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Improved Sustainability in Wine Industry Byproducts: A Scale-up and Economical Feasibility Study for High-Value Compounds Extraction Using Modified SC-CO$_2$

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ABSTRACT: The objective of the present work was to optimize the operating conditions (P, T cosolvent %) and to study the scale-up and the feasibility of the supercritical fluid extraction (SFE) process for polyphenols from grape pomace, the main solid byproduct of the wine industry. Pilot-scale equipment (1 L extraction vessel) was used to study the scale-up prediction for extraction vessels of 50, 100, 500, and 1000 L capacity. The adopted scale-up criteria consisted of maintaining and keeping constant the solvent mass-to-feed mass ratio and the bed geometry dimension. The results indicated an excellent predictive level obtained by Sovová's model and success of the adopted scale-up criteria. At industrial scale, yields were close to 2.3 g$_{GAE}$/100 g$_{DM}$, a value obtained using the pilot-scale equipment. High concentrations of high-added-value phenols such as *cis*-resveratrol glucoside, *cis*-coutaric acid, *trans-p*-coumaric acid, quercetin, and proanthocyanidins were found in the extract. An economic evaluation of the process indicated the feasibility of an industrial SFE plant with a capacity of 500 L for producing in 60 min an extract with an expected phenolics' concentration of approximately 133 g$_{GAE}$/kg $_{extract}$ at an estimated 67€ /kg$_{extract}$ cost of manufacturing. Notably, all values are better than those currently reported in the literature.
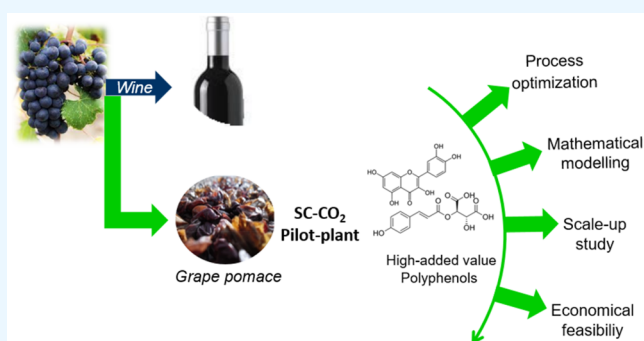
1. INTRODUCTION

Grape crops are one of the main extended agro-economic activities in the world with more than 40 million tons of wine grape produced every year. In 2021, global wine production reached 260 million hectoliters. Italy (50.2 million hectoliters, 19.3% of all wine produced in the world), France (37.6 million hectoliters, 14.5% of global production), and Spain (35.3 million hectoliters, 13.6% of wine produced in the world) represented 47% of world wine production.[1]

Grape pomace or marc is the main solid byproduct of the wine industry consisting of skin, seeds, and pulp residues that remain after the crushing, draining, and pressing stages of wine production.[1] About 8−9 million tons of grape pomace are produced in the world every year, representing approximately 20% (w/w; fresh weight) of the processed grapes' weight.[2] Approximately 70% of the phenolic content of grapes is preserved in the grape pomace after the winemaking process.[2,3] Given the increasing consumer demand for natural compounds, several studies have demonstrated that grape pomace polyphenols could be used whether in food, pharmaceutical, or cosmetic industries.[4−9] The recovery of these bioactive compounds from grape pomace enables both the obtainment of high-value-added biomolecules[10] and the simultaneous reduction of environmental impact due to high organic matter content and seasonal production.[11]

However, a crucial challenge in the valorization of grape pomace as an inexpensive source of polyphenols remains the extraction process, which should be efficient, swift, selective, high solute quality (no thermal degradation of labile compounds), and environmentally friendly.

Supercritical fluid extraction (SFE) is a green technology that enables us to overcome the many limitations of conventional extraction methods that are time-, energy-, and solvent-consuming procedures and increase both environmental and health and safety concerns.
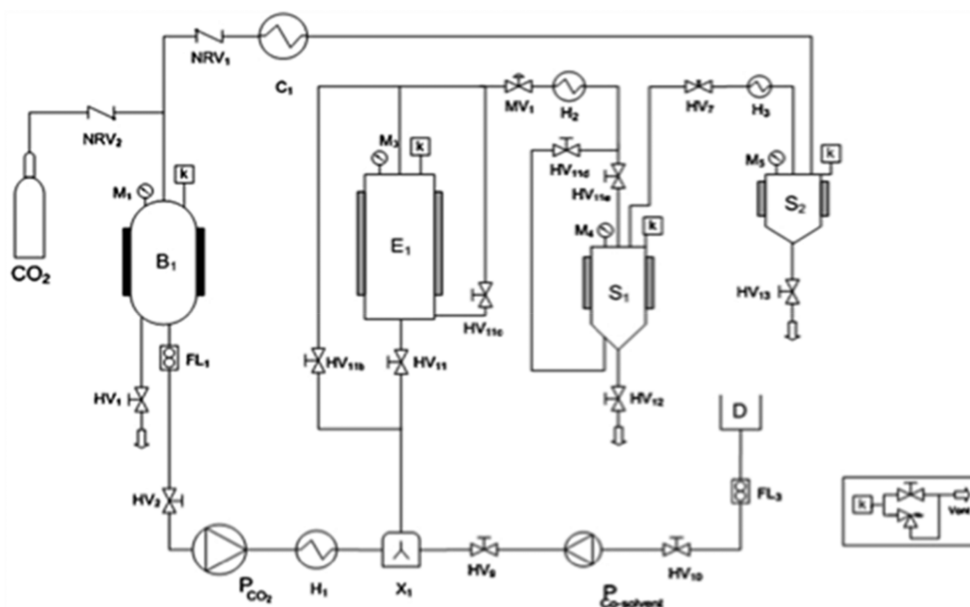
The most popular fluid for SFE is CO$_2$ because of its low critical properties, low toxicity, and chemical inertness. Although CO$_2$ is an excellent solvent for nonpolar compounds, a cosolvent at low concentration can be added to CO$_2$ to

Figure 1. SFE pilot plant flow sheet. (B$_1$) Storage tank; (E1) extraction vessel; (S$_1$,S$_2$) separators; (H#) heater exchangers; (C1) condenser; (HV#) Hand valves; (MV1) membrane valve; (NVR#) no return valves; (P) diaphragm pumps; (F$_1$) flowmeter; (M#) manometers; (k) safety devices; (FL$_1$) Coriolis mass flowmeter; (D) cosolvent storage tank; (X#) mixer.

modify the solvent selectivity toward polar or medium polar molecules.[12] The SFE extracts are of superior quality as compared with those obtained by conventional extraction methods.[13] SFE process advantages are low temperatures, efficiency in terms of increasing yields and lower extraction time, recyclability, tunable selectivity, reduced energy consumption, prevention of oxidation reactions, and operational flexibility.[12,14−17]

One of the most serious drawbacks of SFE is represented by the high cost of equipment compared with that required by conventional extraction processes. However, the most common SFE applications performed on a large industrial scale, such as decaffeination of tea and coffee, extraction of hop constituents, and separation of lecithin from oil, demonstrate that the supercritical process can be economically viable.[18,19]

Among the green or environmental friendly technologies applied for the extraction of bioactive compounds from winery wastes and byproducts,[20] several works focused on supercritical fluid extraction of polyphenols from grape pomace.[5,21−30] However, to successfully move production from SFE laboratory/pilot scale to SFE industrial scale, each raw material needs the optimization of operational conditions and scale-up study. So far, to the best of our knowledge, there has been no work in the literature regarding SFE scale-up of polyphenols from grape pomace using supercritical carbon dioxide with an ethanol−water mixture as a cosolvent.

