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An outlook on modern and sustainable approaches to the management of grape pomace by integrating green processes, biotechnologies and advanced biomedical approaches

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ABSTRACT

Grape pomace is the main solid residue of wine industry, mainly composed of seeds, skins and stalks, all containing high amounts of valuable phytochemicals. Considering its high potential, in this review, an outlook on different resources and products, which can be obtained by the recovery of grape pomace is provided. Special attention has been devoted to the analysis of chemical, physical and biotechnological processes to be applied and also to the high value compounds and products, such as supplements, nutraceuticals and cosmeceuticals, that can be manufactured. In particular, in the first part of the review, an update on the composition of grape pomace has been provided along with the analysis of its traditional fate. In the second part, the more modern and green approaches tested to the sustainable management of grape pomace are reported and discussed.

1. Introduction

By 2050 the world will consume three times the available planet Earth resources; to avoid this eventuality and limit resource dissipation, the European Union aims to achieve climate neutrality by the same year, and the application of the principles of the Circular Economy is functional to the achievement of this objective (European Commission, 2020). Morseletto defines Circular Economy as "an economic model aimed at the efficient use of resources through waste minimisation, long-term value retention, reduction of primary resources, and closed loops of products, product parts, and materials within the boundaries of environmental protection and socioeconomic benefits" that "has the potential to lead to sustainable development, while decoupling economic growth from the negative consequences of resource depletion and environmental degradation" (Morseletto, 2020). Waste management plays a crucial role, as it can pave the way to Circular Economy implementation by closing loops and keeping precious resources within the economic system, or vice versa, continue to represent one of the main burdens for the sustainability of human life on the planet Earth (European Commission, 2015, 2018). Agro-industrial residues represent one of the main waste flows both from a quantitative and qualitative point of view (Yaashikaa et al., 2022). Every year, approximately 1.6 billion tons of wastes are globally generated by the human food chain alone (Freitas et al., 2021). In Europe, around 89 million tons of food waste are produced per year, whilst the total agricultural residue production amounts to 367 million tons per year (Ravindran et al., 2018). From a qualitative point of view, the incorrect management of these residues determines serious environmental impacts such as the production of greenhouse gases (CO_2 and CH_4) and oxygen depletion, among others (Yaashikaa et al., 2022). On the other hand, the same characteristics make them suitable for multiple valorisation options, from the extraction of compounds with high added value, to the production of energy or organic building blocks through more or less intense demolition of the organic matter (Gómez-García et al., 2021; Sodhi et al., 2022). This awareness

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has fuelled an intense research activity focusing on the possible transformation of different agro-industrial wastes and by-products, such as sugarcane straw, garlic skin, spent coffee grounds, apple, olive mill, wineries and breweries (Gómez-García et al., 2021; Hernández et al., 2021; Hernández-Varela et al., 2022; Leite et al., 2021; Roasa et al., 2021; Robledo-Ortíz et al., 2021; Tinoco-Caicedo et al., 2021).

In this vast context, grapes rank fourth as the most produced fruit in the world with almost 80 million tons in 2018 (FAO, 2018). According to FAO (Food and Agriculture Organization) 38 % of global grape production occurs in Europe, followed by Asia (35 %) and Americas (19 %). Italy counts around eight million tons per year and is the leader among the European countries, globally second only to China (FAO, 2018; ISTAT, 2020). Most of the worldwide grape production is used to produce wine and spirits, and the winemaking process is characterised by the generation of a large volume of waste and by-products (i.e., grape pomace) over a limited period of the year, which exacerbates the environmental and economic problems (Kalli et al., 2018). As for other production sectors, the best solution to these problems lies in the adoption of an approach consistent with the dictates of the Circular Economy, which allows to optimize not only waste management, but also energy and water consumption, as well as to open market options previously unthinkable (Goyal et al., 2018). Consistently to this philosophy, in the last few decades different potential strategies have been proposed to recover resources from grape waste and by-products (Allaw et al., 2020; Chebbi et al., 2021; Ferri et al., 2020; Leite et al., 2021).

The review aims is to provide an outlook on different approches and processes, which have been applied using grape pomace along with the resources and products, which can be obtained. Particular attention has been paid to sustainable methodologies capable of allowing the recovery of compounds and products characterized by high added value such as supplements, nutraceuticals and cosmeceuticals, especially the most innovative obtained using nanocarriers. It is in fact the authors' opinion that the greatest potential for valorisation of agro-industrial waste lies in the extraction of the phytochemicals and molecules with high added value that, being present in high amount, make precious these biomasses. To be sustainable and economically exploitable, their management must then be integrated and completed with other treatments aimed at the demolition, stabilization and reorganization of the bulk of the organic matter.

