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The effect of equipment design and process scale-up on supercritical CO_2 extraction: Case study for *Silybum marianum* seeds

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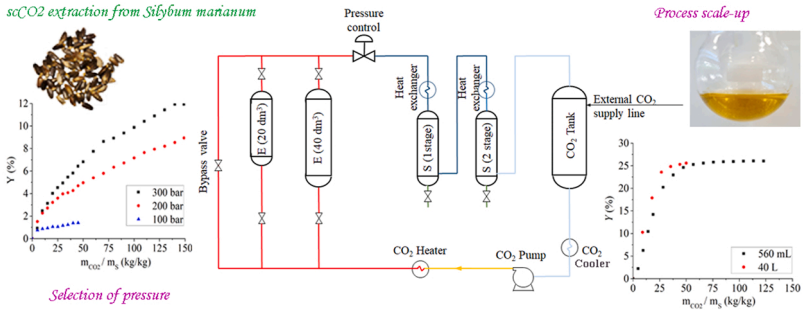
HIGHLIGHTS

- Kinetic of the SFE process significantly differs for four units having volumes from 0.28 to 40 L.
- Three lab-scale units showed variation in extraction yield from 11.9 % to 18.0 %.
- Sovova's model can be used for description the presented SFE process phenomenology.
- Scale-up study showed a good agreement between laboratory and semi-industrial scale unit.
- Economic evaluation indicated optimal industrial process of 3 h and extract cost of 35.9 EUR/kg.

GRAPHICAL ABSTRACT



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ABSTRACT

The present study was focused on improving the supercritical fluid extraction process dedicated to the recovery of highly valuable extract from *Silybum marianum* seeds. At first, the process was tested using supercritical CO_2 at temperatures of 40 and 80 °C and pressures ranging from 100 to 300 bar. Obtained values were described using two literature models with acceptable agreement of experimental and calculated data. Further, the effect of the equipment design and process scale-up was investigated in four high-pressure units having volumes in the range from 280 mL to 40 L resulting in extraction yields up to 26 %. Based on the values of the parameters determined at the laboratory scale, the extraction process was successfully transferred to a semi-industrial scale. Finally, estimated costs for supercritical extract production in Poland for the year 2021 using a 1000 L high-pressure unit amounted to the price of 35.9 EUR per kg of extract.

1. Introduction

The supercritical fluid extraction (SFE) process implies a separation of one compound (extract) from another (matrix) using a supercritical fluid as an extracting solvent. The SFE was shown to be an effective technique for the separation of commercially important extracts from raw plant materials that are rich in valuable bioactive compounds [1–3]. Besides being biologically active, supercritical extracts are pure and

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solvent-free, and therefore are eligible for application in food production, medicine, and pharmacy. Due to its high diffusivity, low viscosity, and near-zero surface tension, the most commonly used supercritical solvent is carbon dioxide (CO_2) [2]. As a solvent, it has the GRAS (Generally Recognized as Safe) status, good solvation power, and can be easily and completely removed from the final product [2].

Although the SFE technique is widely used for the isolation of valuable plant extracts, a scale-up from laboratory to industry level still presents a challenging step. The Cambridge Dictionary defines scale-up as increasing something in size, amount, or production. If this definition is taken into account, one can find a certain number of studies available in the literature that report the scale-up of SFE processes [4–14]. For example, Paula et al. [8] performed SFE scale-up for *B. dracunculifolia* leaves by variation in plant material mass from 12.5 g to 70 g and Fernández-Ponce et al. [9] performed SFE scale-up for mango leaves by an increase in extractor vessel volume from 0.1 L to 5.0 L. However, these studies presented scale-up on small-scale systems (due to the high costs of experimental tests at the industrial scale) while prediction models were used for a larger scale. Nevertheless, the resulting data were generally unreliable concerning the differences observed in processes conducted on significantly different equipment scales [3,9]. The study of intermediate-scale experiments (semi-industrial scale) is a better strategy as it considers the restrictions that may occur on an industrial scale. Therefore, a scale-up of the SFE process proposed in this study was investigated in four high-pressure units, ranging from laboratory to semi-industrial scale, using supercritical CO_2 ($scCO_2$) as the working fluid. *Silybum marianum* (*S. marianum*) was selected as a model plant in this case study due to its high value as an industrial material. In 2018, *S. marianum* was placed among the eight top-selling herbal-based dietary supplements in the US natural retail outlets with sales reaching 9.0 million EUR and ranked 20th in the mainstream multi-outlet channel market in the US with total sales of 14.2 million EUR [15]. $ScCO_2$ extracts from *S. marianum* contain valuable bioactive compounds such as fatty acids [16–18], α- and γ-tocopherol [1,19], and silymarin [17]. Although there are several reports available in the literature that compare the effects of *S. marianum* seeds pretreatment [1], particle size [17], the SFE process pressure/temperature [17,19], and CO_2 flow rate [17] on the extraction yield and extract composition, the present study is the first report that describes the effects of high-pressure equipment design and the process scale-up from 0.28 to 40 L extractor volume. In addition, two literature models were compared for the description of the obtained SFE process kinetics. The first model is based on the adsorption-desorption mechanism that can be described in the following steps: (1) adsorption-desorption equilibrium of extractable component from solid tissue, (2) diffusion of extractable component dissolved in supercritical fluid to the surface, and (3) mass transfer through the external film into the bulk [19–21]. The second model introduced by Sovova [22] is to date the most used. The main assumption of this model is that, during the pretreatment of plant material, a fraction of oil-containing cells is destroyed, making the oil easily accessible to $scCO_2$. The extraction process is thus divided into two periods. In the first period, easily accessible oil is extracted and an external mass transfer and/or oil solubility in $scCO_2$ govern the process rate. In the second period, the oil that remained within the cells of the plant material is extracted, with internal diffusion governing the overall extraction rate.