Therefore, the aim of the present work is to study SFE of polyphenols from grape pomace, evaluating operational parameters on kinetic and modeling, in order to propose an adequate scale-up for this process and to estimate economic feasibility.

2. MATERIAL AND METHODS

2.1. Grape Pomace Characterization and Preparation.
Grape pomace of different white grape varieties (*Vitis vinifera* L.) were collected after winemaking during September− October, 2020, in the Friuli Venezia-Giulia region (Italy). They were dried in an air circulation oven at 323.15 K for 24 h

and stored in dark conditions at 277.15 K until they were used. Prior to supercritical fluid extraction, the grape pomace was milled by a domestic grinder, and the particles were classified according to particle size using a standard sifter with several mesh sizes from 0.5 to 2.0 mm. The mean particle diameter was determined according to Sauter's equation.[31] Moisture content was determined by oven drying to a constant weight at 378.15 K and expressed as a percentage.[32] The true density (ρ_s) of raw material was determined by helium gas pycnometry (Pycnomatic ATC, Thermo Electron Corporation, Milan, Italy). The apparent density (ρ_a) was calculated by dividing the feed mass by the vessel volume. The porosity of the bed (ε) was calculated as $(1 - \rho_a/\rho_s)$.

2.2. Chemicals.
Carbon dioxide (mass fraction purity 0.999 in the liquid phase) was supplied by Sapio S.r.l. (Udine, Italy). Sep-Pak Plus tC18 cartridge WAT 036810 and WAT036800 were purchased from Waters (Milan, Italy). The Folin−Ciocalteau reagent, 2,2-difenil-1-picrylhydrazyl, reagents of analytical grade or higher available purity, (−)-epicatechin, (+)-catechin, gallic acid, 3,4-dihydroxyben-zoic acid (protocatechuic acid), 4-hydroxy-3,5-dimethoxyben-zoic acid (syringic acid), 3,4-dihydroxycinnamic acid (caffeic acid), 4-hydroxy-3-methoxycinnamic acid (ferulic acid), 4-hydroxycinnamicacid (*p*-coumaric acid), and *trans*-resveratrol were purchased from Sigma-Aldrich (Milan, Italy).

The other phenolic compounds were quercetin, isoquercitrin (quercetin-3-*O*-glucoside), kaempferol, kaempferol-3-*O*-gluco-side, rhamnetin, isorhamnetin, isorhamnetin-3-*O*-glucoside, rutin (quercetin-3-*O*-rutinoside), and myricetin and were supplied by Extrasynthese (Lyon, France).

2.3. Total Phenolic Content.
Purification by C18 cartridge was carried out for the samples to eliminate the interference of sugars, nonvolatile acids, and amino acids in determination of total phenols. The total phenolic content (TPC) values of the grape pomace extracts were measured using the Folin−Ciocalteau reagent, according to Yu et al.[33] All analyses were performed in triplicate. Results were expressed as

milligrams of equivalent gallic acid per 100 g of dried matter (mg_{GAE} /100 g_{DM}).

2.4. HPLC-DAD-MS Analysis of Polyphenols. The analysis was carried out in a Dionex Ultimate 3000 UPLC system (Thermo Scientific, San Jose, CA, U.S.A.) equipped with a diode array detector (DAD, 280 and 370 nm) coupled to an electrospray ionization mass spectrometer (ESI-MS) detector. The system and analytical procedures were previously described by Lago-Vanzela et al.[34] Phenolic compounds were identified based on their chromatographic behavior, UV−vis, and mass spectra by comparing the collected data with standard compounds (when available) and data reported in the literature. A calibration curve based on the UV−vis signal for each available phenolic standard was constructed for quantitative analysis. The results were expressed in μg/100 g_{DM}.

2.5. Fractionation of Proanthocyanidins. Proanthocyanidins present in the extract were fractionated on two C18Sep-Pak cartridges assembled (WAT 36800/WAT36810, top and bottom, respectively) into three fractions by different organic solvents, according to Sun et al.[35] Ethyl acetate was used for fraction FI + FII, containing monomeric and oligomeric flavan-3-ols, while methanol was used for fraction FIII, which contains polymeric proanthocyanidins. Results were expressed as $mg_{catechin}$/100 g_{DM}

2.6. Antioxidant Activity. The antioxidant activity of proanthocyanidins fractions was evaluated by the total free radical scavenger capacity (RSC) following the methodology describedby Espin et al.[36] using a UV−vis spectrophotometer (Shimadzu UV 1650, Italy). The RSC is the difference of the concentration of DPPH free radical ($C_{DPPH^{\bullet}i}$) previously dissolved in methanol, after 60 min of reaction with the samples ($C_{DPPH^{\bullet}f}$). The antioxidant activity of the samples was expressed as $mg_{\alpha\text{-tocopherol}}$/100 g_{DM}. Analyses were performed in triplicate.

2.7. Pilot Plant Supercritical Fluid Extraction. A SFE pilot-plant (SCF100 serie 3 PLC-GR-DLMP, Separeco S.r.l, Pinerolo, Italy) equipped with a 1 L extraction vessel, two 0.3 L separators in series, and a storage tank for CO_2 was used (Figure 1).

Prior to extracting polyphenols, the removal of nonpolar compounds from grape pomace was carried out by SC-CO_2, according to a previous methodology.[27,28]

The cylindrical extractor basket (H = 0.339 m; D = 0.062 m) was filled with 0.1 kg of ground defatted grape pomace distributed on glass beads (mean diameter of 0.005 m). Supercritical CO_2 extractions of grape pomace were carried out at a fixed particle size (0.57 mm), CO_2 flow rate (6.0 kg/h), and extraction time (480 min). Different pressures (8, 10, 20 MPa), temperatures (313.15, 323.15, 333.15 K), and percentages (5.0, 7.0, 10.0% w/w) of ethanol−water mixtures at 57% (v/v) were used. Aliquots of grape extract were collected during extractions in a volumetric flask at intervals of 30 min, to assess several data points for the overall extraction curves (OECs). After removal of the cosolvent with a rotary evaporator (Buchi, B465, Switzerland) at 318.15 K, the extracts were weighed and analyzed. All experiments were carried out in triplicate.

2.8. Mathematical Modeling. The broken and intact cells model (BIC), proposed by Sovová et al.[37] and Sovová[38−40], was used for the SFE process from grape pomace. Sovová's model divides the solute-extractible content into accessible solutes (from the broken solid particles) and hardly accessible

solutes (located inside the unruptured intact solid particle structure). In this model, the overall extraction curve (OEC) is divided into three periods: (1) the constant extraction rate (CER) period, where easily accessible solutes are extracted mainly by convection at a constant rate; (2) the falling extraction rate (FER) period, where the diffusion mechanism starts combined with convection; (3) and the diffusion controlled (DC) period, where the mass transfer occurs mainly by slow diffusion in the bed and inside the solid substrate particles.