2. Composition of grape pomace

Grape pomace represents the main solid residue generated during pressing and fermentation processes of winemaking. It is mainly composed of skins, stalks and seeds (Jin, Yang, et al., 2018). The amount of grape pomace produced during the winemaking process depends on various factors, such as grape cultivar, soil characteristics, wine production process and even the kind of equipment used, which in tourn affect their composition as previously reported (Dwyer et al., 2014; Hogervorst et al., 2017; Ioannidou et al., 2022). According to Dwyer et al. (2014), pomace represents approximately 25 % of the original grape weight (Dwyer et al., 2014). According to the Italian Central Statistics Institute, around 88 % of the grape harvested in Italy is used to produce wine, corresponding to 7.231.542 tons of grapes per year, which would produce around 1.807.886 tons of pomace (ISTAT, 2020). Grape pomace is considered a low-value material, mainly used for ethanol distillation but overlooking its high content in bioactive phytochemicals, in particular polyphenols, and its physico-chemical properties (Table 1) (Dwyer et al., 2014).

Grape skin represents the main constituent of grape pomace, approximately 50 % of the total grape pomace weight (Jin, Yang, et al., 2018), characterised by a high content of fibres and sugars. The fibres content is highly variable, spanning the ranges 51–56 % by weight in red grape and 17–28 % in white one, respectively; the skin of red grape is also rich in crude protein, fat and ash (inorganic residue) (Deng et al., 2011). Other compounds contained in high amount are anthocyanins and tannins, useful as supplements for colour development in wine (e.g., Pinot noir) because they increase the concentration of stable pigments by 40 % (de Torres et al., 2015; Pedroza et al., 2013; Sparrow et al., 2020). In recent years, the skin of red and white grape has been studied as a source of phytochemicals having several potential health-promoting effects (Bomfim et al., 2019; Deng et al., 2011; Dwyer et al., 2014; Hogervorst et al., 2017; Kurek et al., 2019; Sri Harsha et al., 2014). Indeed, especially the red one, it is rich in phenolic compounds such as stilbenes, triterpenes, anthocyanins, tannins and hydroxybenzoic derivative acids (Deng et al., 2011; Hogervorst et al., 2017; Liazid et al., 2011; Manconi et al., 2017; Orbán et al., 2009; Pugajeva et al., 2018).

Table 1
Grape pomace: main chemical properties of interest.

Parameter	Value	References
Total polyphenols (mg GAE[a] per 100 g)	5402–6010	(Makris et al., 2007; Spinei & Oroian, 2021)
Ash (g/100 g)	2–7	(Kandylis et al., 2021)
Protein (g/100 g)	5–14	(Bender et al., 2020; Kandylis et al., 2021)
Lipids (g/100 g)	1–13	(Kandylis et al., 2021)
Total dietary fibre (g/100 g)	17–88	(Antonić et al., 2020)
Cellulose (g/100 g)	7–9	(Bender et al., 2020; el Achkar et al., 2016)
Hemicellulose (g/100 g)	6–22	(Bender et al., 2020; el Achkar et al., 2016)
Lignin (g/100 g)	11–23	(Bender et al., 2020; el Achkar et al., 2016)
pH	3.34–3.94	(Bender et al., 2020; el Achkar et al., 2016)
Moisture content (%)	50–82	(Iqbal et al., 2021)
TS[b] (g/kg w/w)	434–451	(da Ros et al., 2016; el Achkar et al., 2016)
VS[c] (g/kg w/w)	371–425	(da Ros et al., 2016; el Achkar et al., 2016)
COD[d] (g O_2/kg w/w)	223–610	(el Achkar et al., 2016; Kassongo et al., 2022)
BMP[e] (L_NCH_4/kg VS)	116–360	(da Ros et al., 2016; Dinuccio et al., 2010)

[a] Gallic Acid Equivalents;
[b] Total Solids;
[c] Volatile Solids;
[d] Chemical Oxygen Demand;
[e] Biochemical Methane Potential.

Stalks, the skeleton of the grape bunch, account for about 25 % by weight of grape pomace (Jin, Yang, et al., 2018; Ping et al., 2011). Grape stalks mainly consist of lignified tissues, due to the high quantities of fibres such as cellulose (30–36 %), hemicelluloses (21–25 %) and lignin (17–40 %); the wide range of values depends on grape variety, colour, vinification processes and even the destemmed used (Ping et al., 2011; Prozil et al., 2012). Stalks are also considered a precious source of valuable compounds (Bertran et al., 2004; Egüés et al., 2013; Manca et al., 2019; Ozdemir et al., 2014; Portinho et al., 2017; Ruiz-Moreno et al., 2015; Spatafora et al., 2013; Villaescusa et al., 2004). Their main phenolics compounds are tannins, essentially procyanidins (Manca et al., 2019; Ping et al., 2011; Teixeira et al., 2018).

Seeds account for another 25 % by weight of grape pomace, and contain mainly oil, around 8–20 % by weight, beside phenolic compounds and oligosaccharides (Bordiga et al., 2019; Jin, Yang, et al., 2018; Khan et al., 2020). The seed oil is a mixture of saturated and unsaturated fatty acids having high nutritional and beneficial effects (Guo et al., 2020; Kim et al., 2020; Manca et al., 2019; Taranu et al., 2019; Unusan, 2020). The oil is rarely recovered despite having a high value on the market, probably due to the difficulties of separating the seeds from the other pomace fractions (Jin et al., 2021).