It is clear that basic research, involving a literature review of the yields, composition, and bioactivity, shows potential for industrial application of the extract from *S. marianum* seeds. On the other hand, the analysis taking into account factors such as raw material prices, equipment, and labor costs, as well as prices on the market for a specific product, etc., can provide an approximate evaluation of the process economics and potential for investment. In that sense, this study provides, for the first time, information on the estimated costs for *S. marianum* extract production based on data obtained using a semi-industrial unit for the SFE process.

2. Materials and methods

2.1. Materials

The *S. marianum* seeds were obtained from the Institute Dr. Josif Pancic (Pancevo, Serbia) and the Prowana (Radzymin, Poland). The seeds were stored in a dark place at room temperature (20 °C) prior to the extraction. Commercial CO_2 (purity 99.9 %) purchased from the Messer-Tehnogas (Belgrade, Serbia) was used for the extraction process in laboratory scale units (units I and II, described in detail below) and CO_2 (purity 99.9 %) produced by the Grupa Azoty (Zaklady Azotowe "Pulawy" S.A., Pulawy, Poland) was used for extraction process in a laboratory-scale unit (unit III, described in detail below) and a semi-industrial scale unit (unit IV, described in detail below).

3. Methods

3.1. Plant material analysis and pretreatment

The moisture content in *S. marianum* seeds was determined using a laboratory moisture analyzer (MAC 50/1/WH, RADWAG®, Radom, Poland). Before the extraction, seeds were milled using a basic mill (Ika® A11, Warszawa, Poland) and sieved. The average particle size of the plant material used for SFE processes was 0.4 mm. The plant material density was 1192 ± 114 kg/m^3. The bed density and porosity were 376 ± 6 kg/m^3 and 68.2 ± 2.5 %, respectively.

3.2. Supercritical fluid extraction processes

Four high-pressure units were tested for the SFE process from *S. marianum* seeds.

3.2.1. Unit I

High-Pressure Extraction Adsorption Unit (HPEA 500, Eurotechnica GmbH, Bargteheide, Germany) was used for the selection of operation parameters (pressure and temperature) that enable the highest extraction yield. It is a versatile unit that can be used for the SFE process as well as for integrated processes of SFE and supercritical impregnation. For the proposed test, the SFE process was performed using only a 280 mL extraction vessel (E) (Fig. 1a), designed for processes operated at the maximum pressure of 534 bar and temperature of 121 °C. Plant material (10.0 g) packed in paper filter bags was placed above the glass beads at the bottom of the extraction vessel. After the desired temperature was achieved using the extractor heating jacket, CO_2 was introduced from a tank and the pressure was elevated by a liquid pump (Milton Roy, Pont-Saint-Pierre, France) with a maximum pressure of 500 bar and maximum liquid flow of 1.5 L/h. A separator for extract collection, at room temperature (20 °C) and atmospheric pressure (1 bar), was placed after a back-pressure regulator (BPR, Tescom, Missouri, US). For the purpose of testing moderate and relatively high temperatures (40 °C and 80 °C), the SFE process was performed at pressures of 100, 200, and 300 bar. $ScCO_2$ flow rate was maintained constant at 0.4 kg/h during the process. Additional information about the unit is given in Table 1.

Kinetics of the SFE process performed at 40 °C and 300 bar were compared with kinetics obtained using Unit II, having the same extractor volume, and Unit III, having two times larger extractor volume. A comparison of the kinetics gave information about the effects of laboratory-scale high-pressure equipment design on the SFE process.