The equations of BIC model to calculate the cumulative mass of extract (e) as a function of time (t) in the different periods can be summarized as follow:

$$\text{CER period: } e = q y_s \left[1 - \exp\left(-\frac{1}{\theta_e} \right) \right] \quad \text{for } 0 \leq q < q_m \tag{1}$$

$$\text{FER period: } e = q y_s - r x_i \theta_e \exp\left(\frac{\beta}{\theta_e} \ln\left\{ 1 + \frac{1}{r} \left[\exp\left(\frac{q - q_m}{\theta_i \gamma} \right) - 1 \right] \right\} - \frac{1}{\theta_e} \right) \quad \text{for } q_m \leq q < q_n \tag{2}$$

$$\text{DC period: } e = x_u \left[1 - \beta \ln\left\{ 1 + (1 - r) \left[\exp\left(\frac{1}{\beta} \right) - 1 \right] \exp\left(\frac{q - q_m}{\gamma \theta_i} \right) \right\} \right] \quad \text{for } q \geq q_n \tag{3}$$

where:

$$\theta_i = \frac{(1 - \varepsilon)\dot{Q}}{\gamma k_s a_s N_m} \tag{4}$$

$$\theta_e = \frac{\varepsilon \dot{Q}}{\gamma k_f a_0 N_m} \tag{5}$$

$$q_m = \frac{r x_u \theta_e}{y_s} \tag{6}$$

$$q_n = q_m + \gamma \theta_i \ln\left[1 - r + r \exp\left(\frac{1}{\beta} \right) \right] \tag{7}$$

$$\beta = \frac{\gamma \theta_i y_s}{x_u} \tag{8}$$

The adjustable parameters θ_e, θ_i, r, k_s, and k_f can be calculated by minimizing the sum of least-squares between the experimental and calculated values of e.

The application of BIC model needs preliminary determination of several parameters, such as experimental extraction yield (e_{exp}) and the relative amount of passed solvent (q):

$$e_{exp} = \frac{E}{N_m} \tag{9}$$

$$q = \frac{M}{N_m} \tag{10}$$

where E is the amount of extract (kg), M is the mass of passed solvent (kg).

The mass of insoluble solid, N_m is calculated as

$$N_m = (1 - c_u)N \tag{11}$$

where c_u is the solute content in the untreated solid, and N is the solid loaded in the extractor. The value of c_u is equal to the asymptotic extraction yield at infinite time. It is calculated by a preliminary fitting of the model equations on experimental data obtained at different pressure and temperature conditions.

The solute weight fraction in the untreated solid (x_u) can be calculated as follows:

$$x_u = \frac{c_u}{1 - c_u} \tag{12}$$

The bed characteristics, porosity (ε), specific surface area per unit volume of extraction bed (a_0), and solvent-to-matrix ratio in the bed (γ) can be calculated with the following equations:

$$\varepsilon = 1 - \frac{\rho_a}{\rho_s} \tag{13}$$

$$a_0 = 6\frac{1 - \varepsilon}{d} \tag{14}$$

$$\gamma = \frac{\rho_f \varepsilon}{\rho_s(1 - \varepsilon)} \tag{15}$$

The values of models parameters and graph plots were calculated by Matlab R2016b (MathWorks, Inc., U.S.A.). The agreement between the experimental and model values were assessed by the absolute average relative deviation (AARD), as reported in following equation:

$$\text{AARD } (\%) = \frac{100}{n} \sum_{p=1}^{n} \frac{X_{calc,p} - X_{exp,p}}{X_{exp,p}} \tag{16}$$

where n is the number of experimental points composing a kinetic curve $X_{exp,p}$ is the experimental value at point p, and $X_{calc,p}$ is the model value at point p.

2.9. Scale-up Method. The scale-up criteria adopted were to keep constant the ratio between solvent flow rate and substrate feed (S/F) and the bed geometry dimension.[41−47] The last one was achieved by keeping constant the ratio between the height (H) and diameter (D) of the cylindrical extractor vessel with increasing capacity. Other parameters such as d_p, moisture content, true and apparent density of raw material were considered the same of the pilot-scale.

The scale-up prediction was investigated for extraction vessels of 50, 100, 500, and 1000 L capacity. Reynolds number was calculated using eq 17:

$$Re = \frac{\rho_f U d_p}{\mu_f} \tag{17}$$

where U is the CO_2 velocity, d_p is the particle diameter, ρ_f is the CO_2 density, and μ_f is CO_2 viscosity.

2.10. Economic Evaluation. Operational data were based on the pilot-scale experiment and the scale-up procedure. The costs of four industrial SFE units as a function of the capacity of extraction vessels (50, 100, 500, and 1000 L) were estimated using eq 18 reported by Rocha-Uribe et al.:[48]

$$C = \left(\frac{I_2}{I_{2019}}\right)[31.901 \times V^{0.6909}] \tag{18}$$

where C is the cost of the equipment in €, V its capacity in liters, I_{2019} the cost of the equipment in the year 2019 with a chemical engineering plant cost index (CEPCI) value of 521.9 and I_2 refers to the CEPCI for the year 2019 (576.1).

The economic analysis was based on the methodology of Turton et al.[49] and Rosa and Meireles.[50] It sets the cost of manufacturing (COM) as a function of investment cost (FI) (SFE units), labor cost (COL) related to operators (number and wage) of the extraction unit, utility cost (CUT) which considers the energy used in the solvent cycle for steam generation, refrigeration and electricity requirements, waste treatment cost (CWT), and raw material cost (CRM), using the following relation:

$$\text{COM} = 0.304\text{FI} + 2.73\text{COL} + 1.23(\text{CUT} + \text{CWT} + \text{CRM}) \tag{19}$$

3. RESULTS AND DISCUSSION

Physical and chemical characterization of grape pomace are reported in Table 1.

Table 1. Physical and Chemical Characterization of Grape Pomace

grape pomace	value
moisture (%)	7.66 ± 0.32
mean particle diameter (d_p) (mm)	0.570 ± 0.008
true density (kg m^{-3})	1055 ± 174
apparent density (kg m^{-3})	98.42 ± 0.36
porosity (ε)	0.905 ± 0.015

The effects of pressure, temperature, and cosolvent percentage on the extraction yield and total polyphenol contents (TPC) were examined using the SFE pilot scale plant previously described. The performed experiments and the respective operating conditions are summarized in Table 2, where the extraction yields and total polyphenol contents are reported.

3.1. Modeling the OECs. In Figure 2, the experimental extraction curves (OECs) of the seven assays (Table 2) are compared with the predicted profiles from the model. As shown in Figure 2, the OECs present three periods: the first part represents a linear period, characterized by extraction at a constant rate and corresponding to the extracted solute solubility; the second part starts where the extraction rate decreases with time, since diffusion phenomena appear; and the third one is where diffusion is dominant.

