphenols bioavailability, including anthocyanins, a study of cranberry (*Vaccinium macrocarpon*) juice consumption in healthy older adults showed antioxidant activity in plasma assessed by ORAC and TAP assays, which correlated with individual metabolites bioavailability (Mckay et al. 2015).

Bioavailability studies through Caco-2 cells of ethanolic extracts from the different varieties (white and red grapes) indicated that Tannat bioavailable fraction showed the highest antioxidant capacity with a TEAC value of 12.34 mmol of trolox/L extract, due to the presence of phenolic acids and flavonols. After intestinal absorption, the bioavailable fraction was mainly characterized by the presence of phenolic acids, with an important content of syringic and caftaric acid, together with smaller notable amounts of quercetin-3-O-glucoside and trans-piceid to a lesser extent. In addition, small amounts of p-cumaric acid and quercetin-3-O-glucuronide were detected in this fraction. Grape seed extracts presented the highest phenolic content and antioxidant activity in the bioavailable fraction after intestinal absorption assays. Thus, wine by-products were found to be important sources of bioavailable phenolic compounds (Nieto Fuentes 2015).

Proanthocyanidins bioavailability relies on the polymerization degree, skin having a higher grade of polymerization than seeds, and can reach tissues such as the connective tissue, lung, kidney and spleen, but most reach the colon in an intact state, which preserve intestinal barrier integrity through anti-inflammation activity and antioxidant capacity, among other mechanisms (Unusan 2020). It has been stated that some polyphenols such as piceido are absorbed through the glucose-dependent transporter SGLT1, generally involved in the transport of glycosylated flavonoids, such as quercetin-3-O-glucoside, being bioavailable. In the case of Tannat grape skin ethanolic extract, anthocyanins malvidin-3-O-glucoside, as well as cyanidin and petunidin derivatives, were bioavailable (Nieto Fuentes 2015). Anthocyanins absorption through intestinal epithelial cells may involve GLUT2 transporter when tested on Caco-2 cells (Faria et al. 2009). Talavéra et al. (2004) found that a high proportion of anthocyanin glycosides was absorbed through the small intestine of rats and the rate of absorption depended on the chemical structure of the anthocyanin and varied from 10.7% (malvidin 3-glucoside) to 22.4% (cyanidin 3-glucoside). The study also showed that anthocyanins are quickly metabolized and present bile and urine excretion as intact glycosides, methylated forms and glucuronidated derivatives (Talavéra et al. 2004). Moreover, 500 mg of aronia berry extract by 6 adults showed anthocyanins bioavailability, an increment of microbial phenolic catabolites (approximately 10-fold more than anthocyanins) in plasma and urine, rapid metabolization of cyanidin-3-O-galactoside into peonidin-3-O-galactoside, and total bioavailability and metabolism of anthocyanins at 24 h (Xie et al. 2016). Still, more studies of grape by-products (pomace, seeds, skin and stem) polyphenols are necessary, mostly of bioavailability studies on other cell types such as normal epithelial small intestinal cells as well as normal epithelial colon cells.

11.5 Food Applications

As previously stated, winemaking byproducts are a source of dietary fiber and polyphenols, and so food industry could use dietary fiber for its physicochemical properties such as organoleptic (texture, viscosity, among others) and sensory characteristics, water retention capacity and prolongation of freshness as well as extending food products shelf-life by polyphenols (Foschia et al. 2013; Iriondo-Dehond et al. 2018; Tseng and Zhao 2013). The most important factor affecting the safety and shelf-life of fruits and vegetables as well as food products is microbial spoilage (Salehi and Aghajanzadeh 2020). For some food products such as meat, it is known that lipids present high susceptibility to peroxidation during cooking and gastrointestinal digestion, forming lipid oxidation products, which may represent negative health effects (Pešić et al. 2019). It is also known that during gastric digestion, lipid rich-foods cause the generation of ROS, which lead to lipid peroxidation, co-oxidation of vitamins, dietary proteins amino acid oxidation of side chains, the formation of protein-protein cross-linkages, and protein fragmentation, reaching the blood when absorbed with the possibility of consuming plasma antioxidants (Urquiaga et al. 2018). As to food processing, such as cooking or boiling, polyphenols stability should be considered before deciding which food product would be ideal for the incorporation of any functional ingredient (Fig. 11.3). Plant cells are broken during heat treatments and chewing with the subsequent release of polyphenols which may interact with cell wall material (Giusti et al. 2019).