3.2.2. Unit II

The SFE process was also performed in an Autoclave Engineers Screening System (AESS, Autoclave Engineers Group, Erle, Pennsylvania, USA) schematically presented in Fig. 1b. The AESS unit is designed for small batch research runs using CO_2 as the supercritical medium. The free volume of the extractor (E) is 280 mL. Heaters are supplied on the extractor vessel for temperature elevation. The maximum allowable

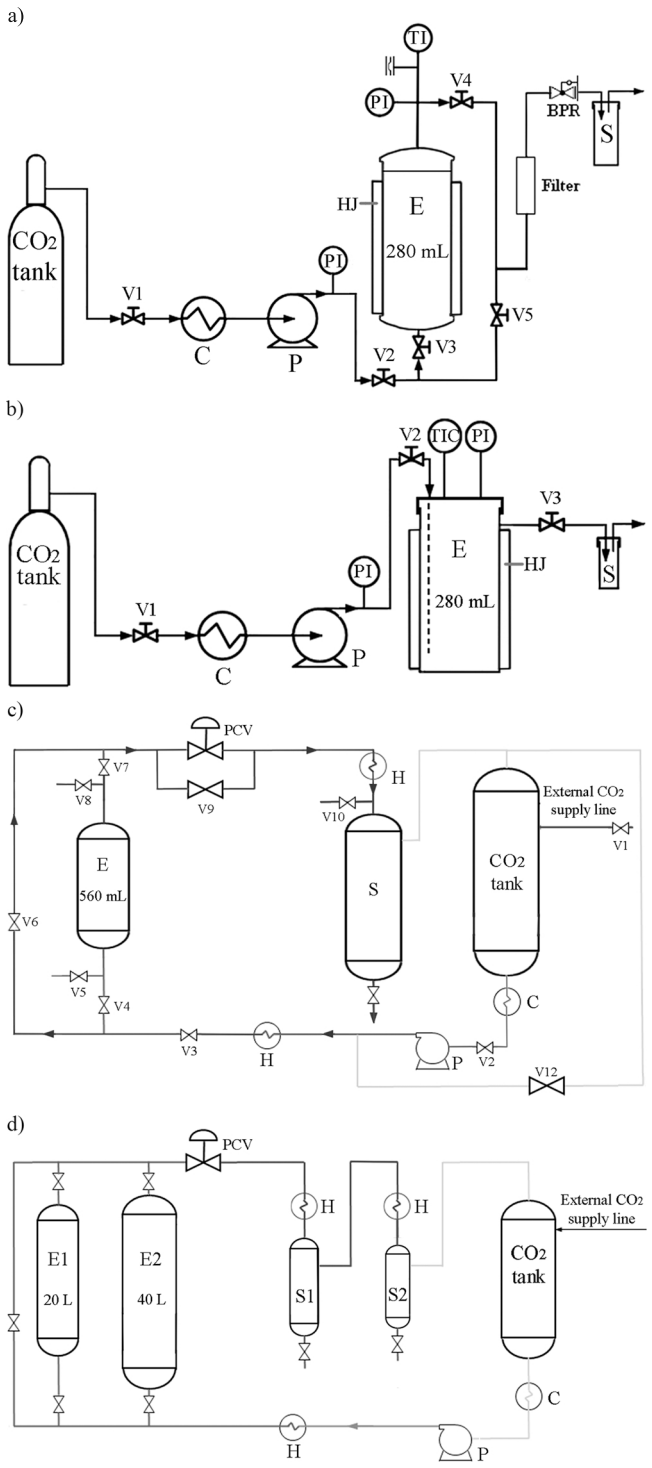

Fig. 1. Schematic presentation of a) unit I, b) unit II, c) unit III, and d) unit IV (C– cryostat, P– pump, PI– pressure indicator, TI– temperature indicator, TIC– temperature indicator and controller, S– separator, HJ– heating jacket, H– heat exchanger, PCV– pressure control valve).

working pressure and temperature are 413 bar and 238 °C, respectively. Plant material (10.0 g) was placed at the bottom of the vessel and after heating, the pressure was elevated using a pump for liquids (Milton Roy, Pont-Saint-Pierre, France) that achieves maximum pressure of 420 bar under the maximum liquid flow of 0.5 L/h. During the process, the extract was collected in a separator (S) at room temperature (20 °C) and atmospheric pressure (1 bar). $ScCO_2$ flow was maintained constant at 0.3 kg/h during the process. Additional information about the unit is given in Table 1.

Table 1
The information about high-pressure units.

	Unit I	Unit II	Unit III	Unit IV
$H_{extractor}$ (cm)	27.2	18.0	12.0	225.0
$D_{extractor}$ (cm)	3.8	4.4	7.7	15.0
$H_{extractor}/D_{extractor}$	7.2	4.1	1.6	15.0
$V_{extractor}$ (cm^3)	280	280	560	39,740
L_{pipes} (cm)	165	22	354	825
Packaging	filter bags	/	basket	/
Extractor filters	/	/	metal filter	paper filter

H– height; *D*– diameter; *V*– volume; L_{pipes}– pipe distance between extractor and separator.