The modeling results are reported in Table 3, where it can be noticed that the absolute average relative deviations (AARD) were in the range of 1.01−5.09%. This indicates that the BIC model is suitable for modeling SFE of grape pomace. It was assumed that cosolvent behaves as an incompressible liquid as suggested by Macías-Sánchez et al.[51] whereby the density of CO_2 plus cosolvent at 5, 7.5 and 10% (w/w) (Table 3) was calculated on the basis of the molar flux composition of each system. The density of ethanol and water at 313.15, 323.15, and 332.15 K for the different pressures was considered the same as that at atmospheric pressure obtained from the literature.[52,53]

Table 2. Operating Conditions, Global Yields, and Total Polyphenol Contents of the Performed Experiments

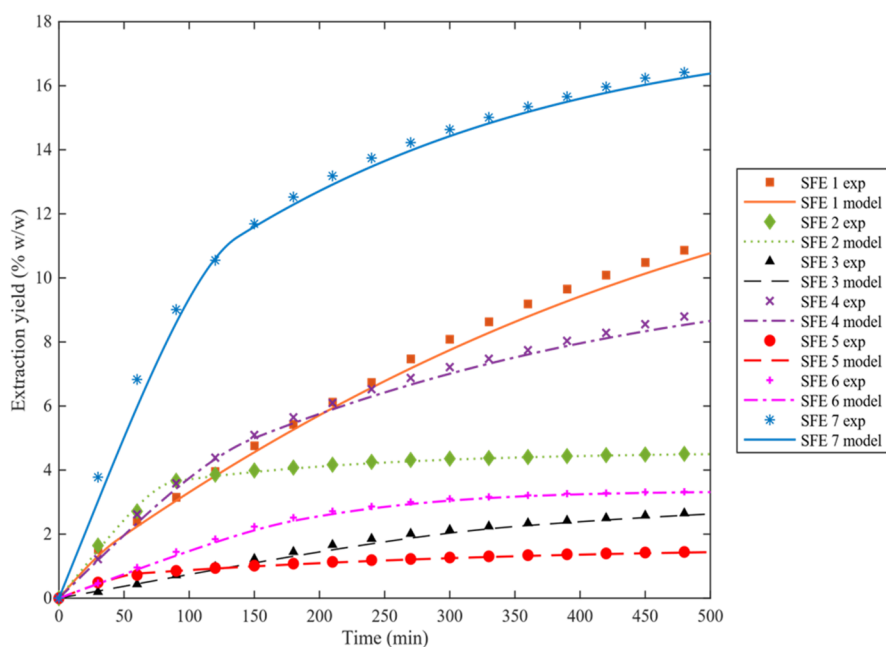| run	pressure	temperature	CO_2 flow rate	cosolvent	global yield	total phenols
N°	(MPa)	(K)	(kg/h)	(% w/w)	(% w/w)	(mg $_{GAE}$/100 g $_{DM}$)
1	8	313.15	6	7.5	10.60 ± 0.24	1488 ± 3
2	10	313.15	6	7.5	4.53 ± 0.12	619 ± 5
3	20	313.15	6	7.5	2.67 ± 0.05	365 ± 4
4	8	323.15	6	7.5	8.80 ± 0.18	1203 ± 55
5	8	333.15	6	7.5	1.60 ± 0.03	218 ± 1
6	8	313.15	6	5.0	3.32 ± 0.10	455 ± 1
7	8	313.15	6	10.0	17.72 ± 0.14	2245 ± 73

Figure 2. Comparison between experimental and predicted extraction curves (OECs)

Table 3. Kinetic Parameters of the Sovová[40] Model Applied to SFE Experimental Overall Extraction Curves from Grape Pomace

run	pressure	temperature	CO_2 flow rate	cosolvent	ρ_f	$k_f a_0$ ($\times 10^{-2}$)	$k_s a_s$ ($\times 10^{-5}$)	y_s ($\times 10^{-4}$)	θ_e	θ_i	t_{CER}	t_{FER}	AARD
N°	(MPa)	(K)	(kg·h^{-1})	(% w/w)	g mL^{-1}	(s^{-1})	(s^{-1})	(g kg$_{CO_2}$$^{-1}$)	(−)	(−)	(min)	(min)	(%)
1	8	313.15	6	7.5	0.356	2.474	0.408	4.699	0.2865	145.03	6.79	45.29	3.057
2	10	313.15	6	7.5	0.664	1.043	0.843	4.108	0.2816	29.11	18.73	89.54	2.879
3	20	313.15	6	7.5	0.842	0.794	0.602	0.758	0.2771	30.52	57.17	348.92	5.088
4	8	323.15	6	7.5	0.304	2.807	0.487	4.058	0.3022	145.01	27.78	149.09	3.590
5	8	333.15	6	7.5	0.279	3.528	0.528	1.674	0.2482	143.20	11.21	61.48	1.798
6	8	313.15	6	5.0	0.331	2.792	1.488	1.534	0.2150	33.68	21.59	182.08	1.014
7	8	313.15	6	10.0	0.381	3.499	0.929	22.013	0.2152	67.63	8.26	52.19	1.057

3.1.1. Effect of Pressure. Increase in pressure from 8 to 20 MPa at 313.15 K and 7.5% (w/w) cosolvent (Run 1, 2 and 3) leads to decrease the extraction yield from 10.60 to 2.67% (w/w) and total polyphenol content from 1488 to 365 mg$_{GAE}$/100 g$_{DM}$ (Table 2).

As can be observed in Table 3, at higher extraction pressures the volumetric solvent phase mass transfer coefficient $k_f a_0$ decreases from 2.474 ·10^{-2} to 0.794 · 10^{-2} s^{-1}, and the volumetric solid phase mass transfer coefficient $k_s a_s$ shows a tendency to increase from 0.408 · 10^{-5} to 0.602· 10^{-5} s^{-1}. It is interesting to note that $k_f a_0$ values are approximately 4 orders of magnitude greater than the $k_s a_s$ ones. This means that convection is more representative than the diffusional

mechanism. These results are consistent with those reported for oil extraction of various vegetable matters.[31,47,54,55]

Although the increase in pressure increases the solvent power through a density increase from 0.336 to 0.842 g mL^{-1}, the solute solubility decreases from 4.699 × 10^{-4} to 0.758 × 10^{-4} g kg$_{CO_2}$$^{-1}$. As suggested by Farias-Campomanes et al.,[25] the low mass-transfer observed at the high pressure could be partially due to the low dispersion coefficient of the modified SC-CO$_2$, which accounts for the axial and radial diffusion mechanisms, the characteristics of the raw material which is not homogeneous (skins and seeds), and the high porosity of the extraction bed. The $k_s a_s$ related to the diffusion of the less
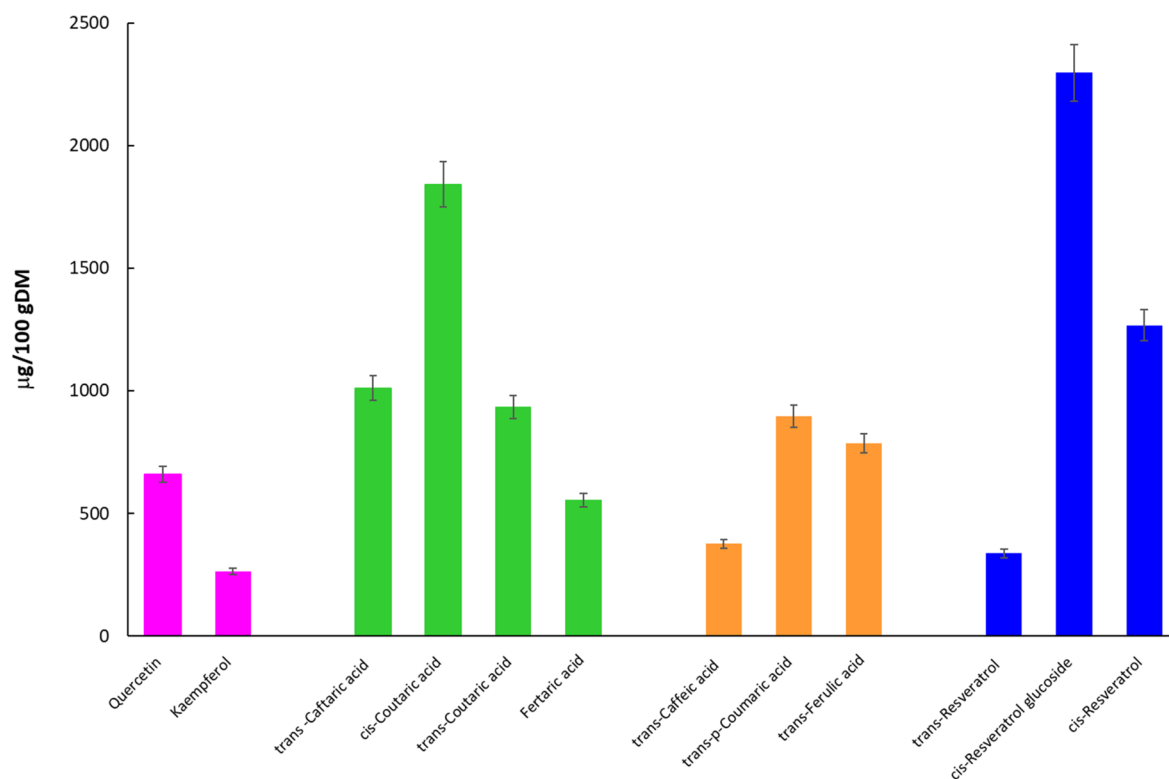
Figure 3. Flavonols, hydroxycinnamoyl tartaric acids, hydroxycinnamic acids, and stilbenes identified and quantified in the grape pomace extract obtained at 8 MPa/313.15 K/cosolvent 10% w/w/240 min.

