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Potential health benefits of phenolic compounds in grape processing by-products

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Abstract Prevention emerges as a powerful approach in minimizing the risk of deleterious lifestyle diseases because therapies do not necessarily guarantee a permanent cure. Accordingly, consumers' growing preference for natural and health-promoting dietary options that are rich in antioxidants has become widespread. Grape (*Vitis vinifera*) is an antioxidant-rich fruit extensively grown for fresh or processed consumption. The long-term consumption of its polyphenolic antioxidants may promote multiple health benefits. However, grape pomace (GP), consisting of peel, seed, stem, and pulp, is discarded during grape processing, including juice extraction and winemaking, despite its substantial antioxidant content. Polyphenolic extraction techniques have been widely explored to date, but the consolidation of reported physiological impacts of GP-derived polyphenolic constituents is limited. Thus, this review highlights current studies of the potential applications of GP extract in disease prevention and treatment, emphasizing the major influence of polyphenolic compositions and origins of different grape varieties.

Keywords Functional food · Grape pomace · Grape processing by-product · Antioxidant · Polyphenol

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Introduction

Grape pomace (GP) is essentially a solid organic waste containing grape skin, stem, pulp, and seed, which are deliberately discarded in various grape processing industries, such as wine or juice manufacturing (Peixoto et al., 2018; Spanghero et al., 2009). Generally, GP accounts for 25–35% of the total weight of grape processed (Oliveira and Duarte, 2016; Teixeira et al., 2014). GP contains significant amounts of dietary fiber and diverse phytochemicals that possess potent antioxidant activities, as determined in various studies (Fig. 1) (Rockenbach et al., 2011; Silva et al., 2018; Souquet et al., 2000; Yu and Ahmedna, 2013). In general, grape polyphenolics vary in chemical structure and activity and may be fundamentally categorized into two major classes: flavonoids and non-flavonoids (Garrido-Bañuelos et al., 2019). Flavonoids, the most abundant polyphenolics in grape, are distributed throughout the peel, seed, and stem, and include anthocyanins, proanthocyanidins (procyanidins and prodelphinidins), and flavan-3-ols (Cotoras et al., 2014; Garrido-Bañuelos et al., 2019). In contrast, hydroxycinnamic acids, the most abundant non-flavonoids in wine, include caftaric acid and coutaric acid (Lu and Foo, 1999). Most of these polyphenolic compounds occur as glycosylated derivatives in plants and foods and undergo enzymatic transformations

Parts of grape bunch	Major phytochemicals
Peel 	• Anthocyanins • Quercetin derivatives (e.g. rutin) • Kaempferol derivatives • Catechins • Resveratrol • Chlorogenic
Seed 	• Catechins • Chlorogenic acid • Quercetin derivatives • Resveratrol
Stem 	• Caftaric acid, coutaric acid • Quercetin derivatives • Kaempferol derivatives • Myricetin derivatives • Catechins • Astilbin, engeletin

(Rockenbach et al., 2011; Souquet et al., 2000)

Fig. 1 Major phytochemicals present in grape processing by-products

in the gut before intestinal absorption (Bang et al., 2015; Marín et al., 2015).

In vinification, bioactive polyphenolic compounds are partially extracted while the majority remain as glycosides embedded in the grape peel, pulp, or seed (Chafer et al., 2005). Additionally, the amount of polyphenols released into the final wine product greatly depends on the fermentation process, suggesting that an insufficient extraction technique prevents the liberation of phytochemicals that are essentially confined in grape cell walls and pulp cell vacuoles (Adams, 2006; Canals et al., 2005; Yacco et al., 2016). Despite the notable abundance of antioxidant phytochemicals in GP and intensive research efforts involving extraction strategies to optimize the recovery of antioxidants from GP for food or drug development (Otero-Pareja et al., 2015; Romero-Perez et al., 2001), enormous quantities of GP are still being disposed worldwide annually (Rondeau et al., 2013). In the context of the current environmental concerns, the conversion of GP to a safe and usable form introduces a practical approach to sustainable environmental waste management (Boussetta et al., 2009).

The abundance of bioactive polyphenols and minor quantities of other essential phytochemicals, such as carotenoids (lutein and β-carotene), especially the volatile ones, in GP, is influenced predominantly by converging factors, like the type of cultivar, climate, topography, and soil quality (Parker et al., 2011; Yuan and Qian, 2016). The techniques for extracting polyphenols from GP, considering environmental and economic implications, as mentioned above, have been reflected in various methodologies with a common objective, that is, to explore suitable conditions for maximum recovery of bioactive compounds from different grape varieties (Chafer et al., 2005; Cho et al., 2006; Meini et al., 2019; Otero-Pareja et al., 2015; Pintać et al., 2018; Romero-Perez et al., 2001). Conventional and emerging strategies for the extraction of bioactive components from GP operate via different mechanisms, and extraction techniques considering crucial parameters, such as temperature, pressure, length of extraction time, type of solvent, physicochemical characteristics of the source, operational cost, and environmental effects, have been explored (Castro-López et al., 2016).

GP extract has been extensively studied for its wide range of activities, including cardioprotective, anti-cancer, anti-inflammatory, anti-aging, anti-microbial, and other health-promoting properties (Peixoto et al., 2018; Yu and Ahmedna, 2013). Given that the bioactive components of GP extract are strongly correlated with a broad spectrum of beneficial effects, exploring the underlying mechanisms could lead to promising functional applications. Collectively, this review discusses the compelling potential of GP-derived bioactive polyphenols in disease prevention and/or therapy, considering critical factors, such as origin, variety, and polyphenolic composition.