3.2.3. Unit III

The third unit tested for SFE from *S. marianum* seeds was a high-pressure micronization unit (SITEC, Zurich, Switzerland) schematically presented in Fig. 1c. The maximum operating pressure for the unit is 550 bar at the maximum operating temperature of 220 °C. Plant material was placed in a metal basket closed with metal filters from the top and the bottom. After placing the basket in the extractor and achieving the desired temperature in the system, the pressure was elevated using a diaphragm pump (LEWA, Leonberg, Germany) that achieves maximum pressure of 500 bar under the maximum liquid flow of 30 L/h. The pressure was regulated by an automatic pressure controller. During the process, $scCO_2$ flow was maintained constant at 8.8 kg/h and the extract was collected at 50 bar and 20 °C, in a separator which has a volume of 1.2 L (P_{max} = 100 bar and T_{max} = 60 °C). The mass of plant material placed in the extractor was 40.0 g and 211.5 g (results for this set of experiments were further marked as Unit IIIa and Unit IIIb, respectively). A part of the moisture was separated with an extract from the plant material during the SFE process using Unit III (primarily it was determined that the moisture content present in *S. marianum* seeds grown in Serbia and Poland were 5.15 % and 5.77 %, respectively). Therefore, it was necessary to remove moisture using a rotary vacuum evaporator to obtain the final extraction yield presented in the Result section. Additional information about the unit is given in Table 1.

3.2.4. Unit IV

The SFE process from *S. marianum* seeds was also tested in a semi-industrial scale unit that was in-house built (ELAB, Łukasiewicz - New Chemical Syntheses Institute, Puławy, Poland). The unit was designed for maximum operating pressure of 330 bar and a maximum operating temperature of 85 °C. Plant material (15.0 kg) was placed directly in the extractor vessel. Paper filters placed at the top and the bottom of the vessel protected the rest of the unit from clogging with plant material during the process. After achieving the desired temperature, the pressure was elevated using a pump (LEWA, Leonberg, Germany) with a maximum liquid flow of 140 kg/h. The pressure in the system was controlled by an automatic pressure controller. During the process, $scCO_2$ flow was maintained at around 131.5 kg/h and the extract was collected in two separators (P_{max}= 200 bar and T_{max}= 100 °C) having volumes of 6.6 L (S1) at 65 bar and 50 °C and 3.5 L (S2) at 56 bar and 20 °C. Further information about the unit is given in Table 1.

The extraction yield (*Y*, %) was calculated as a ratio of the mass of separated extract and plant material placed in an extractor. Another important factor for the SFE process is the solvent residence time (t_{res}), which can be calculated by Eq. 1 [8]:

$$t_{res} = \frac{V_{BED}\varepsilon_{BED}\quad \rho_{CO2}}{\dot{m}} \tag{1}$$

where V_{BED} is the bed volume; ε_{BED} is the bed porosity, ρ_{CO2} is the CO_2 density, and $\dot{m}$ is the CO_2 mass flow rate.

Dimensionless Reynolds number (Re_p) and Biot number (*Bi*) were

calculated using Eq. 2 [12,23] and Eq. 3 [19], respectively:

$$Re_p = \frac{\rho_{CO_2} d_p u}{\mu} \quad (2)$$

$$Bi = \frac{k_f d_p}{D_e} \quad (3)$$

where *d*p is the average diameter of plant material, u and μ are the velocity and viscosity of CO_2, respectively, and the D_e is the effective intraparticle diffusion coefficient.

3.3. Modelling of SFE kinetics

Two literature models were used for modelling the SFE kinetics obtained at a temperature of 40 °C and pressures of 100, 200, and 300 bar. The first model is based on the adsorption-desorption mechanism [19–21]. The main feature of the model is that the adsorption-desorption equilibrium is linear, with equilibrium constant K being the only fitting parameter. The phenomenological meaning of the K values is that for $K<<1$, the oil would be desorbed from the tissue into the pores filled with $scCO_2$. Under the assumption that the equilibrium is established instantaneously, the analytical solution of the model differential equations is possible, making the model easy to use. Parameters such as external and overall mass transfer coefficients, as well as the effective diffusion coefficient are calculated using appropriate literature models [19]. The second model applied is the widely used model introduced by Sovova [22]. The external mass transfer coefficient is calculated analogously to the first model, while the internal diffusion coefficient (k) and grinding efficiency (G) were used as fitting parameters. For both models values for the initial concentration of the extractable material for every set of experiments were adopted from experimental data. The values of fitting parameters for models were obtained by minimizing the average absolute relative deviation (AARD), given in Eq. 4, as an optimization criterion:

$$AARD(\%) = \frac{100}{N}\sum_{i=1}^{N}\frac{\left|Y_{calc} - Y_{exp}\right|}{Y_{calc}} \quad (4)$$

where N is the total number of experiments for one set of experimental data, while Y_{exp} and Y_{calc} are the yields obtained in experiments and calculated by the model, respectively.

3.4. Fatty acids content

The effect of high-pressure equipment design on the composition of extracts obtained using Units I, II, and III was determined by comparing the content of its dominant compounds i.e. fatty acids [24]. Derivatization of the samples was performed according to the previously described method [18,25].