accessible solute increases due to the damage/destruction of the cell wall under high pressure.[56]

With regard to the extraction periods, the results in Table 3 show that Sovová model predicted a large decrease of t_{CER} and t_{FER} as pressure decrease. Therefore, the lower the pressure, the shorter the extraction time, for both the compounds present on the surface of the matrix and the less accessible ones. Similar pressure effects were observed by Jia et al.,[57] Rezaei et al.,[58] Döker et al.,[59] Bensebia et al.,[60] García-Risco et al.,[61] Ciftci et al.,[62] and Wagner et al.[63]

3.1.2. Effect of Temperature. Increase in temperature from 313.15 to 333.15 K at 8 MPa and 7.5% (w/w) cosolvent (Run 1, 4 and 5) decreases the extraction yield from 10.60 to 1.60% w/w and TPC from 1488 to 218 $mg_{GAE}/100\ g_{DM}$ (Table 2). Similar results related to extraction temperature effect on phenolic compounds were reported by Zulkafli et al.[64] for phenolic compounds extracted from bamboo leaves.

As can be seen in Table 3, $k_f a_0$ increases from 2.47×10^{-2} to $3.53 \times 10^{-2}\ s^{-1}$, and $k_s a_s$ increases from 0.408×10^{-5} to $0.508 \times 10^{-5}\ s^{-1}$, whereby both external mass transfer resistance (θ_e) and internal mass transfer resistance (θ_i) decrease. In supercritical fluids, a temperature increase can have two opposite effects: it reduces the solvent power through density reduction, and conversely, it enhances solubility by increasing the vapor pressure of the solutes.[12] However, at relatively low pressure, a decrease of density and solvent power with increasing temperature prevails, as shown by the decrease of y_s values from 4.699×10^{-4} to $1.674 \times 10^{-4}\ g\ kg_{CO_2}^{-1}$ at 313.15 and 333.15 K, respectively. This leads to the observed decrease of the extraction yield due to the decrease in solvent driving force. With respect to extraction periods, the results in Table 3 show that t_{CER} and t_{FER} are extended as temperature increases, and this is due to the slow kinetics.

3.1.3. Effect of Cosolvent. The extraction curves obtained increasing the percentage of cosolvent from 5 to 10% (w/w) (Run 6, 1, and 7) are shown in Figure 2. As can be observed, the cosolvent percentage enhancement leads to an increase in the slope of the linear part of the curve, which means higher solute solubility. The increase of the cosolvent percentage from 5 to 10% (w/w) at 8 MPa and 313.15 K (Run 6, 1 and 7) increased both extraction yield from 3.32 to 17.77% (w/w) and TPC content from 455 to 2245 $mg_{GAE}/100\ g_{DM}$ (Table 2). This is not unexpected since as reported by Ting et al.,[65,66] Kopcak et al.[67] and Zhang et al.,[68] the addition of polar cosolvent to supercritical fluids may increase the following: (i) the mixture density leading to the solute solubility enhancement; (ii) the supercritical mixture critical point; (iii) the difference between the local density (around solute molecule) and the bulk density; (iv) the solubility due to specific interactions between the solute and cosolvent molecules.