Through soaking water processing, anthocyanins, flavonoids and tannins have shown to leach, as well as gallic acid. In the case of boiling water, some polyphenols may be released from food matrix compounds such as anthocyanins and can also be lost like delphinidin 3-glucoside possibly because of thermal degradation of anthocyanins. In the same way, the cooking process caused a reduction of free and bound phenolic compounds content by thermal degradation, but the food matrix can protect thermally labile polyphenols such as anthocyanins (Giusti et al. 2019). Moreover, the effects of baking conditions and dough formulations on polyphenols stability of cookies made from anthocyanin-rich corn flour showed an increase on total flavonoids and anthocyanins content by the addition of citric acid in the cookies prepared from blue popping corn and blue-standard corn, and also an increase by

Fig. 11.3 Food applications of red grape by-products for improving shelf-life, physicochemical properties, food processing effects, and bioaccessibility of bioactive compounds

baking at 150 °C for 7 min compared to 200 °C for 10 min (control cookies) (Žilić et al. 2016). Also, baking conditions reduced free water-soluble polyphenols (total flavonoids and anthocyanins) content in control corn cookies. However, antioxidant capacity was reduced because of Maillard reaction inhibition at low pH with 0.5 and 1 g/100 g citric acid of anthocyanins-rich blue popping corn and blue standard corn cookies (Žilić et al. 2016).

Anthocyanins degradation by food processing can be improved by encapsulation prolonging half-life. Barberry (*Berberis vulgaris*) extract as a rich source of anthocyanins, when encapsulated with three different wall materials which include a combination of Arabic gum and maltodextrin, a combination of maltodextrin and gelatin, and maltodextrin by the spray drying process, all increased anthocyanins half-life storage compared to non-encapsulated ones. The combination of Arabic gum and maltodextrin lowered degradation of anthocyanins in all the tested temperatures and was found as the most effective wall material in stabilizing the pigments. The encapsulated pigments were used as natural colorants for jelly powder instead of synthetic color, finding that the addition of 7% encapsulated color presented higher scores than the commercial jelly containing synthetic color for the sensory attributes evaluated as well as better rheological jelly properties (syneresis and solubility) (Akhavan Mahdavi et al. 2016).

The addition of Chardonnay white grape skin to tomato puree (3%) and to a flatbread (10%), resulted in phenolics enriched foods except for the higher mass proanthocyanidin oligomers (firstly because of binding to food matrix and secondly to heat degradation) which was detected a higher mammalian α-amylase and α-glucosidase (from rat intestine) inhibition for the enriched foods than for unfortified foods. The expected increase in the inhibition was lower in the case of flatbread probably because of the binding of the higher mass proanthocyanidin to the food matrix. Although phenolics interactions with the food matrix could negatively affect bioavailability, the digestion process can enhance bioavailability by releasing them from the food matrix. The amount of white grape skin added to both food products was stated by previous sensory analysis with consumers. Hence, both enriched foods may potentially alleviate the damage caused by hyperglycemia (Lavelli et al. 2016).

Red wine ("Xueyuanpai" red wine Cabernet Sauvignon) polyphenol bioaccessibility has been studied by in vitro gastrointestinal digestion showing a good release of polyphenols at mouth and stomach (release rates of 88.59% to 95.86% at the stomach) steps, and after stomach digestion, a release rate of 40–50% was reported at the "serum-available" fraction (foodstuffs at the small intestine and are absorbed), while others were released in a rate of 20% in the "colon-available" fraction, serving as substrates for gut microbiota as well as influencing microbiota ecosystem or continuing the absorption into the serum (Sun et al. 2020). In the same study, decrease in the inhibitory effects of α-amylase and α-glucosidase along digestion steps was reported, and a moderate wine intake and drinking after the meal were suggested because of showing a higher serum and lower colon-available total polyphenol value than drinking before a meal in all three wine drinking amounts (Sun et al. 2020).