Cardiovascular and metabolic health

In the past years, moderate regular intake of red wine has often been depicted in the prevention or amelioration of risk of coronary ailments (Avellone et al., 2006; Leikert et al., 2002; Ribeiro et al., 2016). However, GP (*Vitis vinifera* L. Syrah, Brazil) extract has been reported to contain significantly greater total anthocyanin, flavonol, stilbene, and flavanol contents than the red wine from which it is produced and, thus, most likely also possesses the biological activities of wine (de Oliveira et al., 2017). Accordingly, the levels of very-low-density lipoprotein cholesterol and triacylglycerols in Wistar rats were suppressed more effectively by GP extract compared to its wine counterpart, suggesting that GP could be used in food and nutraceutical industries as an inexpensive source of bioactive phenolics against coronary and other age-associated ailments (de Oliveira et al., 2017). Likewise, the symptoms of cardiovascular pathologies were significantly mitigated by the dietary administration of powdered GP (*V. vinifera* L. Malbec variety, Argentina) through concomitant induction of endothelial-derived nitric oxide in high-fat-fructose-fed Wistar rats (Perdicaro et al., 2017). The cardioprotective effect of GP observed could be attributed to the abundance of significant quantities of flavonoids (flavanols, tannins, and flavonols), non-flavonoids (hydroxybenzoic acids, hydroxycinnamic acids, stilbenes, and phenylethanol analogs), flavanols [(+)-catechin, (−)-epicatechin and (−)-epicatechin gallate], and anthocyanins (malvidin 3-*O*-glucoside, malvidin 3-*O*-*p*-coumaroylglucoside, and petunidin 3-*O*-glucoside) (Perdicaro et al., 2017).

The long-term cardioprotective effect of a polyphenol-rich mixture of Cabernet Sauvignon, Marselan, and Syrah varieties was also confirmed using middle-aged Wistar rats (Chacar et al., 2019). Among the polyphenols identified in the extract were malvidin, delphinidin, rutin, quercetin, catechin, coumaric acid, kaempferol, and *trans*-cinnamic acid, which could explain the prevention of hypertrophy, inflammation, fibrosis, and cardiomyocyte apoptosis observed upon administration of the extract (Chacar et al., 2018; 2019). In addition, the potential in vivo cardioprotective effect of fresh (high condensed tannins and anthocyanin contents) and fermented (high polyphenolic content) GP extracts from *V. vinifera* L. Pinot noir cultivar from Romania was demonstrated (Balea et al., 2018). In accordance with other studies, GP polyphenols could promote cardioprotection via different mechanisms. For instance, GP treatment effectively attenuated myocardial infarction in rats by reducing serum oxidative biomarkers, such as malondialdehyde, and increasing the serum total oxidative status and antioxidant reserves (Annapurna et al., 2009; Balea et al., 2018).

Furthermore, the effect of supplementing GP (*V. vinifera* L. Pinot noir variety, Poland) in a baking product formulation was demonstrated by measuring the levels of N^{ε}-(carboxymethyl)lysine (CML), a stable marker of advanced glycation end-products (Mildner-Szkudlarz et al., 2015). CML is generated by excessive thermal treatment in food preparations and is correlated with numerous variable pathologies, such as diabetes, atherosclerosis, Alzheimer's disease, and normal aging (Holik et al., 2018; Nerlich and Schleicher, 1999). Although further studies are required to identify the specific phenolic compounds responsible for preventing CML formation in the baking product formulation, the study demonstrated the propitious preliminary value of GP for food valorization and as an anti-aging agent (Mildner-Szkudlarz et al., 2015).

Evidence for the in vivo anti-inflammatory, antioxidant, and anti-hypertensive properties of GP (da Costa et al., 2017; Lanzi et al., 2016; Rasines-Perea et al., 2018) emphasize that high-fat diets associated with obesity and other metabolic disorders can be reversed through diets enriched with phytochemicals found in GP. To further elucidate the potential efficacy of GP in the prevention and therapy of obesity-related metabolic syndrome, GP (*V. vinifera* L.) of Brazilian origin was extracted and co-administered with a high-fat diet to male mice (da Costa et al., 2017). In agreement with other studies, antioxidant-rich GP extract mediated insulin sensitivity and glucose homeostasis, attenuated oxidative stress by lowering the malondialdehyde and carbonyl levels in the muscle and adipose tissues, and mitigated inflammatory markers (tumor necrosis factor-α and interleukin-6) (da Costa et al., 2017; Li et al., 2016). The beneficial impacts of GP extract could be attributed to its anthocyanidin-rich composition, including peonidin-3-*O*-glucoside, petunidin-3-*O*-glucoside, malvidin-3-*O*-glucoside, and malvidin-3-(6-*O*-*trans*-*p*-coumaryl)-5-*O*-diglucoside (da Costa et al., 2017). Collectively, the antioxidant-rich GP extract exhibits promising applications in coronary care and overall protection from serious risks of metabolic syndromes.

Cancer prevention

Along with studies relating dietary polyphenols to cardiac health and metabolic health, research efforts are increasingly focusing on the anti-cancer properties of polyphenols (Khurana et al., 2013; Petrovski et al., 2011). The major chemopreventive mechanisms of grape-derived polyphenols may include the alteration of phase I and II drug-metabolizing enzymes; antioxidant properties; inhibition of protein kinases; blocking of receptor-mediated functions; attenuation of protease activities; alteration of cell-cycle checkpoint controls, transcription factor expression and apoptosis; and inhibition of angiogenesis, invasion, and metastasis (Dashwood, 2007; Kundu and Surh, 2008). Resveratrol is a polyphenolic compound of great abundance in grape peel. This compound has been shown to inhibit chemical carcinogenesis, a process consisting of initiation, promotion, and progression, through induction of phase II detoxifying enzymes via activation of the Nrf2/Keap1 signaling pathway, one of the most important cell defense and survival pathways (Jang et al., 1997). In addition, resveratrol induces apoptosis in prostate cancer cell lines, by upregulating the expression of Bax, Bak, PUMA, Noxa, Bim, p53, TRAIL, TRAIL-R1/DR4, and TRAIL-R2/DR5 while downregulating the expression of Bcl-2, Bcl-X_L, and survivin (Shankar et al., 2007). Resveratrol also potentiates the apoptotic effects of cytokines, chemotherapeutic agents, and gamma-radiation (Radhakrishnan et al., 2011; Yu and Ahmedna, 2013).