As can be seen in Table 3, with a cosolvent percentage increase from 5 to 10% (w/w), the $k_f a_0$ and $k_s a_s$ values increased due to decrease of mass transfer resistance both in SC-CO$_2$ and grape pomace phases, which determines the increase in driving force and convention. It is worth pointing out the extremely high increase of y_s values from 1.334×10^{-4} to $22.013 \times 10^{-4}\ g\ kg_{CO_2}^{-1}$ due to cosolvent increase from 5 to 10% w/w, respectively. Hence, these results clearly indicate that the cosolvent increase considerably promotes the rate of removal of solutes from both the external and the interior of the biomass particles. As far as extraction periods, the Sovová model predicts a large decrease of t_{CER} as the cosolvent percentage increases according to the $k_f a_0$ values. Therefore, the higher the cosolvent percentage, the faster the extraction rate. Similar cosolvent effects were observed by Castro-Vargas et al.,[69] Akay et al.,[70] Andrade et al.,[71] and Zulkafli et al.[64]
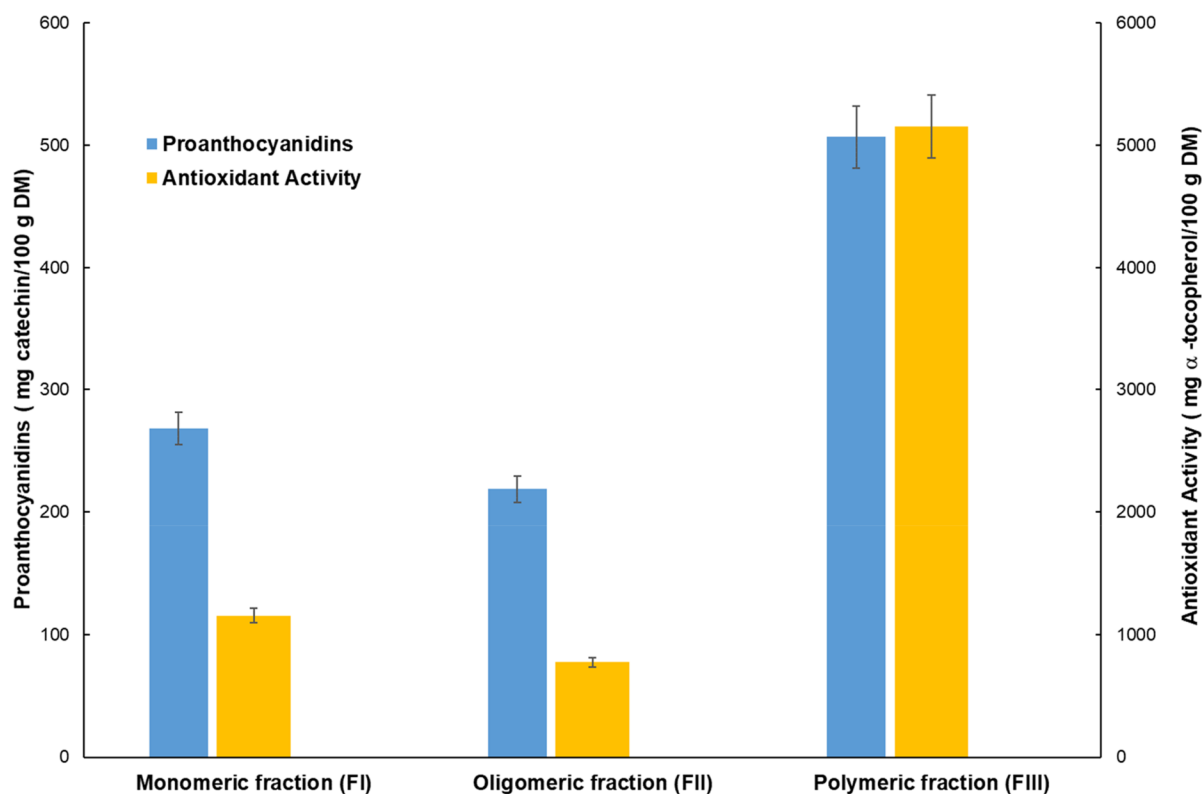
Figure 4. Proanthocyanidins' fractions and antioxidant activity of the grape pomace extract obtained at 8 MPa/313.15 K/cosolvent 10% w/w/240 min.
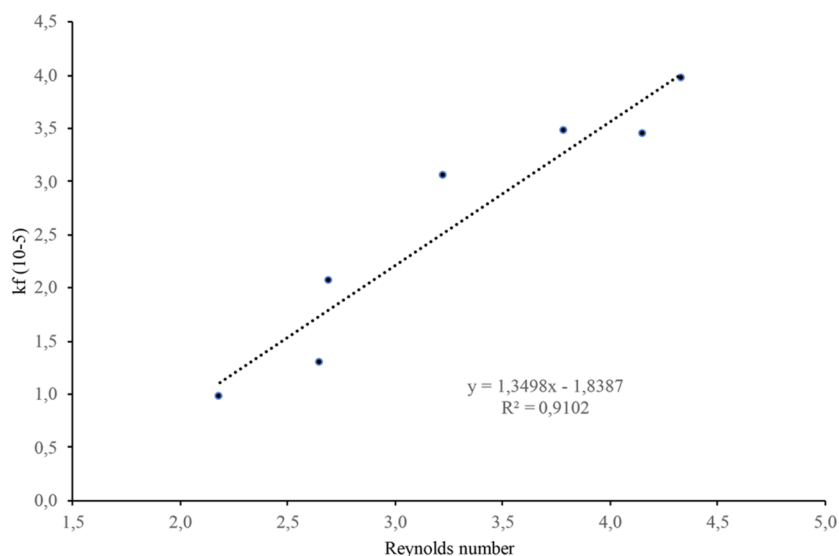
Figure 5. Correlation between the volumetric mass transfer coefficients ($k_f a_0$) and Reynolds number (Re).

Globally, the commented results show that 8 MPa, 313.15 K, and 10% (w/w) cosolvent are the best set experimetal conditions to obtain the highest yield and polyphenol content. It was considered economically advantageous to stop the SFE process at 240 min, which corresponds to 84% of the total extraction yield. Both yield and total phenol content found in this work are higher than those reported in the literature.[5,21,23,25,72−75]

3.2. Phenolic Composition of the Extract. HPLC analysis of the extract obtained at 8 MPa/313.15 K/10% (w/w) cosolvent/240 min extraction time was performed.

Flavonols, hydroxycinnamoyl tartaric acids, hydroxycinnamic acids, and stilbenes were identified and quantified as depicted in Figure 3. The major compounds detected were *cis*-resveratrol glucoside (2296.88 ± 0.02 μg/100 g_{DM}), *cis*-coutaric acid (1841.16 ± 0.02 μg/100 g_{DM}), *trans-p*-coumaric acid (896.70 ± 0.05 μg/100g_{DM}), and quercetin (658.69 ± 0.01 μg/100 g_{DM}). Extensive studies have focused on these bioactive compounds due to their health benefits and disease prevention effects.[76−78]

Figure 4 shows the results of proanthocyanidins' fractionation and antioxidant activity evaluation performed on the grape

Table 4. Scale-up Predicted Parameters for Extraction Vessel of 50, 100, 500, and 1000 L Capacity

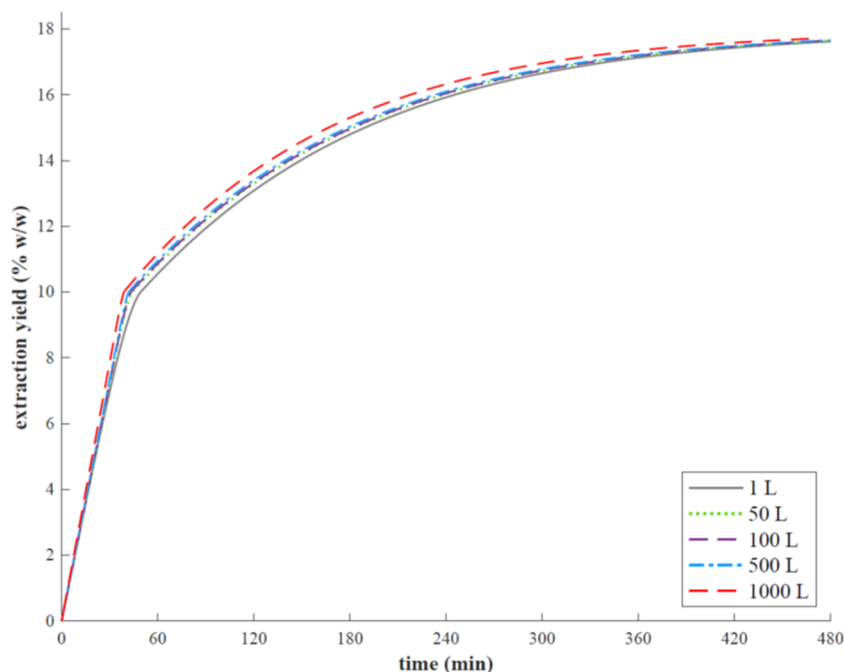| extraction vessel	H/D	H	D	S/F	F	S	Re	$k_f \, 10^{-5}$
(L)	(−)	(m)	(m)	(−)	(kg)	(kg/s)	(−)	(s^{-1})
50	5.47	1.249	0.228	66	5	0.0917	9.941	11.580
100	5.47	1.573	0.288	66	10	0.1833	12.525	15.068
500	5.47	2.691	0.492	66	50	0.9167	21.418	27.071
1000	5.47	3.390	0.620	66	100	1.8333	26.985	34.85

Figure 6. Predicted OECs for SFE scale-up from grape pomace.

pomace extract under the operating conditions previously reported. The amount of total proanthocyanidins extracted from grape marc was 0.994 $g_{catechin}$ /100 g_{DM}, which in comparison with 3.5 g/100 g of grape seed reported by Gu et al.[79] can be considered a good recovery taking into account that raw material consists of skin, seeds, and pulp residues. Polymeric proanthocyanidins were the predominant form (506 ± 10.8 $mg_{catechin}$/100 g_{DM}) followed by monomeric (268 ± 4.5 $mg_{catechin}$/100 g_{DM}) and oligomeric (218 ± 5.2 $mg_{catechin}$/100 g_{DM}) ones. The highest antioxidant activity was evaluated for the polymeric fraction (5154 ± 18.5 $mg_{\alpha\text{-tochoferol}}$/100 g_{DM}) due to the high degree of polyphenol polymerization.[80]

The results show that grape pomace is a potential source for proanthocyanidins. Recently, Unusan[81] reported that proanthocyanidins appear to exert pharmacological effects, including antioxidant, antimicrobial, antiobesity, antidiabetic, antineurodegenerative, antiosteoarthritis, anticancer, and cardio- and eye-protective properties. These potential health benefits of proanthocyanidins make them a promising source as nutraceuticals.