Qualitative analysis of fatty acids was determined using a gas chromatograph equipped with a mass spectrometer (7000 C Triple Quadrupole GC-MS, Agilent Technologies, US) and a DB-EUPAH column (60 m x 0.25 mm, 0.25 μm). Helium was used as a carrier gas (99.99 %) at a flow rate of 0.6 mL/min. Derivatized samples (100 μL) were diluted with a solution of methyl tert-butyl ether in methanol (9:1 v/v) at a ratio of 1:10 v/v. The oven temperature of 60 °C was increased to 310 °C at a rate of 3 °C/min. The identification of fatty acids was carried out using MassHunter software (C.01.03) and NIST Mass Spectral Library.

Quantitative analysis was performed using a gas chromatograph equipped with a flame ionization detector (GC-FID System 7820 A, Agilent Technologies, US) and a HP-88 column (100 m x 0.25 mm, 0.2 μm). Derivatized samples (500 μL) were dissolved with 500 μL methyl tert-butyl ether and placed into the autosampler. The FID detector temperature was set at 300 °C and the injector temperature was set at 250 °C. The initial oven temperature of 50 °C was raised to 240 °C (8 °C/min) and held for 5 min. Helium was the carrier gas with a flow rate of 2 mL/min. The injection of all samples (1 μL) was performed in a split mode (100:1) with a purge time of 0.75 min

3.5. Cost estimation

The cost estimation for the process of SFE from *S. marianum* seeds was based on the results obtained using the semi-industrial unit (unit IV) and the methodology proposed by Turton et al. [26], which defines the manufacturing cost as a sum of defined costs, as shown in Eq. 5:

$$C_{OM} = 0{\cdot}304\ F_{CI} + 2{\cdot}73\ C_{OL} + 1{\cdot}23\ (C_{UT} + C_{WT} + C_{RM}) \quad (5)$$

where C_{OM} (EUR/year) is the manufacturing cost, F_{CI} (EUR/year) is the fixed capital investment, C_{OL} (EUR/year) is the operational labor cost, C_{UT} (EUR/year) is the utility cost, C_{WT} (EUR/year) is the waste treatment cost, and C_{RM} (EUR/year) is the raw material cost [8,27–31]. **The fixed capital investment (F_{CI})** is related to the cost of the SFE equipment and the amount of CO_2 needed for extraction assuming that the high-pressure unit works continuously for 24 h per 330 days. The other 35 days in one year are intended for the maintenance of a high-pressure unit. It was previously reported that a sharp transition wave develops when extracting from small particles (≤1 mm) separating extracted (downstream) from virtually unextracted (upstream) substrate within extraction vessels [32]. Therefore, the use of two-vessel industrial SFE plants for small particles (like the ones used in our study), and three- or four-vessel plants for medium-to-large (≥2 mm) was suggested [32]. Besides two extractors that could be operated 24 h/day, a typical industrial supercritical extraction unit is composed of a series of separators (for extract fractionation/separation/collection), coolers, heaters, a CO_2 reservoir, and a CO_2 pump. The literature report on the cost of this equipment composed of two extractors each having volume of 500 L was 1272,577.50 EUR [30,33]. **The operational labor cost (C_{OL})** included the operation and maintenance of the high-pressure unit for 365 days. C_{OL} was calculated assuming that 6 workers were required for three 8-h-daily shifts (2 workers per shift) and that 2 additional workers were required for rotation of shifts [28,29,31,32]. The price of a working hour of 4 EUR/h per worker was estimated based on the minimum gross wage per hour in Poland in 2021 (18.3 PLN) [34]. **The utility cost (C_{UT})** includes three types of costs: costs associated with the electric power used by a CO_2 pump (dependent on the CO_2 amount used in a process), costs stemming from the CO_2 heating, and costs of refrigeration. The C_{UT} was estimated considering the energy involved in the solvent cycle using the pure CO_2 temperature–entropy diagram. The value of specific enthalpy of CO_2 at selected operating conditions (300 bar and 40 °C) is 270.2 kJ/kg. Other important data are total operation time (7920 h/year), CO_2 cost (0.10 EUR/kg including CO_2 losses of around 2 %), and wholesale electricity prices in Poland that averaged 0.18 EUR/kWh in the year 2021 [35]. **The waste treatment cost (C_{WT})** can be neglected considering that CO_2 used for the SFE process is recyclable and that the only waste in the proposed industrial process will be the exhausted plant material. In the case of SFE from *S. marianum*, the accumulated waste can be further used in conventional extraction processes and for composting. **The cost of raw material (C_{RM})** was estimated based on the price of *S. marianum* seeds grown in Poland of 2.39 EUR/kg [36]. Due to economic reasons, the SFE process scale-up was performed using material produced in Poland considering that the price of *S. marianum* seeds produced in Serbia was 22.05 EUR/kg [37]. Furthermore, C_{RM} was estimated at 2500 EUR/t including transport and plant material pre-treatment (drying and milling). Based on the obtained results, **the specific cost (*SC*)**, defined as the manufacturing cost divided by the total mass of produced extract, was estimated as a function of the extraction time.