There is consistent evidence to support the multi-targeted putative cancer preventive property of phytochemicals in GP (Del Pino-García et al., 2017; Luo et al., 2017; Mokni et al., 2016). In cancer chemoprevention, chronic administration of phytochemicals may impede the occurrence of cell malignancy through attenuation of reactive oxygen (ROS)/nitrogen species, which could result in irreversible DNA damage and/or inhibition of cancer cell proliferation (Landis-Piwowar and Iyer, 2014; Manson et al., 2000; Steward and Brown, 2013). Such anti-proliferative and anti-genotoxic effects of red wine pomace (*V. vinifera* cv. Tempranillo variety, Spain) seasonings against colon cancer cells have emphasized the relevant contribution of hydroxybenzoic acids and hydroxycinnamic acids (Del Pino-García et al., 2017).

Current strategies in skin cancer prevention and therapy also take advantage of the potential of GP-derived polyphenol-rich extracts against cancer invasiveness and metastasis (Chojnacka and Lewandowska, 2018; Mohan-srinivasan et al., 2015). In a skin cancer cell-line model, grape (*V. vinifera* L. Burgund Mare variety, Romania) seed extract rich in proanthocyanidins, anthocyanidins, and catechins significantly alleviated apoptosis, lipid peroxide levels, lesion scores, and DNA damage (Perde-Schrepler et al., 2013). Furthermore, the novel integration of GP extract (*V. vinifera*) as a stabilizing agent in the synthesis of gold nanoparticles (AuNPs) significantly inhibited cancer cell proliferation and induced cell death by inducing the generation of ROS and disrupting the mitochondrial membrane potential (Nirmala et al., 2017). The remarkable protective function against skin cancer and the synergistic action of GP-derived polyphenols with AuNPs displayed the potential applications of GP extract in skin care and drug delivery, respectively (Nirmala et al., 2017; Perde-Schrepler et al., 2013).

Skin health

With the growing consumer concern about premature skin aging, the incorporation of anti-aging products into the diet and lifestyle has become widespread in recent years. Consequently, strategies to preserve the external appearance of the skin, such as the development of skin anti-aging formulations, are constantly emerging (Ganceviciene et al., 2012).

Skin aging is a complex natural process involving the breakdown of collagen and elastin fibers, which maintain the integrity of the extracellular matrix (ECM) (Fisher et al., 1996). Excessive degradation of the ECM, due to multiple factors stimulating the action of proteases (collagenases and elastases), leads to skin wrinkling and accelerated skin aging. Considering the adverse role of proteases in skin health, collective efforts to explore the inhibitory capacity of GP-derived polyphenols that target collagenase and elastase have been conducted (Maidin et al., 2018; Wittenauer et al., 2015). A comparison of the GP (*V. vinifera* L. Barbera variety, Italy) extracts obtained using water and ethanol as separate solvents exhibited different polyphenolic compositions, with stronger inhibitory activity of the skin-related enzymes exhibited by the aqueous extract (Maidin et al., 2018). Additionally, fractionation enhanced the active polyphenols present in both crude extracts and intensified the inhibitory activity against collagenase, suggesting the suitability of the extracts for topical cosmetic formulations, which commonly contain between 25 and 100 μmol polyphenols/L (Maidin et al., 2018; Zillich et al., 2015). The potential of GP-derived polyphenols as an antioxidant material in cosmetic formulations was confirmed in another study in which GP extract diminished the cytotoxicity of hydrogen peroxide (H_2O_2) in mouse fibroblasts (Maluf et al., 2018).

In skin aging and other forms of skin damage, the generation of ROS exceeds the capacity of the endogenous antioxidant defense system of the skin, thereby resulting in oxidative stress (Kruk and Duchnik, 2014). In recent work, supplementation of GP-derived polyphenols modulated the cellular antioxidant system of the skin, maintaining its internal redox balance (Averilla et al., 2019; Manca et al., 2016). In particular, GP (Cannonau variety, Italy) extract incorporated in innovative phospholipid vesicles significantly mitigated skin damage by regulating H_2O_2-induced oxidative stress in keratinocytes and fibroblasts (Manca et al., 2016). Consistent with this study, grape (*Vitis labrusca* Campbell variety, South Korea) peel extract enriched with resveratrol and other antioxidants exhibited cytoprotective activity against H_2O_2-induced oxidative stress in human keratinocytes by enhancing reduced glutathione levels and, consequently, attenuating the accumulation of intracellular ROS (Averilla et al., 2019). Although understanding the exact mechanism was proposed for further studies, these results initially confirmed GP extract could be an ideal candidate in formulating cosmetic and pharmaceutical products (Averilla et al., 2019; Manca et al., 2016).

Gut health

Despite the extensive reporting of the potency of polyphenolics present in GP, limited information surrounds the gut health, immunity, and metabolic health associated with the consumption of these compounds (Pasinetti et al., 2015; Peixoto et al., 2018; Reinisalo et al., 2015). In this context, the gut microbial health implication of consistent long-term administration (2.5–20.0 mg polyphenolics/kg body weight/day) of GP (a mixture of Cabernet Sauvignon, Marselan, and Syrah varieties) extract was investigated in rats (Chacar et al., 2018). Interestingly, the polyphenol-rich GP extract stimulated microbial gut homeostasis, which resulted in notable beneficial effects against aging (Chacar et al., 2018).