3.3. Scale-up Study. As reported in section 2.9, the scale-up criteria adopted were to keep constant both the S/F and the bed geometry dimension. The experimental conditions selected to perform the scale-up were 8 MPa, 313.15 K, 6 kg/h CO_2 flow rate, and 10% (w/w) cosolvent. The scale-up prediction was investigated for extraction vessels of 50, 100, 500, and 1000 L capacity,

The volumetric mass transfer coefficients ($k_f a_0$) determined through modeling of the experimental OACs data were correlated as a function of the dimensionless Reynolds number (Re).[46,82,83]

Figure 5 shows the good correlation ($R^2 = 0.9102$) obtained. This result allowed to predict the mass transfer coefficients as a function of Re for scaling up.

In Table 4 are reported the grape pomace mass (F) to fill the extraction vessels calculated using the apparent density of the raw material determined at the pilot scale, the calculated values of Re and k_f for extraction vessel of 50, 100, 500, and 1000 L capacity. The constant ratio of H/D and the values of Re allow us to suppose solvent flow pattern in the extraction vessels as plug flow.

Figure 6 shows the predicted OECs by Sovová model at 50, 100, 500, and 1000 L and the OAC obtained from grape pomace at SFE pilot-scale (1 L). As can be seen, the OECs at industrial scale presented similar shapes, and global yields are close to each other, around 17% (w/w) at 480 min extraction time. These results confirm the excellent predictive level of the BIC model and the success of the scale-up criteria used. Similar findings are in agreement with other scale-up studies conducted by Prado et al.[42,43]

3.4. Cost Estimation. In order to perform an economic evaluation of the process, four scales of SFE units, all with the same design but with extractor volumes of 50, 100, 500, and 1000 L were evaluated. The SFE extracting conditions were 8 MPa, 313.15 K, S/F ratio of 66, 10% w/w cosolvent, 240 min

extraction time. The list of economic parameters used for cost of manufacturing estimation are presented in Table 5.

Table 5. Economic Parameters Needed for COM Estimation

FI	2 extraction vessels of 50 L[a]	620.000 €
	2 extraction vessels of 100 L[a]	1.000.000 €
	2 extraction vessels of 500 L[a]	3.000.000 €
	2 extraction vessels of 1000 L[a]	5.000.000 €
	depreciation rate[a]	10% year
	annual mantenance rate[a]	6% year
COL	labor cost	18 €/h
	2 extraction vessels of 50 L	2 operators
	2 extraction vessels of 100 L	2 operators
	2 extraction vessels of 500 L	3 operators
	2 extraction vessels of 1000 L	3 operators
CRM	grape marc	0.025 €/kg
CWM	cost of waste treatment	0.015 €/kg
CUT	carbon dioxide[b]	2.50 €/kg
	ethanol[c]	4.50 €/L
	electricity[d]	0.15 €/kWh
	water	1.44 €/m³

[a]Calculated by the equation proposed by Rocha-Uribe et al;[48] [b]Sapio S.r.l.. [c]Sigma-Aldrich. [d]Sorgenia SPA.

Capital investment or equipment costs (FI) were estimated using eq 18. The SFE unit was considered as working 24 h per day with three daily shifts, for 330 days per year, representing a total of 7920 h per year. The number of operators per shift varies according to the capacity of the plant, at a cost of € 18.00/h. The raw material masses to fill the extraction vessels were calculated from the apparent density of the raw material determined at the pilot scale. The cost of the raw material (CRM) was calculated as the cost of drying and milling, for a total of € 0.025/kg. Also, a loss of 2% of CO_2 in the raw material cost according to Leal et al.[84] was considered. The

cost of the waste treatment (CWT) was considered as € 0.015/kg. In Figure 7, the COM was calculated for SFE units (2 × 50/100/500/1000L) as a function of the extraction time. It can be observed that the COM values exhibited a similar trend in all cases, namely they increased with the extraction time and decreased with plant scale increase. The lowest COMs corresponding to € 67/kg extract and € 45/kg extract were obtained at 60 min for 2 × 500 L unit and 2 × 1000 L unit, respectively.

Farias-Campomanes et al.[25] reported the lowest COM corresponding to US$ 133.16/kg_extract for a 2 × 500 L unit, working at 20 MPa, 313.15 K, $S\,(CO_2)/F$ ratio of 47, 10% (w/w) cosolvent (96% ethanol), 180 min extraction time, and achieving 5.5% w/w as grape pomace global yield with an as-expected 23 g/kg_extract phenolics' concentration. Under our experimental conditions, at 60 min extraction time, the global yield was 7.0% w/w and an expected 133 g_GAE/kg_extract phenolics' concentration. Therefore, the improvement of the SFE operating conditions led to COM reduction.

The COMs of conventional methods in industrial units for the grape pomace extracts are higher than € 45–67/kg_extract[25,75]