3. Direct uses of grape pomace

Direct uses of grape pomace include distillation, animal feeding and land spreading in a controlled manner (Badouard et al., 2021; Ilyas et al., 2021). Distillation is the traditional use of grape pomace, especially in the Old Continent and over time has given rise to different local names for spirits (e.g., *Grappa* in Italy, *Zivania* in Cyprus, *Eaux de vie de marc* in France) (Botelho et al., 2020). In Italy, with around 135 distilleries, spirit production from grape pomace distillation is an important industrial activity, with a production of 85,000 hL of pure alcohol equivalents in 2018 (Cisneros-Yupanqui et al., 2021; Giannetti et al., 2019). Pomace distillation consists in heating them to lead the evaporation of ethanol and other volatile substances, cooling of the vapours to obtain a liquid enriched in ethanol. The liquid may be redistilled, or rectified, several times to increase the purity and achieve a flavoured spirit (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. et al., 1988). Spirit production through distillation entails the use of resources, as well as significant costs and carbon dioxide emissions. Moreover, the process yields huge volumes of distilled pomace, to be managed as waste, and acid wastewater, which is characterised by high chemical oxygen demand, darkish colour, and the presence of phenolic compounds that may inhibit biological treatment (Strong & Burgess, 2008). The distilled grape pomace is a processed residue rich in fibres and polyphenols, that could be extracted and recovered, though the process proved to be difficult as compared to the application to fresh pomace. This has led to the study of highly effective extraction methods such as those based on the combined use of pulsed solvents and enzymes (Guerrero et al., 2008). Overall, the extraction of valuable compounds from distilled pomace is a little studied topic (Cisneros-Yupanqui et al., 2021). However, several authors have underlined the possibility of extracting valuable compounds from “the waste of the waste” of wine production despite the severe operating conditions to which the pomace is subjected during distillation (Bordiga et al., 2015; Peralbo-Molina et al., 2012).

If pomace is not used for the distillation of spirits, it is often spread on open areas. This management method involves significant environmental risks as pomace may retard or inhibit germination due to its chemical composition (Ahmad et al., 2020; Ilyas et al., 2021; Nayak et al., 2018). In fact, the phenolic compounds contained in the grape pomace have phytotoxic and antimicrobic effects (de Melo et al., 2017; Olszewska et al., 2020). Furthermore, the contribution to the chemical characteristics of the soil is limited by the high presence of lignin, whose difficult degradability in the absence of pre-treatments prevents the release of polysaccharides that would be beneficial to soil (Troncozo et al., 2019). For these reasons, in several European countries the land spreading must be subjected to dosage limits, whilst the use of pomace is encouraged for the production of high-quality composted soil improvers (Cortés et al., 2020).

As an alternative to spreading on soil, the pomace is used as it is, for animal feeding. In this respect, negative effects on livestock health should be emphasized; in particular, the high content of lignified fibres and secondary metabolites (i.e., tannins and anthocyanins) can exert negative effects on digestion. Lignin is contained in high amounts in seeds and is digestion resistant, therefore it has a low nutritional intake (Rouches et al., 2016). On the other hand, Guerra-Rivas et al. (2017) reported that the nutritive value of grape pomace from red wine depends on the grape pulp presence as increasing contents lead to better digestibility and higher intake of polyphenols and linoleic acid, with beneficial effects on the quality of meat and milk (Guerra-Rivas et al., 2017).

4. Alternative approaches for grape pomace valorisation

4.1. Biological treatments

Treatment of pomace through aerobic composting makes spreading on soil virtuous instead of causing soil impairment and pollution. Indeed, quality compost produced from grape pomace can significantly contribute to the improvement of soils characterised by depleted organic matter contents (Cortés et al., 2020). It is reasonable to assume that pomace is composted in a mixture with other residues typical of an agro-industrial context. In this respect, Martinez et al. evaluated the evolution of chemical, microbiological, biochemical and phytotoxicity parameters during composting of grape pomace mixed with different other residues such as horse and goat manure, pruning residues, oat straw, and yeast fermentation residues (Martínez Salgado et al., 2019). Not surprisingly, the final products obtained in a mixture with animal waste such as goat or horse manure proved to be suitable as fertilising soil improvers, thanks to the content of nutrients and classified as a category according to Chilean National Standard. The same authors in previous studies had applied innovative criteria for qualitative analysis of composts produced from pomace and goat residues observing promising results (Martínez et al., 2016). The possibility of obtaining good quality composts from pomace does not seem to necessarily derive from co-treatment with other residual substrates. Moldes et al. have produced composts starting only from grape seeds, stalks and skins, obtained from white grape variety cultivated in Ourense (Spain), mixed in different proportions, obtaining a product that has been effective on land cultivated with ray grass crops (Moldes et al., 2007). Nistor et al. composted for six months fresh local grape pomace (Paulian village, Arad County) and applied the final product in a local vineyard according to a 20 t/ha dosage; the quality of produced grape did not change and the wine did not undergo any detrimental effect (Nistor et al., 2014).