4. Results

4.1. The SFE process in the lab-scale unit

The influence of pressure and temperature in the selected range was investigated using *S. marianum* seeds grown in Serbia and Unit I. The results obtained at 40 °C at various pressures are presented in Fig. 2a. It can be seen that pressure significantly affected the extraction yield. The highest yields obtained at 40 °C and 100, 200, and 300 bar were 1.4 %, 8.9 %, and 11.9 %, respectively. An increase in extraction yield with increasing pressure from 160 to 220 bar at 40 °C was also reported by Çelik et al. [17] using *S. marianum* seeds grown in Turkey. On the other hand, Hadolin et al. [19] reported an increase in extraction yield from 1.5 % to 20.0 % with increasing pressure only up to 200 bar at a temperature of 40 °C, while a further increase to 300 bar led to a decrease of extraction yield to 16.5 % for *S. marianum* seeds grown in Slovenia. Differences in results obtained in SFE from the same plant species can be attributed to the origin of the plant material, material pre-treatment, construction of the high-pressure unit, and CO_2 consumption in relation to an amount of the plant material.

The increase in temperature to 80 °C led to a decrease in extraction yields (Fig. 2b) compared with those obtained at 40 °C for all pressures applied probably due to a decrease in $scCO_2$ density. Namely, the density of $scCO_2$ is decreasing with an increase in temperature from 40° to 80°C, but the magnitude of such density change becomes smaller at higher pressures such as 300 bar [38]. The density of $scCO_2$ is directly related to its solvent power and resulting extraction yield [38–40]. Furthermore, obtained results indicate that cross-over pressure (the pressure at which an increase in temperature results in the extraction yield increase) was not achieved. Final extraction yields at 80 °C were 2.3 % and 11.3 % obtained at 200 and 300 bar, respectively. At 100 bar the density of $scCO_2$ was apparently too low to allow separation of extract from tested plant material, as previously reported [19]. Therefore, the temperature of 80 °C was not considered for further investigation.

Based on these preliminary tests, process conditions of 300 bar and 40 °C and solvent to feed ratio up to 150 kg/kg were selected for analysis of the influence of equipment design and scale-up of the SFE process from *S. marianum* seeds. Modelling results are depicted in Fig. 2a, while the parameter values for both models are shown in Table 2 along with the values of the optimization criterion. Based on the values of AARD, Sovova's model gave better results than the model of Goto et al. [21], which is expected considering that the number of fitting parameters is larger (two against one). It can be seen from the graph that the main difference between the results of these two models is in the early stage of the extraction. Obviously, the conclusion is that Sovova's model describes the phenomenology of the SFE process more accurately. However, the results from applying the model of Goto et al. [21] can still provide some insight regarding the reliability of our results, since the same model was used by Hadolin et al. [19] for modelling the SFE from the same plant covering the same range of process conditions.

The values for equilibrium constant K, in the model of Goto et al. [21], are generally in agreement with values obtained in the work of Hadolin et al. [19] with the same plant (K=176.56 at 200 bar, and K=89.34 at 300 bar). However, there is a large discrepancy regarding the results for 100 bars. In our work, the value is 70.79, which is significantly different compared with 6003.62 obtained by Hadolin et al. [19]. Although, in general it is expected that K decreases with increasing the pressure, a value larger than 6000 is somewhat strange especially combined with the fact that the AARD in the work of Hadolin et al. [19] for 100 bar was significantly larger (23.1 %) than in other experiments for which the values of AARD are comparable with those obtained in our work. The reason for this could be that the SFE at 100 bar is significantly different compared to the SFE at higher pressures, due to significantly different extract composition. It has been widely established that at 100 bar the extract mostly contains highly volatile components, mainly essential oil, while at pressures of 200 and/or 300 bar, there is a large fraction of heavy compounds. The main reason for this, of course, is a large difference in $scCO_2$ density, which is 629, 840, and 910 kg/m^3 at 100, 200, and 300 bar, respectively. Nonetheless, it is worth noticing that, despite the fact that the model of Goto et al. [21] is relatively simple regarding the level of details in the description of the phenomenology of the SFE process, some conclusions about the prevailing mechanisms can be made taking into account the values of some parameters. According to Hadolin et al. [19], for $K << 1$, all of the oil could be considered desorbed from the plant matrix and, thus, easily accessible for $scCO_2$. Accordingly, relatively high values for K in our results (see Table 2) imply that only a small fraction of extract is easily accessible to $scCO_2$. Another parameter that can be used to assess the prevailing mechanism(s) is the dimensionless Biot number, an index of the ratio of resistances to mass transfer inside the particle (internal diffusion) and on the surface of the particle (external convection) – if $Bi >> 5$ intraparticle diffusion resistance would dominate over the external mass-transfer resistance [19]. In our case, the values for Bi are 1.92, 2.01, and 2.25 for 300 bar, 200 bar, and 100 bar, respectively. Thus, a conclusion can be made that the intraparticle diffusion is not the only prevailing mechanism of SFE from *S. marianum* seeds within the range of process conditions used in this work.