Figure 8 depicts the contribution of each component of COM for grape pomace extracts obtained by SFE units with different extractor capacities. The labor cost (COL) and the fixed cost of investment (FI) comprise the largest portions in the distribution of costs within the COM, followed by the CUT. The labor costs associated with the number of operators required to operate the larger-capacity extractors demonstrate an economy of scale, resulting in a decrease of the influence of the COL (from 71 to 32%) on the COM as the production rate increases. Instead, the FCI increases from 15 to 38% as SFE plant capacity increases, and the CUT increases from 13 to 38%. The other costs, CRM and CWT, had a much smaller influence on the COM, accounting together for less than or
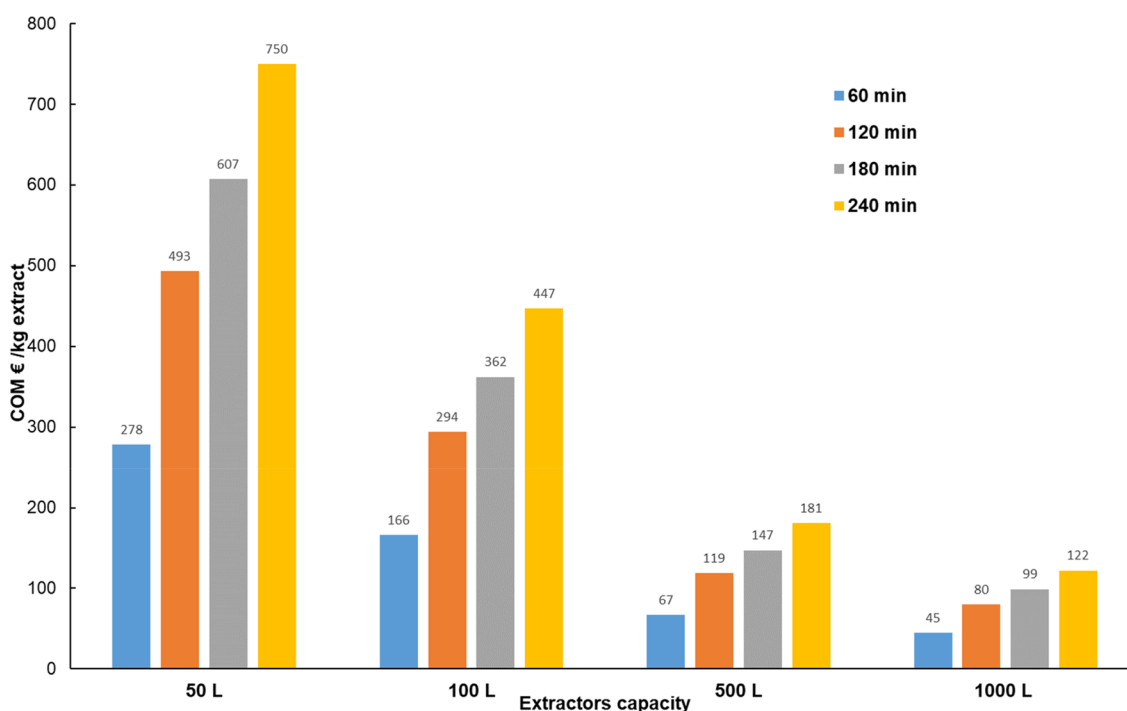
Figure 7. COM calculated for SFE units (2 × 50/100/500/1000L) as a function of the extraction time.
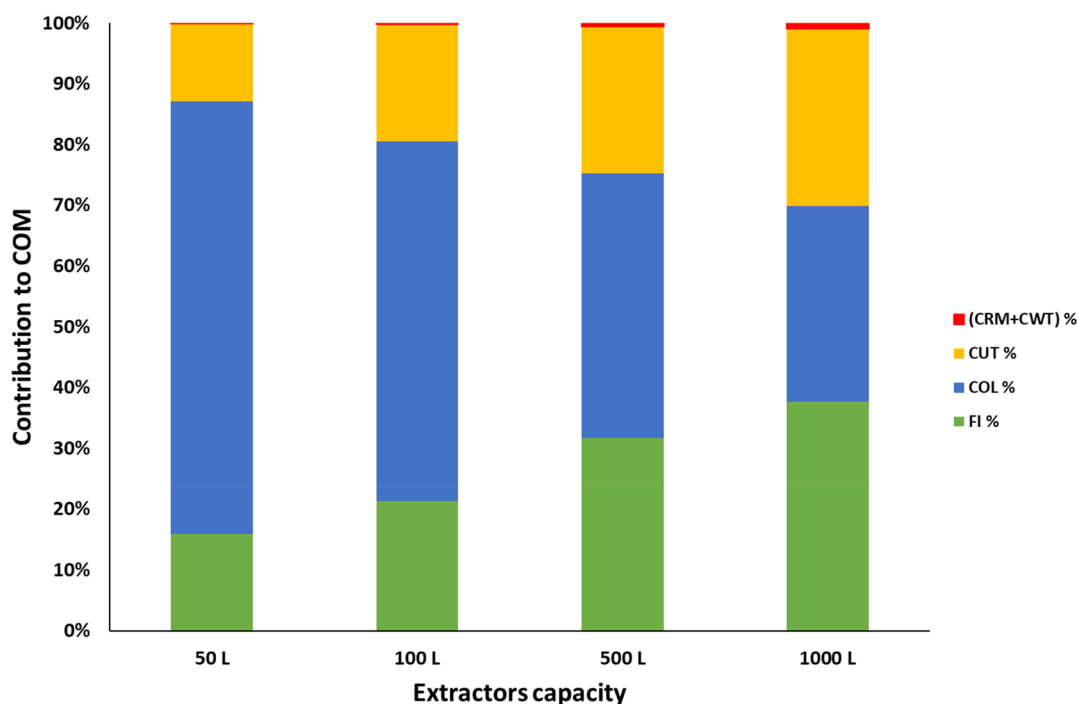
Figure 8. Contribution of each component of COM for grape pomace extracts obtained by SFE units with different extractor capacity.

equal to 1%. These results are in agreement with the literature.[43]

CONCLUSIONS

The results obtained in this study indicate the excellent predictive level obtained by means of Sovová's model and the successf of the scale-up criteria adopted, proving that industrial-scale SFE could be developed for the separation process of polyphenols from grape pomace at a competitive cost. High quality extracts mantaining their biological activities, suitable to be used by food, cosmetic, and/or pharmaceutical industries, can be produced using the SFE process. SFE at an industrial level could be the technological advancement required to really take off an integrated biorefinery to valorize the winery byproducts so promoting a major sustainability of wine making process.

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https://pubs.acs.org/10.1021/acsomega.2c02631

Notes

NOMENCLATURE

CEPCI	chemical engineering plant cost index
a_0	specific surface area per unit volume of extraction bed (m^{-1})
a_s	specific area between the regions of intact and broken cells (m^{-1})
c_u	$(= x_u/(1+x_u))$, solute content in the untreated solid $(kg/kg_{insoluble\ solid})$
d	extractor diameter (m)
d_p	particle diameter (m)
e	extraction yield $(kg/kg_{insoluble\ solid})$
E	extract mass (kg)
G	initial fraction of extract in open cells
H	extraction bed length (m)
D	internal diameter (m)
k_f	fluid-phase mass transfer coefficient $(m \cdot s^{-1})$
k_s	solid-phase mass transfer coefficient $(m \cdot s^{-1})$
N	solid charge in the extractor (kg)
N_m	$(= (1-c_u)N)$ charge of insoluble solid (kg)
q	relative amount of the passed solvent $(kg_{CO_2}/kg_{insoluble\ solid})$
q_m	relative amount of passed solvent at the end of CER period $(kg_{CO_2}/kg_{insoluble\ solid})$
q_n	relative amount of passed solvent at the end of FER period $(kg_{CO_2}/kg_{insoluble\ solid})$
q_s	relative amount of passed solvent at the end of first period when only two periods of extraction are considered $(kg_{CO_2}/kg_{insoluble\ solid})$
Q	solvent flow rate (kg/s)
r	grinding efficiency (fraction of broken cells)
t	extraction time (min)
t_{CER}	$(= (q_m \cdot N_m)/(Q \cdot 60))$ extraction time at the end of CER period (min)
t_{FER}	$(= (q_n \cdot N_m)/(Q \cdot 60))$ extraction time at the end of FER period (min)

x_u concentration in the untreated solid (kg/kg$_{CO_2}$)

y fluid-phase concentration (kg/kg$_{CO_2}$)

y_0 initial fluid-phase concentration (kg/kg$_{CO_2}$)

y_s solute solubility (g/kg$_{CO_2}$)

■ GREEK LETTERS

γ solvent to matrix ratio in the bed (kg$_{CO_2}$/kg$_{insoluble\ solid}$)

ρ_a solid apparent density (kg/m^3)

ρ_f solvent density (kg/m^3)

ρ_s solid real density (kg/m^3)

θ_e dimensionless external mass transfer resistance

θ_i dimensionless internal mass transfer resistance

ε bed void fraction

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