Grape pomace has relatively low nitrogen and phosphorus contents, an aspect that could negatively affect aerobic treatments while is much less relevant in anaerobic treatments, as biomass production per unit mass of degraded substrate is significantly lower (Cáceres et al., 2012; da Ros et al., 2016). Pomace has sufficient trace elements for anaerobic bacterial growth, and the high content of water does not have the negative effects it would have in the case of aerobic treatments where it slows down oxygen diffusion (Cáceres et al., 2012). Most of all, anaerobic digestion is considered to be one of the main future contributors to energy supply in many areas such as Europe (da Ros et al., 2016). El Achkar et al. demonstrated that grape pomace can be an important energy source by performing batch anaerobic digestion aimed at methane production. They also upscaled their study by managing a continuous-fed pilot scale reactor that confirmed the biogas yields achievable at lab scale (el Achkar et al., 2016). By way of illustration, da Ros et al. estimated that the combustion of the biogas theoretically generated through anaerobic digestion of the global production of grape pomace could generate 1520 GWh/y of heat and 1245 GWh/y of electricity to be used by wineries themselves (da Ros et al., 2016).

Anaerobic treatments do not necessarily have to be pushed to the methanization of substrate. Acid-alcoholic fermentation is the fundamental intermediate phase of anaerobic degradation and stopping the process at this stage allows the recovery of products of great interest both in gaseous (H_2) and in liquid phase (mainly volatile fatty acids). Among the volatile fatty acids, the production of succinic acid, a C-4 dicarboxylic acid with different applications in agricultural, food and pharmaceutical fields, is of particular interest (Filippi et al., 2021). Filippi et al. developed a novel process to obtain both a high antioxidant extract and succinic acid from Greek red grape pomace. The substrates, pre-treated with both alkaline and acidic solutions, were enzymatically hydrolysed into a high sugar-content hydrolysate. The free sugars in the hydrolysate can be efficiently used as the substrate by *Actinobacillus succinogenes* for succinic acid production (Filippi et al., 2021). The volatile fatty acid pool obtained through grape pomace fermentation can be also used for the production of biopolymers (Altan Kamer et al., 2021; Joulak et al., 2021). Altan Kamer et al. successfully used Turkish red grape pomace as the substrate for *Sphingomonas paucimobilis* to produce a biosynthesized gellan gum with better stability against temperature changes than commercial gellan gum (Altan Kamer et al., 2021).

Fossil fuels represent one of the main sources to satisfy the constantly growing demand for electricity, heat and cooling. However, increasing attention to climate change requires the use of greener approaches such as renewable biofuels (Sirohi et al., 2020). Due to their abundance in carbohydrates, agro-industrial residues represent interesting renewable lignocellulosic biomass sources for biofuel production (Hernández et al., 2021; Rodríguez et al., 2010). Jin et al. developed an integrated approach for the valorisation of grape pomace obtaining, among the others, valuable biofuels. The red grape pomaces were collected in Virginia (USA), during fall. In particular, they use the reducing sugars obtained from the hydrolysation of cellulose and hemicellulose derived from red grape pomace, to fed *Clostridium beijerinckii* and produce butanol, acetone and ethanol through fermentation (Jin, Neilson, et al., 2018).

4.2. Thermal treatments

Like all organic materials, pomace is potentially suitable for the thermal treatments of combustion, gasification and pyrolysis. As far as combustion is concerned, Benetto et al. evaluated the production of pellets from grape pomace (Benetto et al., 2015). The results of the study highlighted that the energetic potential of these pellets is equivalent to 19.8 GJ/t dry matter on average, a promising value in view of full-scale applications. Pyrolysis, performed at temperatures spanning 300–800 °C, is of great interest from a circular economy perspective since, compared to thermal oxidation by combustion, it allows the chemical value of the feed material to be recovered. Furthermore, the characteristics of the process mean that no organochlorine micropollutants are produced.

In an agro-industrial context, pyrolysis could be used to convert agricultural wastes to organic biochar (Sirohi et al., 2020). Madadian et al. investigated the application of pyrolysis to different wine residues and found that the activation energy for grape pomace spans 29.96–41.32 kJ/mol, enough to support the feasibility of using this by-product as a source of energy for agro-industrial activities (Madadian et al., 2022). A recent study focused on the valorisation of grape pomace through solid–liquid extraction followed by pyrolysis, also assessing the impact of extraction of phenols on pomace thermal conversion (Almeida et al., 2022). The use as adsorbent material of the char produced through pyrolysis of grape pomace is of great interest. In recent years, several studies were performed aiming at recovering adsorbent materials for heavy metals and pesticides (Diaz-Ramirez et al., 2021; Yoon et al., 2021). Yoon et al. were able to produce a biochar at low pyrolytic temperature (i.e., 350 °C) and tested it as an adsorbent to remove the pesticide cymoxanil achieving a maximum adsorption capacity of 161 mg cymoxanil /g biochar at pH 7 (Yoon et al., 2021).