In other work, proanthocyanidins present in grape seed extract (French origin) mediated parameters involved in metabolic disorders in female Wistar rats (Casanova-Marti et al., 2018). Previous assertions that grape seed proanthocyanidins upregulate plasma glucagon-like peptide-1 (GLP-1) levels and prompt satiety agents consequently stimulated investigations into whether these phytochemicals also potentially influence gut microbial modifications and enterohormone secretions (González-Abuin et al.,

Table 1 Summary of health benefits, biological activities, and compositions of GP extracts from various sources

Benefits	Variety	Source	Composition/Active components	Biological activity	References
Cardio-vascular and metabolic health	Syrah	Brazil	Anthocyanins, flavonols, stilbenes, flavanol	Suppressed levels of cholesterol and triacylglycerides	de Oliveira et al. (2017)
	Malbec	Argentina	Flavonoids, syringic acid, (+)-catechin, (−)-epicatechin and (−)-epicatechin gallate, malvidin 3-*O*-glucoside, malvidin 3-*O*-*p*-coumaroylglucoside, petunidin 3-*O*-glucoside	Increased nitric oxide level in high-fat-fructose-fed Wistar rats	Perdicaro et al. (2017)
	Cabernet Sauvignon, Marselan, Syrah	Not specified	Malvidin, delphinidin, rutin, quercetin, catechin, coumaric acid, kaempferol, *trans*-cinnamic acid	Attenuated hypertrophy, inflammation, fibrosis, and cardiomyocyte apoptosis	Chacar et al. (2019)
	Pinot Noir	Romania	Stilbenes, (+)-catechins, (−)-epicatechin, epicatechin-3-*O*-gallate, proanthocyanidins	Attenuated serum oxidative biomarkers in vivo	Balea et al. (2018)
	Pinot Noir	Poland	Gallic acid, epicatechin, catechin, procyanidin, procyanidin B2, quercetin-β-D-glucoside	Inhibited formation of CMLs thus reducing aging-related symptoms	Mildner-Szkudlarz, et al. (2015)
	V. vinifera	Brazil	Peonidin-3-*O*-glucoside, petunidin-3-*O*-glucoside, malvidin-3-*O*-glucoside, malvidin-3-(6-O-*trans*-*p*-coumaryl)-5-*O*-diglucoside	Mediated insulin sensitivity and glucose homeostasis, attenuated oxidative stress, and mitigated TNF-α and IL-6	da Costa et al., (2017)
Cancer prevention	Tempranillo	Spain	Hydroxybenzoic acids, hydroxycinnamic acids	Attenuated colon cancer cell proliferation and limits oxidative DNA damage in the colon	Del Pino-García et al. (2017)
	Burgund Mare	Romania	Epigallocatechin, epicatechin, catechin hydrate, gallic acid, procyanidin B	Induced antioxidant activity against skin cancer	Perde-Schrepler et al. (2013)
	V. vinifera	Not specified	Anthocyanins, (−)-epicatechin, (+)-catechin, (+)-gallocatechin, stilbenes (resveratrol), phenolic acids	Induced cancer cell apoptosis by increasing ROS and disrupting the mitochondrial membrane potential	Nirmala et al. (2017)
Skin health	Barbera	Italy	Phenolic acids, anthoxanthins, stilbenes, anthocyanins	Inhibited collagenase and elastase activity	Maidin et al. (2018)
	Cannonau	Italy	Polyphenols	Reduced H_2O_2-induced cytotoxicity in human keratinocytes and fibroblasts	Manca et al. (2016)
	Campbell	Korea	Anthocyanins, flavonoids, resveratrol	Reduced intracellular ROS in human keratinocytes	Averilla, et al. (2019)
Gut health	Cabernet Sauvignon, Marselan, Syrah	Not specified	Malvidin, delphinidin, rutin, quercetin, catechin, coumaric acid, kaempferol, *trans*-cinnamic acid	Constrained growth of non-beneficial bacteria while promoting growth of beneficial bacteria	Chacar et al. (2018)
	Not specified	France	Proanthocyanidins (21.3% monomeric, 17.4% dimeric, 16.3% trimeric, 13.3% tetrameric, 31.7% oligomeric)	Increased plasma GLP-1 levels in female Wistar rats and reduced gut Firmicutes to Bacteroidetes ratio	Casanova-Marti et al. (2018)

Table 1 continued

Benefits	Variety	Source	Composition/Active components	Biological activity	References
Microbial growth inhibition	Cabernet Sauvignon	Chile	Quercetin, gallic acid, protocatechuic acid, luteolin, (+)-catechins, (−)-epicatechin, vanillic acid, kaempferol, syringic acid, *p*-coumaric acid, ellagic acid	Exhibited synergistic effect with antibiotics against multi-drug resistant clinical isolates of *S. aureus* and *Escherichia coli*	Sanhueza et al. (2017)
	Touriga Nacional and Preto Martinho	Portugal	Polyphenols, anthocyanins, tannins	Inhibit gram-positive bacteria *S. epidermis*, *Listeria monocytogenes*, and *S. aureus* and gram-negative *Klebsiella pneumoniae*	Silva et al. (2018)

2014; Serrano et al., 2016). Oral administration of the extract had a positive short-term consequence on the variations in the microbiota that was accompanied by a reduction in the ratio of *Firmicutes*-to-*Bacteroidetes* in the gut and augmentation of the plasma GLP-1 level that was allegedly attributed to the harmonious execution of metabolic processes (Casanova-Marti et al., 2018).

Protection from microbial infection

Besides the bioactivities of its phytochemicals in promoting the growth of beneficial gut microbiota and healthy somatic cells, GP is also known to actively inhibit the growth of infectious microorganisms (Gouvinhas et al., 2018). With the widespread antibiotic resistance, researchers continuously survey natural products containing compounds that show synergistic interactions with antibiotics. Remarkably, the polyphenols in GP extract obtained from Cabernet Sauvignon grape (Chile) potentiated the effects of various classes of antibiotics against *Staphylococcus aureus* and *Escherichia coli*, especially the multi-drug resistant clinical isolates (Sanhueza et al., 2017). Moreover, the same GP extract was found to contain polyphenolic components, such as quercetin, gallic acid, protocatechuic acid, luteolin, (+)-catechin, (−)-epicatechin, vanillic acid, kaempferol, syringic acid, *p*-coumaric acid, and ellagic acid (de la Cerda-Carrasco et al., 2015; Sanhueza et al., 2017). Despite the unclear mechanism of synergism between polyphenols and antibiotics, the correlation between the polyphenolic components and beneficial effects introduced the potential uses of polyphenols in improving the potency of currently existing antibiotics (Sanhueza et al., 2017).