This reasoning regarding the amount of easily accessible solute and prevailing mechanisms is practically confirmed by results of the Sovova's model. Namely, the obtained values for grinding efficiency (G) and

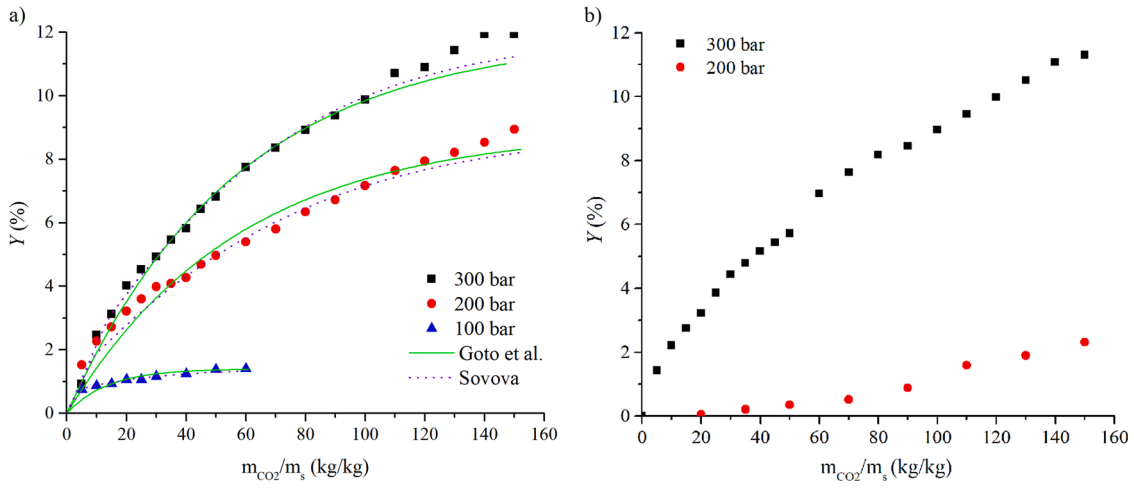

Fig. 2. Change of extraction yield with pressure at a) 40 °C and b) 80 °C using Unit I for *S. marianum* seeds grown in Serbia.

Table 2
Parameter values and optimization criterion.

	Goto et al.				Sovova			
P (bar)	$k_p \cdot 10^5$ (m/s)	K	$k_f \cdot 10^5$ (m/s)	AARD (%)	G	$k_s \cdot 10^9$ (m/s)	$k_f \cdot 10^5$ (m/s)	AARD (%)
300	3.15	218.74	4.36	5.16	0.148	5.4	4.36	3.72
200	3.85	239.79	5.40	10.57	0.140	4.8	5.40	6.99
100	6.83	70.79	9.91	9.83	0.507	14.0	9.91	2.55

k– mass-transfer coefficients; K– equilibrium coefficients; G– grinding efficiency

internal mass transfer coefficient (k_s) are comparable for results at 200 and 300 bar, while the same parameters values for results at 100 bar are significantly greater. The results for G can be perceived as somewhat ambiguous, since it is generally regarded that if the same plant material was subjected to the same pre-treatment, the value for G should be the same, regardless of the conditions of pressure and temperature. However, there is a rather logical explanation for the obtained discrepancy. Although G is perceived as a pre-treatment parameter, not influenced by process conditions, it is directly related to the amount of easily accessible solute (higher values for G imply larger fractions of 'free' solute). On the other hand, the amount of extractable solute, and by logic the amount of easily accessible solute, is dependent on process conditions, thus, making it logical for G to also depend on the pressure and temperature used in experiments. At lower pressure, the extract predominantly consists of essential oil that is located in the specific secretory structures like trichomes, ducts, cavities, or epidermal cells within the plant material [41]. Specifically, the essential oil of *S. marianum* is located in secretory ducts and it has been argued that, during the pre-treatment, a large fraction of ducts can be opened, making a large fraction of the extractable solute easily accessible to $scCO_2$ [23]. This fact is in complete agreement with our result for G on 100 bar. Moreover, experimental results on 100 bar are also in agreement with this reasoning since it is obvious that the fast extraction period lasts considerably longer compared with the case of two higher pressures.

Based on the results of SFE experiments and modeling it can be concluded that: (1) for all pressures applied, there is a fast extraction and a slow extraction period, indicating an easily available fraction of oil at the surface and a fraction that remained inside the plant material, respectively, (2) at 100 bar the fast extraction period lasts considerably longer indicating considerably different extract composition, which is in agreement with previously published studies on the effects of pressure on extract composition [2,42–46], and (3) at higher pressures the slow extraction is prevailing, making the internal diffusion a mechanism controlling the overall rate of the process.