Hydrothermal carbonization, also known as wet pyrolysis, appears to be even more suitable for the valorisation of agro-industrial residues as the reactions involved require the presence of water, therefore the process is directly applicable to biomasses characterized by significant water content. This process simulates the natural formation of coal by the decomposition of organic matter in process water, under temperature conditions spanning 180–250 °C (Garrido et al., 2021). The process yields carbonaceous materials that can be used for different purposes. Salaudeen et al. studied the effects of hydrothermal carbonization on the steam gasification of different fruit wastes, including grape pomace. The work disclosed that the process can potentially reduce tar formation by removing low quality volatile compounds, but further studies are needed (Salaudeen et al., 2021).

4.3. Extraction of valuable compounds

The extraction of valuable compounds is particularly consistent with the principles of the Circular Economy as it allows the recovery of products with high added value, in turn favouring the effective integration of residual flows into an economic market system. In perspective, it is not unthinkable to hypothesize that the extraction of valuable compounds could be combined with other processes useful to complete the valorisation, i.e., composting (Perra et al., 2022).

Alibade et al. developed a green and highly efficient methodology to recover anthocyanin pigments from Greek red grape pomace (Alibade et al., 2021). Such pigments are among the most valuable phytochemicals present in this by-product, indeed, cyanidin, delphinidin and malvidin have beneficial properties and are widely used as pigments and functional ingredients for beverages, foods, cosmetics and pharmaceuticals (Soceanu et al., 2021). To be effectively sustainable, the recovery of valuable compounds must be carried out using low-impact extraction methods. In this respect, Alibade et al. tested the recover efficiency of two glycerol-based deep eutectic solvents. The process was also integrated with ultrasonic pre-treatment, which significantly increased the extraction efficiency. The effectiveness of the two deep eutectic solvents was compared with that of water and water–ethanol, which proved to be far less effective (Alibade et al., 2021).

Guo et al. found out that a 0.5 % grape seed extract solution can: decrease the growth rate of various bacteria and yeast in roast chicken during low-temperature storage; reduce the fat oxidation rate; and maintain colour stability. Compared with normal packaging, the innovative storage method, which combines the use of grape seed extract solution with modified atmosphere packaging, may effectively extend the shelf life of food, preserving its quality for more than 21 days (Guo et al., 2020).

4.4. Extraction of polyphenols and manufacturing of health-promoting added-value products: An example of optimal economic valorisation

As already mentioned, grape pomace is characterised by a high content of valuable phytochemicals with health-promoting properties, which can be used to manufacture food nutrients, supplements, nutraceuticals, cosmeceuticals and medical devices, meeting the interest of consumers (Hoss et al., 2021; Sirohi et al., 2020). Indeed, modern society is increasingly paying attention to these products to counteract the risks connected with the modern lifestyle worldwide, characterized by stress, lack of both sleep and physical activity, consumption of junk food, alcohol, smoke and drugs. These unhealthy habits together with environmental pollution can cause oxidative stress, which is a pre-pathological condition characterised by an overproduction of reactive oxygen species (ROS) that endogenous antioxidants are not capable of completely neutralizing. Oxidative stress plays a crucial role in the pathogenesis of severe conditions and chronic diseases causing alteration of membrane, lipids, proteins, and nucleic acids, which is primarily associated with ageing, but also with a wide range of pathological processes including atherosclerosis, carcinogenesis, ischemia reperfusion injury, and neurodegenerative disorders (Farías et al., 2016). However, when the endogenous defence is not able to mitigate the damaging effects of ROS, external antioxidants can be introduced by the daily consumption of crops, food matrices or supplements aiming at reducing, or at least slowing down, the oxidation processes in the whole body (Lobo et al., 2010; Manca et al., 2020; Winiarska-Mieczan et al., 2020). The long-term daily intake or the topical application of natural antioxidants, especially polyphenolic compounds, can prevent the onset of damages associated with oxidative stress, contributing to the maintenance of human health (Bacchetti et al., 2019). Phenolic compounds, vitamins and some minerals (selenium and zinc) are the most important and effective agents against oxidative stress (Brewer, 2011). They act by scavenging oxidative species, quenching singlet oxygen, chelating metals, breaking free radical chain reactions and reducing the concentration of ROS. The antioxidant power is strictly dependent on the mechanism adopted by each compound and the ability to reduce or avoid peroxidation processes: phenolic compounds are effective in trapping free radicals, but less in chelating metals; flavonoids can effectively scavenge free radicals and chelate metals. Phenolic compounds represent one of the most important groups of natural products in plants, with more than 5000 chemicals (Fiore et al., 2020). They are generally classified into two groups: flavonoids and non-flavonoids. Because of their ever-growing demand, polyphenols have a huge market potential (Leite et al., 2021). Their market value was 580 million US$ in 2011 and it is expected to reach 2.08 billion by 2025 (Leite et al., 2021).