In a study conducted on red wine grape pomace (*Vitis vinifera* L. cv. Pinot Noir), it was demonstrated that wine grape pomace could be added to yogurt and as a salad dressing as a source of dietary fiber and polyphenols. Its addition caused the extending shelf-life of food products and the possibility to be used as a functional food ingredient for promoting human health. Its addition decreased yogurt viscosity and syneresis was not observed in 4 week storage time except for 3% addition (Tseng and Zhao 2013). In the case of fortified yogurt, there were no significant differences between control, 1% WP and 2% WP (w/w yogurt) samples in appearance liking and overall liking, but 2% WP yogurt received a lower score on flavor and texture liking. As to fortified Italian dressing there was no difference ($P > 0.05$) on all measured sensory attributes for control, 0.5% WP and 1% WP and for fortified Thousand Island dressing there was no significant difference ($P > 0.05$) on appearance, overall and flavor liking for control, 1% WP and 2% WP (Tseng and Zhao 2013). Red grape skins and grape seeds incorporation (0, 5, 10, and 15% to the weight of flour) in cookies resulted in changed rheological parameters (increased water absorption and reduced dough stability for grape skin and the opposite for grape seeds, reduced volume, thickness, hardness, and fracturability) along with good overall acceptability for 5%-enriched cookies (Kuchtová et al. 2018). To extend fish shelf-life during storage by delaying lipid oxidation because of high unsaturated lipid content that is very susceptible, red grape antioxidant dietary fiber was added to minced horse mackerel (*Trachurus trachurus*) fish muscle finding considerably delayed lipid oxidation during the first 3 months of frozen storage (Sánchez-Alonso et al. 2006). Grape seed flour has been incorporated into frankfurters resulting in a decline in the oxidation level of the products (Zhu et al. 2015). Red grape skin has been used as a seasoning of marinated chicken breasts as a salt replacer obtaining the same shelf-life of 0.5% replace of salt and 2% of seasoning than the one with 2% of salt but presenting lower sensory scores in color, texture and overall linking (3.1–3.3) and related to consumers' willingness to accept new products (Ortega-Heras et al. 2020). Five formulations of whole-wheat muffins with white and red grape pomace were studied (100% whole-wheat flour control muffin, muffins+10% white pomace, muffin+20% white pomace, muffin+10% red grape pomace, and muffin+20% red grape pomace) with "high-fiber content", leading to changes in sensory attributes (decrease in cohesiveness, springiness, resilience and color, and increase in hardness and chewiness) but with high acceptability levels in muffin+10% grape pomace, representing a healthier alternative for muffins formulations development (Ortega-Heras et al. 2019). Grape pomace can also be incorporated into bakery products such as cakes that are worldwide consumed but organoleptic properties, texture, and color are affected, as a consequence of insoluble and soluble fiber that can enhance cake technological attributes as water binders, gelling agents, fat replacers and texture improvers, which may improve cake quality (preventing the augment of air bubbles which are incorporated toward the surface during the baking process and increasing viscosity of the batter). Grape pomace powder has been found as a suitable replacer of wheat flour in muffin formulations (Salehi and Aghajanzadeh 2020). Particularly, Riesling and Tannat skin flour as wheat flour replacers in muffins (5, 7.5, and 10%) showed decreased lightness of the flour, cohesiveness value, as well as increased the lightness values (L*) of the muffin crumbs and crusts and hardness of muffins with an increased percentage of the skin flour replacement, with no changes in color, taste, flavor, texture, and overall acceptability (from 5.2 to 5.7 on a 7-point hedonic scale) of the muffins determined by sensory analysis, resulting in suitable alternative to increase the dietary fiber content of muffins (Bender et al. 2017). Red Traminer, Alibernet, and Cabernet grape pomaces (3%) were found suitable for gluten-free products (muffins and knäckebrots), being Cabernet pomace muffins the ones with the highest sensory quality (Matejová et al. 2019).

Besides techno-functional properties, wine grape by-products could have a health-promoting effect by their addition to different food products, in which case structure and composition of the food product's matrix effect on the bioaccessibility of grape by-products bioactive compounds should be considered. Food product's matrix can impair/enhance the release and stability of grape bioactive compounds during digestion compromising their biological effect (Iriondo-Dehond et al. 2018; Pineda-Vadillo et al. 2016). Dairy and egg products are excellent foods to be fortified because of worldwide acceptance by all age groups, nutritional properties, which could be represented by numerous forms and structures and can be eaten daily (Pineda-Vadillo et al. 2016). Yogurt formulation enriched with grape pomace aqueous extract from white wine Pinot noir was tested for sensory panelists resulting in an overall liking score of 6.2 out of 9.0 and 51% of panelists would buy the product. The incorporation of the extract in yogurt was found as a potential antioxidant dietary fiber ingredient (Beres et al. 2019). Antioxidant dietary fiber from red grape pomace has been reported as promising sources of functional ingredients for enriched meat-based functional foods by ameliorating oxidative changes in meat products and providing health benefits. Nevertheless, physical characteristics change because of grape pomace addition to meat products, such as color in raw and cooked chicken hamburgers but sensory values were improved (0.5%, 1.0%, 1.5% and 2.0% of grape pomace addition) (Das et al. 2020). Red grape pomace (Vitis vinifera L cv. Corvina) has also been used to fortified durum wheat pasta (spaghetti) replacing semolina with 0, 5, and 10 g/100 g of grape pomace, enhancing total polyphenol content and antioxidant capacity (ABTS and FRAP values) accompanied by the reduction of cooking time and swelling index, enhanced firmness and adhesiveness of the pasta, and good overall acceptability (Tolve et al. 2020). However, there are few bioaccessibility studies on enriched food products with grape by-products such as dairy, bakery and egg products (Pešić et al. 2019). Pešić et al. (2019) studied the bioaccessibility of bioactive compounds in an infant puree composed of turkey meat, potato, corn and rice that was enriched with red grape skin and seed extracts. Polyphenols recovery of red grape skin extract's addition to the food matrix was not affected in contrast with their digestion without food matrix, mostly because of food matrix polyphenols contribution to total polyphenols content before digestion. On the other hand, the addition of red grape seed extract to infant puree increased the total recovery of flavan-3-ols and non-flavan-3-ol compared to the digestion of the extract alone. Digestion of red grape extracts with infant puree showed higher total phenolic content, finding better antioxidant capacity in the grape skin extract than in red grape seeds extract due to flavan-3-ols binding capacity with antioxidant components from food matrix and digestive fluids. Moreover, anthocyanins stability was decreased by the food matrix resulting in the disappearance of malvidin-3-O-glucoside and to a lower extent the release of malvidin-3,5-di-O-glucoside in the final digest compared to that in digested grape skin extract (Pešić et al. 2019). Red grape marc enriched durum wheat spaghetti improved the amount of phenolic compounds and antioxidant capacity, and the bioaccessible fraction showed higher amount of polyphenols including anthocyanins and antioxidant capacity but a lower amount of glucose with sensory acceptance (Marinelli et al. 2018).