A recent comparative study of the antioxidant and antibacterial activities of two red grape varieties (Touriga Nacional and Preto Martinho) from Portugal confirmed the effective inhibition of the Gram-negative (*Klebsiella pneumoniae*) and Gram-positive bacteria (*S. epidermis*, *Listeria monocytogenes*, and *S. aureus*) by the anthocyanins and tannins present in GP (Silva et al., 2018). Both grape varieties exhibited substantial antimicrobial activity, especially the seed extracts, indicating that GP-derived polyphenols may function as an adjunctive substance to intensify the effects of available antibiotics (Silva et al., 2018).

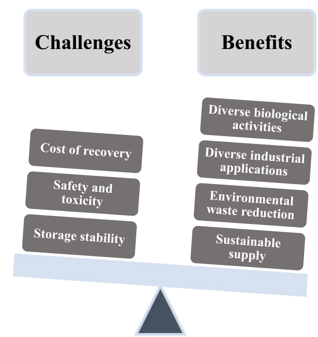

Fig. 2 Potential benefits and challenges of GP utilization

Concluding remarks and future prospects

The varying compositions of different varieties of GP originating from diverse locations displayed remarkable biological activities, as summarized in Table 1. Therefore, the crude or highly purified form of GP extract could be recommended for further studies to resolve some of the potential limitations of GP utilization, such as toxicity (e.g., products of polyphenol metabolism or compatibility with other food/drug constituents), storage stability, and the cost and method of recovery (Fig. 2). Despite these potential challenges, the promising health benefits, sustainability, and environmental impact of GP utilization encourage discoveries of new applications in pharmacological, agricultural, food processing, and other related industries (Del Pino-García et al., 2017).

Given the potent synergistic or antagonistic effects of combinations of polyphenols and other food, drug, or cosmetic constituents, feasible formulations that simultaneously prevent and treat diseases require further investigation. Understanding the association of the polyphenol-mediated modulation of the gut microbial metabolism with pathological diseases may introduce new perspectives in developing techniques for suitable modes of delivery to the systemic circulation, processing, handling, and packaging. Moreover, investigating the formation and characteristics of polyphenolic metabolites, their stability in the gut, and the digestive-resistance of some phytochemicals, such as anthocyanins, may provide possible solutions to the limited bioaccessibility of several phytochemicals (Lingua et al., 2018). Lastly, identifying possible sources of hazardous contaminants during handling, such as pesticides, heavy metals, or the presence of pathogenic microorganisms, may be useful to ensure the safety of GP as a food additive, food preservative, drug stabilizer/carrier, cosmetic component, and in many other industrial uses (Mildner-Szkudlarz et al., 2015; Yu, et al., 2018).

As evidenced in prior research, GP-derived polyphenolic constituents have multiple targets and multiple mechanisms of action that vary, depending largely on several factors, such as the grape composition, variety, and origin. Accordingly, GP could be considered as a natural source of functional polyphenolic components for oral or topical use and is recommended for further investigation. In conclusion, the integration of the polyphenol-rich GP in various applications for human consumption may potentially promote health and ameliorate many types of detrimental diseases.

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Compliance with ethical standards

Conflict of interest The authors declare that no conflict of interest exists.

References

Adams DO. Phenolics and ripening in grape berries. Am. J. Enol. Vitic. 57: 249–256 (2006).

Annapurna A, Reddy CS, Akondi RB, Rao SRC. Cardioprotective actions of two bioflavonoids, quercetin and rutin, in experimental myocardial infarction in both normal and streptozotocin-induced type I diabetic rats. J. Pharm. Pharmacol. 61: 1365–74 (2009).

Avellone G, Di Garbo V, Campisi D, De Simone R, Raneli G, Scaglione R, Licata G. Effects of moderate Sicilian red wine consumption on inflammatory biomarkers of atherosclerosis. Eur. J. Clin. Nutr. 60: 41–47 (2006).

Averilla JN, Oh J, Wu Z, Liu KH, Jang CH, Kim HJ, Kim JS, Kim JS. Improved extraction of resveratrol and antioxidants from grape peel using heat and enzymatic treatments. J. Sci. Food. Agric. 99: 4043–4053 (2019). https://doi.org/10.1002/jsfa.9632.

Balea ŞS, Pârvu AE, Pop N, Marín FZ, Andreicuţ A, Pârvu M. Phytochemical profiling, antioxidant and cardio-protective properties of Pinot noir cultivar pomace extracts. Farmacia 66: 432–441 (2018).

Bang SH, Hyun YJ, Shim J, Hong SW, Kim DH. Metabolism of rutin and poncirin by human intestinal microbiota and cloning of their metabolizing α-L-rhamnosidase from *Bifidobacterium dentium*. J. Microbiol. Biotechnol. 25: 18–25 (2015).

Boussetta N, Lanoisellé JL, Bedel-Cloutour C, Vorobiev E. Extraction of soluble matter from grape pomace by high voltage electrical discharges for polyphenol recovery: Effect of sulphur dioxide and thermal treatments. J. Food Eng. 95: 192–198 (2009).

Canals R, Llaudy MC, Valls J, Canals JM, Zamora F. Influence of ethanol concentration on the extraction of color and phenolic compounds from the skin and seeds of Tempranillo grapes at different stages of ripening. J. Agric. Food Chem. 53: 4019–4025 (2005).