Like fresh fruits, grape pomace is a largely available and cheap source of polyphenols, since the main part of these phytochemicals does not pass in the wine but remains in the residual product. It has been estimated that approximately 70 % of the phenolics remain within the pomace after the winemaking process (Dwyer et al., 2014). Several studies confirmed the health-promoting effects of grape and grape-derived products, which are connected to their phytochemical content characterised by high antioxidant power (Nassiri-Asl & Hosseinzadeh, 2009). In vitro and in vivo studies have shown that the consumption of fresh grape is associated with the reduction of pathological processes, mainly because of antioxidant, anti-inflammatory, anti-age, anti-cholesterolemic, antimicrobial, antiviral, cardioprotective, neuroprotective and anti-cancer properties of the phytochemicals contained in this fruit (Barbalho et al., 2020; Yang & Xiao, 2013). Epidemiological evidence has linked the consumption of grapes with a reduced risk of chronic diseases, including neurodegenerative and cardiovascular diseases (Bertelli & Das, n.d.; Dohadwala & Vita, 2009). Singh et al. reported that the consumption of grape powder in SKH-1 hairless mice resulted in a marked inhibition of skin tumour incidence and a delay in the onset of tumorigenesis (Singh et al., 2019). The treatment was associated with an enhanced repair of damaged DNA in the skin, a reduced proliferation and increased apoptosis of cancer cells, and a modulation of several oxidative markers, especially those connected with the inhibition of oxidative stress and the metabolism of ROS. Ammollo et al. evaluated the effect of grape consumption on coagulation and fibrinolysis in healthy volunteers. They concluded that chronic grape consumption induces sustained anticoagulant and profibrinolytic effects with potential benefits for human health (Ammollo et al., 2017). Svezia et al. evaluated the in vivo effects of long-term intake of Tuscany Sangiovese grape juice in a murine model of myocardial ischemia and in healthy human subjects. Results supported the development of a novel grape nutraceutical product for cardio protection (Svezia et al., 2020). Nash et al. provided an overview of recent trials on the positive effects of the consumption of grape and red wine polyphenols on gut microbiota in humans (Nash et al., 2018). They concluded that, despite the limited number of studies available, dietary intake of polyphenols derived from red wine and grape juice seems to modulate the gut microbiota and contribute to beneficial microbial ecology, enhancing human health. Vislocky and Fernandez (2010) examined the published studies on the human health benefits associated with grapes and grape products. Several beneficial activities have been underlined, such as improved endothelial function, decreased LDL oxidation, reduction of atherosclerosis and oxidative processes (Vislocky & Fernandez, 2010). Furthermore, other studies confirmed the positive effect of grape products in counteracting cardiovascular, diabetes, cancer and Alzheimer's or other neurodegenerative diseases connected with the stimulation of the immune system as antivirals, even if these data must be confirmed by further studies. The antioxidant, anti-inflammatory, antiproliferative, anti-lipid-oxidation, anti-neurodegenerative and anti-cardiovascular activities related to the consumption of grape have also been confirmed by Yang and Xiao (Yang & Xiao, 2013). Overall results underline the preventive and health-promoting properties of grape and its by-products.

As reported above, extraction of phytochemicals represents one of the main steps towards grape pomace valorisation, to achieve a lower environmental impact and to make this winemaking by-product a valuable source of profit. In order to do this, easy, scalable, environmental and economical suitable methods are needed to be industrially exploited. The study of such methods is the focus of new green chemistry and technologies, which avoid the use of expensive and environmental harmful organic solvents (methanol, acetone, hexane, chloroform) or acidic solutions typically used in the conventional extraction procedures (Chowdhary et al., 2021; Portilla Rivera et al., 2021).

Solid-liquid extraction is one of the classical conventional methods applied to extract phytochemicals from grape pomace. It relies on the interaction between phytochemicals and different solvents and involves the use of different concentrations of solvents. The main disadvantages of this method are the high cost of used solvents, the low yield of extraction, the high temperature required and the long extraction time (Sirohi et al., 2020). These problems can be overcome by coupling solid–liquid extraction with ultrasound and/or grinding of the raw material to reduce the time and temperature of extraction (da Rocha & Noreña, 2020; Perra et al., 2021). Indeed, during conventional extraction, bioactive compounds are exposed to high temperatures for long periods, which can cause oxidation and degradation (da Rocha & Noreña, 2020). Ultrasounds and grinding can accelerate the interaction between phytochemicals and the extractive solution, thus avoiding the application of high temperatures and long times of extraction, enhancing extraction yield and phytochemical composition, and reducing environmental and economic issues (da Rocha & Noreña, 2020). The advantages of ultrasound-assisted extraction have been investigated for several years. The mechanism involved is cavitation, that generates bubbles on the surface of the solid matrix, which can cause, among the others, particle breakdown, surface peeling and erosion (Alibade et al., 2021). In their study, Goula et al. confirmed the advantages of the ultrasound-assisted extraction process in terms of time needed and extraction yield of polyphenols. Indeed, only 10 min in aqueous ethanol were needed to recover polyphenols from Greek red grape pomace with a high yield against conventional extraction that was 100 times longer (Goula et al., 2016).