In other polyphenols bioaccessibility study conducted on dairy and egg products enriched with red grape extracts (custard dessert, milkshake, pancake and omelet), results showed a great impact on anthocyanins and proanthocyanidins release and solubility during digestion (Pineda-Vadillo et al. 2016). The biggest impact was detected in solid food matrices and in oral and gastric digestion phases as well as showing protection of the degradation of anthocyanins by food matrices during the intestinal digestion phase. Moreover, antioxidant activity remained constant during oral and gastric phases, increasing during the intestinal phase. Comparing all food matrices, omelet presented the highest total phenolics and antioxidant activity (FRAP antioxidant activity and ORAC-FL) recoveries at the end of digestion. In pancake and omelet anthocyanins, proanthocyanidins and total phenolics were mostly recovered in the insoluble fraction during oral and gastric digestion phases, and anthocyanins were actually protected from degradation during intestinal digestion phase (Pineda-Vadillo et al. 2016).

Another source of anthocyanins (black carrot pomace) was added to cake and studied bioactive compounds bioaccessibility, finding no difference between the 100 g/kg and 150 g/kg pomace addition after digestion in the content of polyphenols. During oral and gastric phases the amount of anthocyanins and phenolic acids were reduced significantly, and after intestinal phase anthocyanins were not detected, but total phenolic content and total antioxidant capacity were increased during gastric and intestinal phases (up to 5- and 12-fold respectively) (Kamiloglu et al. 2017).

In addition to bioaccessibility studies of grape pomace by-products in different food matrices, more bioavailability and/or in vivo bioactivity studies are needed to ensure grape byproducts effects on human health as a consequence of the interactions between grape by-products and different food matrices that could have a positive or negative effect on bioavailability with the subsequent effect on in vivo bioactivity. In a three-month intervention study conducted on 27 male volunteers, each with some components of metabolic syndrome, Cabernet sauvignon grape pomace meat burgers were formulated with 7% of containing 3.5% fiber, 1.2 mg GE/g of polyphenols, and 17.2 μmol TE/g of ORAC compared to raw control-burger containing no fiber, 0.396 mg GE/g of polyphenols, and 1.82 μmol TE/g of ORAC (Urquiaga et al. 2018). Cabernet Sauvignon grape pomace burger intake showed an increase in plasma of the essential contributor to plasma antioxidant defense vitamin C, compared to control-burger intake decreased concentration (up to baseline levels) (Urquiaga et al. 2018). Moreover, grape pomace burger intake showed a significant reduction of glycemia and HOMA index values (a measurement of insulin resistance), as well as significantly decreased advanced oxidation protein products and oxidized low-density lipoprotein levels, finding potential as a functional ingredient for the prevention and/or treatment of diabetes mellitus and cardiovascular disease (Urquiaga et al. 2018).

11.6 Conclusions

Vast evidence of the polyphenolic composition of red wines and by-products is available, especially for anthocyanins, but there is scarce knowledge of the by-products bioactivities after digestion, including antioxidant, anti-inflammatory, anti-diabetic, and anti-obesity, among others. Furthermore, the loss or gain of red grape by-products bioactivity during gastrointestinal digestion, colonic fermentation process, and intestinal barrier passage should be further studied to be considered for the development of new functional foods. Also, the by-products addition to food products should be studied regarding sensory analysis to achieve consumers' acceptance, along with bioaccessibility and bioavailability of the new red wine byproduct-added functional foods, considering the variable effects of food matrix on these accounts, determining bioactive properties other than antioxidant to ensure a global approach on the risk reduction of chronic diseases.

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