Casanova-Marti À, Serrano J, Portune KJ, Sanz Y, Blay MT, Terra X, Ardévol A, Pinent M. Grape seed proanthocyanidins influence gut microbiota and enteroendocrine secretions in female rats. Food Funct. 9: 1672–1682 (2018).

Castro-López C, Rojas R, Sánchez-Alejo EJ, Niño-Medina G, Martínez-Ávila GCG. Phenolic compounds recovery from grape fruit and by-products: An overview of extraction methods. pp. 103–123. In: A Morata (Ed.), Grape and Wine Biotechnology. InTech, London, UK (2016).

Chacar S, Hajal J, Saliba Y, Bois P, Louka N, Maroun RG, Faivre JF, Fares N. Long-term intake of phenolic compounds attenuates age-related cardiac remodeling. Aging Cell 18: e12894 (2019).

Chacar S, Itani T, Hajal J, Saliba Y, Louka N, Faivre JF, Maroun R, Fares N. The impact of long-term intake of phenolic compounds-rich grape pomace on rat gut microbiota. J. Food Sci. 83: 246–251 (2018).

Chafer A, Pascual-Martí MC, Salvador A, Berna A. Supercritical fluid extraction and HPLC determination of relevant polyphenolic compounds in grape skin. J. Sep. Sci. 28: 2050–2056 (2005).

Cho YJ, Hong JY, Chun HS, Lee SK, Min HY. Ultrasonication-assisted extraction of resveratrol from grapes. J. Food Eng. 77: 725–730 (2006).

Chojnacka K, Lewandowska U. Chemopreventive effects of polyphenol-rich extracts against cancer invasiveness and metastasis by inhibition of type IV collagenases expression and activity. J. Funct. Foods 46: 295–311 (2018).

Cotoras M, Vivanco H, Melo R, Aguirre M, Silva E, Mendoza L. *In vitro* and in vivo evaluation of the antioxidant and prooxidant activity of phenolic compounds obtained from grape (*Vitis vinifera*) pomace. Molecules 19: 21154–21167 (2014).

da Costa GF, Santos IB, de Bem GF, Cordeiro VSC, da Costa CA, de Carvalho L, Ognibene DT, Resende AC, de Moura RS. The beneficial effect of anthocyanidin-rich *Vitis vinifera* L. grape skin extract on metabolic changes induced by high-fat diet in mice involves antiinflammatory and antioxidant actions. Phytother. Res. 31: 1621–1632 (2017).

Dashwood RH. Frontiers in polyphenols and cancer prevention. J. Nutr. 137: 267S–269S (2007).

de la Cerda-Carrasco A, López-Solís R, Nuñez-Kalasic H, Peña-Neira Á, Obreque-Slier E. Phenolic composition and antioxidant capacity of pomaces from four grape varieties (*Vitis vinifera* L.). J. Sci. Food Agric. 95: 1521–1527 (2015).

de Oliveira WP, Biasoto ACT, Marques VF, dos Santos IM, Magalhães K, Correa LC, Negro-Dellacqua M, Miranda MS, de Camargo AC, Shahidi F. Phenolics from winemaking by-products better decrease VLDL-cholesterol and triacylglycerol levels than those of red wine in Wistar rats. J. Food Sci. 82: 2432–2437 (2017).

Del Pino-García R, Rivero-Pérez MD, González-SanJose ML, Ortega-Heras M, Garcia Lomillo JG, Muñiz P. Chemopreventive potential of powdered red wine pomace seasonings against colorectal cancer in HT-29 cells. J. Agric. Food Chem. 65: 66–73 (2017).

Fisher GJ, Datta SC, Talwar HS, Wang ZQ, Varani J, Kang S, Voorhees JJ. Molecular basis of sun-induced premature skin ageing and retinoid antagonism. Nature 379: 335–9 (1996).

Ganceviciene R, Liakou AI, Theodoridis A, Makrantonaki E, Zouboulis CC. Skin anti-aging strategies. Dermato-endocrinology 4: 308–19 (2012).

Garrido-Bañuelos G, Buica A, Schückel J, Zietsman AJJ, Willats WGT, Moore JP, Du Toit WJ. Investigating the relationship between cell wall polysaccharide composition and the extractability of grape phenolic compounds into Shiraz wines. Part II: Extractability during fermentation into wines made from grapes of different ripeness levels. Food Chem. 278: 26–35 (2019).

González-Abuin N, Martínez-Micaelo N, Margalef M, Blay M, Arola-Arnal A, Muguerza B, Ardévol A, Pinent M. A grape seed extract increases active glucagon-like peptide-1 levels after an oral glucose load in rats. Food Funct. 9: 2357–2364 (2014).

Gouvinhas I, Santos RA, Queiroz M, Leal C, Saavedra MJ, Domínguez-Perles R, Rodrigues M, Barros AIRNA. Monitoring the antioxidant and antimicrobial power of grape (*Vitis vinifera* L.) stems phenolics over long-term storage. Ind. Crops Prod. 126: 83–91 (2018).

Holik AK, Stöger V, Hölz K, Somoza MM, Somoza V. Impact of free N^{ε}-carboxymethyllysine, its precursor glyoxal and AGE-modified BSA on serotonin release from human parietal cells in culture. Food Funct. 9: 3906–3915 (2018).

Jang M, Cai L, Udeani GO, Slowing KV, Thomas CF, Beecher CWW, Fong HHS, Farnsworth NR, Kinghorn AD, Mehta RG, Moon RC, Pezzuto JM. Cancer chemopreventive activity of resveratrol, a natural product derived from grapes. Science 275: 218–220 (1997).

Khurana S, Venkataraman K, Hollingsworth A, Piche M, Tai TC. Polyphenols: benefits to the cardiovascular system in health and in aging. Nutrients 5: 3779–3827 (2013).

Kruk J, Duchnik E. Oxidative stress and skin diseases: possible role of physical activity. Asian Pac. J. Cancer Prev. 15: 561–568 (2014).