Besides ultrasound-assisted extraction, other green and innovative techniques are microwave-assisted, supercritical fluid and pressurised liquid extractions. The first method involves the heating of the solid sample suspended in a proper solvent with microwaves. By applying a direct electromagnetic field, this extraction increases cell breakdowns and the consequent release of bioactive molecules under less aggressive conditions (Figueroa et al., 2021). Microwave-assisted extraction can be successfully coupled with eutectic solvents, considerably reducing extraction time from 3.56 to 1 h, and still obtaining a high yield of proanthocyanidins (Neto et al., 2022). In recent years, pressurised liquid extraction has gained considerable interest as a promising and green extraction technology (Leyva-Jiménez et al., 2021). It is based on the application of high temperatures and pressures that produces high-quality extracts by modifying the dielectric constant of solvents used (Leyva-Jiménez et al., 2021). Li et al. developed a green and efficient extraction method using pressurised liquid extraction to separate antioxidants from grape skins. The skins were obtained from different grape varieties cultivated in the Jilin province (China). The developed method reduces run time and has higher extraction yields than those of conventional solvent extraction, it can also be utilized to extract phytochemicals from all grape species (Li et al., 2019). Supercritical fluid extraction has been receiving growing interest as a sustainable technology that uses supercritical fluid to obtain phytochemicals without the need of organic solvents (Leyva-Jiménez et al., 2020). This extraction is generally used to obtain purified phytochemicals from grape pomace, especially for thermosensitive compounds (Pazir et al., 2021; Sirohi et al., 2020). Despite its merits, it is less efficient when compared to pressurised liquid extraction (Otero-Pareja et al., 2015). Otero-Pareja et al. compared the efficiency of the two high-pressure extraction techniques, supercritical fluid extraction and pressurised liquid extraction, to obtain phytochemicals from grape pomace. The study underlines that pressurised liquid extraction using a hydro-alcoholic mixture as solvent, is more efficient than the pressurised liquid extraction using CO_2 and 20 % of ethanol, and it achieves a higher phenolic and anthocyanin extraction yield (Otero-Pareja et al., 2015).

Another key step to the actual manufacturing of health-promoting products from grape pomace is the development of adequate dosage forms to be used in food nutrients, supplements, nutraceuticals, cosmeceuticals and medical devices (Balea et al., 2018; Carra et al., 2022;

Kulichová et al., 2018). The suitable design of the formulations can facilitate the phytochemical administration and, above all, improve their bioavailability and efficacy. However, it is possible to use the extract of pomace as it is, as proved by Balea et al. that demonstrated the cardioprotective effect against myocardial ischemia by reducing oxidative stress (Balea et al., 2018). Unfortunately, most of the naturally occurring phenols are characterised by poor water solubility and high instability, which can result in a reduced efficacy in vivo. The formulation in products ad hoc tailored for the selected administration rout can permit to overcome these limitations. In recent decades, the delivery of phytochemicals from grape pomace in micro or nanocarriers has been proposed as an advanced and smart approach to improve their stability, bioavailability and biological activities at the target sites (Gaber Ahmed et al., 2020; Simonetti et al., 2019; Vorobyova et al., 2021). For example, Carra et al. efficiently developed microcapsules containing grape pomace skin extract to enhance the thermal stability of grape phytochemicals and obtained a biocompatible and biodegradable product, which has the potential for nutraceutical and cosmeceutical applications (Carra et al., 2022). Simonetti et al. developed innovative polymeric nanoparticles to improve the antifungal activity of grape pomace extract against *Candida albicans.* In particular, they obtained grape pomace extract-loaded nanoparticles with high entrapment efficiency (~90 %), able to reduce, at 16 μg/ml, biofilm formation and mature biofilm by 63 % and 50 %, respectively. While at 50 μg/ml the designed nanoparticles reduced biofilm by 37 %, proving to be a promising nano delivery system with antifungal properties (Simonetti et al., 2019). Grape pomace extract has also been successfully encapsulated into innovative chitosan and soy protein nanocapsules via nanoemulsification (Gaber Ahmed et al., 2020). The obtained grape pomace extract-loaded nanocapsules had high encapsulation efficiency, ~95 % for soy protein nanocapsules and carried high quantities of polyphenols as indicated by FTIR spectra. Both nanocapsules exerted a protective effect on the encapsulated polyphenols which were kinetically released from them, proving to be potentially used as food antioxidant materials (Gaber Ahmed et al., 2020).