Kundu JK, Surh YJ. Cancer chemopreventive and therapeutic potential of resveratrol: Mechanistic perspectives. Cancer Lett. 269: 243–261 (2008).

Landis-Piwowar KR, Iyer NR. Cancer chemoprevention: current state of the art. Cancer Growth Metastasis 7: 19–25 (2014).

Lanzi CR, Perdicaro DJ, Antoniolli A, Fontana AR, Miatello RM, Bottini R, Prieto MAV. Grape pomace and grape pomace extract improve insulin signaling in high-fat-fructose fed rat-induced metabolic syndrome. Food Funct. 7: 1544–1553 (2016).

Leikert JF, Räthel TR, Wohlfart P, Cheynier V, Vollmar AM, Dirsch VM. Red wine polyphenols enhance endothelial nitric oxide synthase expression and subsequent nitric oxide release from endothelial cells. Circulation 106: 1614–1617 (2002).

Li H, Parry J, Weeda S, Ren S, Castonguay TW, Guo TL. Grape pomace aqueous extract (GPE) prevents high fat diet-induced diabetes and attenuates systemic inflammation. Food Nutr. Sci. 7: 647–660 (2016).

Lingua MS, Wunderlin DA, Baroni MV. Effect of simulated digestion on the phenolic components of red grapes and their corresponding wines. J. Funct. Foods 44: 86–94 (2018).

Lu Y, Foo LY. The polyphenol constituents of grape pomace. Food Chem. 65: 1–8 (1999).

Luo J, Wei Z, Zhang S, Peng X, Huang Y, Zhang Y, Lu J. Phenolic fractions from Muscadine grape "Noble" pomace can inhibit breast cancer cell MDA-MB-231 better than those from European grape "Cabernet Sauvignon" and induce S-phase arrest and apoptosis. J. Food Sci. 82: 1254–1263 (2017).

Maidin NM, Michael N, Oruna-Concha MJ, Jauregi P. Polyphenols extracted from red grape pomace by a surfactant based method show enhanced collagenase and elastase inhibitory activity. J. Chem. Technol. Biotechnol. 93: 1916–1924 (2018).

Maluf DF, Gonçalves M, D'Angelo RWO, Girassol AB, Tulio AP, Pupo YM, Farago PV. Cytoprotection of antioxidant biocompounds from grape pomace: further exfoliant phytoactive ingredients for cosmetic products. Cosmetics 5: 46 (2018).

Manca ML, Marongiu F, Castangia I, Catalán-Latorre A, Caddeo C, Bacchetta G, Ennas G, Zaru M, Fadda AM, Manconi M. Protective effect of grape extract phospholipid vesicles against oxidative stress skin damages. Ind. Crops Prod. 83: 561–567 (2016).

Manson MM, Gescher A, Hudson EA, Plummer SM, Squires MS, Prigent SA. Blocking and suppressing mechanisms of chemoprevention by dietary constituents. Toxicol. Lett. 112–113: 499–505 (2000).

Marín L, Miguélez EM, Villar CJ, Lombó F. Bioavailability of dietary polyphenols and gut microbiota metabolism: antimicrobial properties. Biomed. Res. Int. 2015: 905215 (2015).

Meini MR, Cabezudo I, Boschetti CE, Romanini D. Recovery of phenolic antioxidants from Syrah grape pomace through the optimization of an enzymatic extraction process. Food Chem. 283: 257–264 (2019).

Mildner-Szkudlarz S, Siger A, Szwengiel A, Bajerska J. Natural compounds from grape by-products enhance nutritive value and reduce formation of CML in model muffins. Food Chem. 172: 78–85 (2015).

Mohansrinivasan V, Devi CS, Deori M, Biswas A, Naine SJ. Exploring the anticancer activity of grape seed extract on skin cancer cell lines A431. Braz. Arch. Biol. Technol. 58: 540–546 (2015).

Mokni M, Hamlaoui S, Kadri S, Limam F, Amri M, Marzouki L, Aouani E. Grape seed and skin extract protects kidney from doxorubicin-induced oxidative injury. Pak. J. Pharm. Sci. 29: 961–968 (2016).

Nerlich AG, Schleicher ED. N^{ε}-(carboxymethyl)lysine in atherosclerotic vascular lesions as a marker for local oxidative stress. Atherosclerosis 144: 41–47 (1999).

Nirmala JG, Akila S, Narendhirakannan RT, Chatterjee S. *Vitis vinifera* peel polyphenols stabilized gold nanoparticles induce cytotoxicity and apoptotic cell death in A431 skin cancer cell lines. Adv. Powder Technol. 28: 1170–1184 (2017).

Oliveira M, Duarte E. Integrated approach to winery waste: waste generation and data consolidation. Front. Environ. Sci. Eng. 10: 168–176 (2016).

Otero-Pareja MJ, Casas L, Fernández-Ponce MT, Mantell C, Martinez de la Ossa EJ. Green extraction of antioxidants from different varieties of red grape pomace. Molecules 20: 9686–9702 (2015).

Parker AK, de Cortázar-Atauri IG, van Leeuwen C, Chuine I. General phenological model to characterise the timing of flowering and veraison of *Vitis vinifera* L. Aus. J. Grape Wine Res. 17: 206–216 (2011).

Pasinetti GM, Wang J, Ho L, Zhao W, Dubner L. Roles of resveratrol and other grape-derived polyphenols in Alzheimer's disease prevention and treatment. Biochim. Biophys. Acta Mol. Basis Dis. 1852: 1202–1208 (2015).

Peixoto CM, Dias MI, Alves MJ, Calhelha RC, Barros L, Pinho SP, Ferreira ICFR. Grape pomace as a source of phenolic compounds and diverse bioactive properties. Food Chem. 253: 132–138 (2018).

Perde-Schrepler M, Chereches G, Brie I, Tatomir C, Postescu ID, Soran L, Filip A. Grape seed extract as photochemopreventive agent against UVB-induced skin cancer. J. Photochem. Photobiol. B Biol. 118: 16–21 (2013).

Perdicaro DJ, Lanzi CR, Fontana AR, Antoniolli A, Piccoli P, Miatello RM, Diez ER, Prieto MAV. Grape pomace reduced reperfusion arrhythmias in rats with a high-fat-fructose diet. Food Funct. 10: 3501–3509 (2017).

Petrovski G, Gurusamy N, Das DK. Resveratrol in cardiovascular health and disease. Ann. N. Y. Acad. Sci. 1215: 22–33 (2011).

Pintać D, Majkić T, Torović L, Orčić D, Beara I, Simin N, Mimica–Dukić N, Lesjak M. Solvent selection for efficient extraction of bioactive compounds from grape pomace. Ind. Crops Prod. 111: 379–390 (2018).

Radhakrishnan S, Reddivari L, Sclafani R, Das UN, Vanamala J. Resveratrol potentiates grape seed extract induced human colon cancer cell apoptosis. Front. Biosci. E3: 1509–1523 (2011).

Rasines-Perea Z, Ky I, Cros G, Crozier A, Teissedre PL. Grape pomace: antioxidant activity, potential effect against hypertension and metabolites characterization after intake. Diseases 6: 60 (2018).

Reinisalo M, Kårlund A, Koskela A, Kaarniranta K, Karjalainen RO. Polyphenol stilbenes: molecular mechanisms of defence against oxidative stress and aging-related diseases. Oxid. Med. Cell Longev. 2015: 340520 (2015).

Ribeiro TP, Oliveira AC, Mendes-Junior LG, França KC, Nakao LS, Schini-Kerth VB, Medeiros IA. Cardiovascular effects induced by northeastern Brazilian red wine: Role of nitric oxide and redox sensitive pathways. J. Funct. Foods 22: 82–92 (2016).

Rockenbach II, Gonzaga LV, Rizelio VM, Gonçalves AEDSS, Genovese MI, Fett R. Phenolic compounds and antioxidant activity of seed and skin extracts of red grape (*Vitis vinifera* and *Vitis labrusca*) pomace from Brazilian winemaking. Food Res. Int. 44: 897–901 (2011).

Romero-Perez AI, Lamuela-Raventos RM, Andres-Lacueva C, de La Torre-Boronat MC. Method for the quantitative extraction of resveratrol and piceid isomers in grape berry skins. Effect of powdery mildew on the stilbene content. J. Agric. Food Chem. 49: 210–215 (2001).

Rondeau P, Gambier F, Jolibert F, Brosse N. Compositions and chemical variability of grape pomaces from French vineyard. 43: 251–254 (2013).

Sanhueza L, Melo R, Montero R, Maisey K, Mendoza L, Wilkens M. Synergistic interactions between phenolic compounds identified in grape pomace extract with antibiotics of different classes against *Staphylococcus aureus* and *Escherichia coli*. PLoS One 12: e0172273 (2017).

Serrano J, Casanova-Marti À, Gil-Cardoso K, Blay MT, Terra X, Pinent M, Ardévol A. Acutely administered grape-seed proanthocyanidin extract acts as a satiating agent. Food Funct. 7: 483–490 (2016).

Shankar S, Siddiqui I, Srivastava RK. Molecular mechanisms of resveratrol (3,4,5-trihydroxy-*trans*-stilbene) and its interaction with TNF-related apoptosis inducing ligand (TRAIL) in androgen-insensitive prostate cancer cells. Mol. Cell Biochem. 304: 273–285 (2007).

Silva V, Igrejas G, Falco V, Santos TP, Torres C, Oliveira AMP, Pereira JE, Amaral JS, Poeta P. Chemical composition, antioxidant and antimicrobial activity of phenolic compounds extracted from wine industry by-products. Food Control 92: 516–522 (2018).

Souquet JM, Labarbe B, Le Guernevé C, Cheynier V, Moutounet M. Phenolic composition of grape stems. J. Agric. Food Chem. 48: 1076–1080 (2000).

Spanghero M, Salem AZM, Robinson PH. Chemical composition, including secondary metabolites, and rumen fermentability of seeds and pulp of Californian (USA) and Italian grape pomaces. Anim. Feed Sci. Technol. 152: 243–255 (2009).

Steward WP, Brown K. Cancer chemoprevention: a rapidly evolving field. Br. J. Cancer 109: 1–7 (2013).

Teixeira A, Baenas N, Dominguez-Perles R, Barros A, Rosa E, Moreno DA, Garcia-Viguera C. Natural bioactive compounds from winery by-products as health promoters: a review. Int. J. Mol. Sci. 15: 15638–15678 (2014).

Wittenauer J, Mäckle S, Sußmann D, Schweiggert-Weisz U, Carle R. Inhibitory effects of polyphenols from grape pomace extract on collagenase and elastase activity. Fitoterapia 101: 179–187 (2015).

Yacco RS, Watrelot AA, Kennedy JA. Red wine tannin structure–activity relationships during fermentation and maceration. J Agric Food Chem 64: 860–869 (2016).

Yu J, Ahmedna M. Functional components of grape pomace: their composition, biological properties and potential applications. Int. J. Food Sci. Technol. 48: 221–237 (2013).

Yu J, Smith I, Karlton-Senaye B, Mikiashvili N, Williams L. Impacts of different drying methods on mold viability and ochratoxin A content of grape pomace. Int. J. Appl. Agric. Sci. 4: 35–42 (2018).

Yuan F, Qian MC. Development of C_{13}-norisoprenoids, carotenoids and other volatile compounds in *Vitis vinifera* L. Cv. Pinot noir grapes. Food Chem 192: 633–641 (2016).

Zillich OV, Schweiggert-Weisz U, Eisner P, Kerscher M. Polyphenols as active ingredients for cosmetic products. Int. J. Cosmet. Sci. 37: 455–464 (2015).