Phospholipid vesicles ad hoc modified with specific ingredients seem to be the ideal carriers for the delivery of these bioactive molecules, as they are able to potentiate the efficacy of extracts and natural molecules locally (e.g., in skin and intestines) and systemically by improving their bioavailability (Casula et al., 2021; Catalán-Latorre et al., 2018; Manca et al., 2020; Manconi et al., 2016; Perra et al., 2021). Manconi et al. in their work performed an environmentally friendly extraction to obtain a grape pomace extract with high phenolic content and antioxidant activity. They used fresh Sardinian red grape pomaces, harvested in Oliena (Italy) during fall. The obtained extract was incorporated in ad hoc modified liposomes, obtaining polymer-associated liposomes with small sizes and high entrapment efficiency. The polymer-associated liposomes were more biocompatible and exerted a higher protective effect against oxidative stress in Caco-2 cells than the free extract, suggesting the potential application of the novel formulations in the nutraceutical field (Manconi et al., 2016). More recently, Perra et al. formulated innovative nanovesicles capable of both avoiding skin damages and promoting skincare. Conventional phospholipid vesicles were modified with glycerol or Montanov 82® or a combination of both, and were used as innovative carriers. The vesicles were characterised by high entrapment efficiency (~100 %), were highly biocompatible and capable of

Fig. 1. Schematic representation of the different /processes aimed at valorising grape pomace.

protecting skin cells against oxidative damage to a better extent than the free grape pomace skins extract, pointing out their potential application into cosmeceutical and pharmaceutical fields (Perra et al., 2021).

5. Conclusion

Considering the analysed studies and their promising results, it is possible to confirm that a transition of the wine-chain towards Circular Economy based on more sustainable practices, reduced environmental impacts and recovery of valuable resources is possible, Fig. 1 (Goyal et al., 2018).

Although many of the approaches to grape pomace management mentioned above are of considerable interest even taken individually, the qualitative and quantitative optimization of recovery and the desire to approximate the objective zero-waste require more articulated and integrated strategies. In the process chain approach, the phases of extraction of valuable compounds must be the first in the treatment chain to preserve their integrity and the possibility of an effective commercialization. Once the valuable compounds are extracted, other treatments aimed at the valorisation of the bulk organic matter follow. In this respect, the chain of processes that can be applied in sequence could start, for instance, from the recovery of polyphenols through green extraction, followed by more conventional treatments such as anaerobic biodegradation to produce biogas combined with composting of the exhausted biomasses. Combination of treatments such as the one just mentioned can give the management of agro-industrial waste matrices, those characteristics of profitability required by the principles of the circular economy. By way of example, in their work, Farru et al. developed a cascade biorefinery starting from polyphenols recovery, through an eco-friendly and economic solid–liquid extraction, followed by the valorisation of the exhausted biomasses by hydrothermal carbonization and biogas production. In particular, the authors found that the integration of processes can exert positive effects in terms of quality, as it has an improved biostability and reduced phytotoxicity. Moreover, the biogas production from the process waters, obtained during the exhausted grape pomaces hydrothermal carbonization, indicates that energetic valorisation through this method may be a feasible option (Farru et al., 2022). Jin et al. performed a comparative techno-economic analysis of three different treatment chains for grape pomace. The authors compared the combined recovery of seed oil, polyphenol and biochar with the combined recovering of seed oil and polyphenols and the recovery of seed oil alone. The most complex combination provided the best economic incomes in terms of net present value, internal rate of return and payback period of 111.7 million US-$, 34.3 %, and 2.5 years, respectively (Jin et al., 2021). As previously reported, in their recent study Almeida et al., also applied a multi-step process for the valorisation of grape pomace, starting from solid-liquid extraction and ending with pyrolysis. The extract obtained using ethanol as solvent had a total phenolic content of ~ 56 mg GAE/g of extract. By evaluating the biochemical methane potential before and after the extraction process, the authors concluded that the latter did not affect the methane potential, making grape pomace an interesting substrate for this multi-step approach (Almeida et al., 2022).

The full implementation of these combined approaches requires the improvement of the knowledge of individual processes, possibly through implementation on a pilot scale, and the in-depth study of aspects that have not yet been studied enough, such as the treatment of the winery waste of waste, i.e., the pomace subjected to distillation. The correct management of residues by turning them into resources is an essential element for increasing the economic competitiveness and resilience of the agro-industrial sector.

Ethics statements

Our research did not include any human subjects and animal experiments.

CRediT authorship contribution statement

Matteo Perra: Investigation, Formal analysis, Data curation, Writing – original draft. **Gianluigi Bacchetta:** Supervision, Project administration, Validation, Writing – review & editing. **Aldo Muntoni:** Methodology, Validation, Writing – review & editing. **Giorgia De Gioannis:** Methodology, Validation, Writing – review & editing. **Ines Castangia:** Investigation, Formal analysis, Data curation, Writing – review & editing. **Hiba N. Rajha:** Data curation, Writing – review & editing. **Maria Letizia Manca:** Investigation, Data curation, Writing – original draft. **Maria Manconi:** Supervision, Project administration, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The authors are unable or have chosen not to specify which data has been used.

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