4.2. The effect of high-pressure equipment design at a laboratory scale

The effect of high-pressure equipment design on the process of SFE from *S. marianum* seeds grown in Serbia was investigated using Units I, II, and III (Fig. 1). The SFE process was performed at 300 bar and 40 °C until plant material exhaustion or until solvent to feed ratio reached 150 kg/kg. The crucial parameters related to the three Units are presented in Table 3. The highest extraction yields achieved were 11.9 %, 18.0 %, and 17.5 % using Units I, II, and IIIa, respectively.

One parameter that significantly differs for Units I, II, and IIIa is the CO_2 flow ($\dot{m}$) (Table 3). The operating CO_2 flow is determined by the pump used (its characteristics) as well as the rest of the high-pressure equipment. Namely, relatively low CO_2 flow in Units I and II is necessary to enable the extract collection in separators at atmospheric pressure and temperature. On the other hand, a relatively high CO_2 flow of 8.8 kg/h in Unit IIIa is necessary for keeping systems' parameters stable (pressure and temperature). The results lead to a conclusion that the plant material was exhausted in Units II and III, regardless of the significantly different $scCO_2$ flow rates. Although Çelik et al. [17] reported an increase in *S. marianum* seeds extraction yield from 15 % to 17 % by increasing CO_2 flow from 0.18 to 0.30 kg/h, our study showed that CO_2 flow rate possibly affected only extraction kinetics without any effect on the final extraction yield. Indeed, a review by De Melo et al. [3] emphasized that an increase in $scCO_2$ velocity influences axial dispersion, convective mass transfer coefficient, and accumulation in the bulk, leading to an increase in extraction rate.

Table 3
Parameters of the SFE process at 300 bar and 40 °C for *S. marianum* seeds (Serbia).

	Unit I	Unit II	Unit IIIa
d_P (mm)	0.4	0.4	0.4
ρ_{BED} (kg/m^3)	376	376	376
ε_{BED} (%)	68.2	68.2	68.2
$\dot{m}$ (kg/h)	0.4	0.3	8.8
ρ_{CO2} (kg/m^3)	910	910	910
m^F_{CO2} (kg)	1.50	1.40	5.65
m^F_{CO2}/m_s (kg/kg)	149	140	141
t_{res} (min)	2.48	3.30	0.45
F_{CO2} (kg/cm^2 h)	0.0353	0.0197	0.5659
u (mm/s)	0.1077	0.0603	0.5771
Re_p	1.3060	0.7307	6.9990
Y (%)	11.9	18.0	17.5

d_P– average particle size of milled plant material; ρ_{BED}– density of the packed plant material; ε_{BED}– porosity of the packed plant material; $\dot{m}$– CO_2 flow; m^F_{CO2}– mass of CO_2 consumed at the end of the experiment; m^F_{CO2}/m_s– solvent to feed ratio (mass of CO_2 consumed per initial mass of plant material) at the end of the experiment; ρ_{CO2}– density of $scCO_2$; t_{res}– $scCO_2$ residence time; F_{CO2}– CO_2 flux; u– $scCO_2$ velocity; Re_p– Reynolds number; Y– the final extraction yield

An additional difference between tested units is the separator for extract collection. While separators of Units I and II enabled the collection of the extract only at atmospheric conditions (1 bar and 20 °C), the separator of Unit III gave the possibility of extract collection at controlled pressure and temperature (50 bar and 20 °C). This led to the separation of moisture with the extract from the plant material during the SFE process using Unit IIIa. Therefore, it was necessary to remove moisture using a rotary vacuum evaporator to obtain the final extraction yield presented in Table 3 and Fig. 3. On the other hand, Units I and II enabled the separation of moisture-free extract. The reason for this result could be a relatively high CO_2 flow in Unit IIIa compared with relatively low flows in Units I and II as well as the higher pressure in the separator of Unit IIIa. Additionally, it can be hypothesized that the moisture did not have an effect on the final yield but could have a small effect on the kinetics of the process, as can be seen in Fig. 3b for Units II and IIIa. However, additional research is necessary to confirm which parameter had a dominant effect on the SFE process.

The lowest extraction yield of 11.9 % was obtained in Unit I regardless of the somewhat higher CO_2 flow and similar CO_2 consumption compared with the process performed in Unit II (Table 3). Considering that the volume of the extractor, amount of plant material, amount of CO_2 used, and separation pressure and temperature were the same for Units I and II, and having in mind that the difference in $scCO_2$ velocity could not be the reason for such large discrepancy, it can be concluded that the construction of the high-pressure unit had a significant effect. Namely, Unit II enabled the collection of the extract after passing a straight 22 cm long pipe (Table 1), while for Unit I the

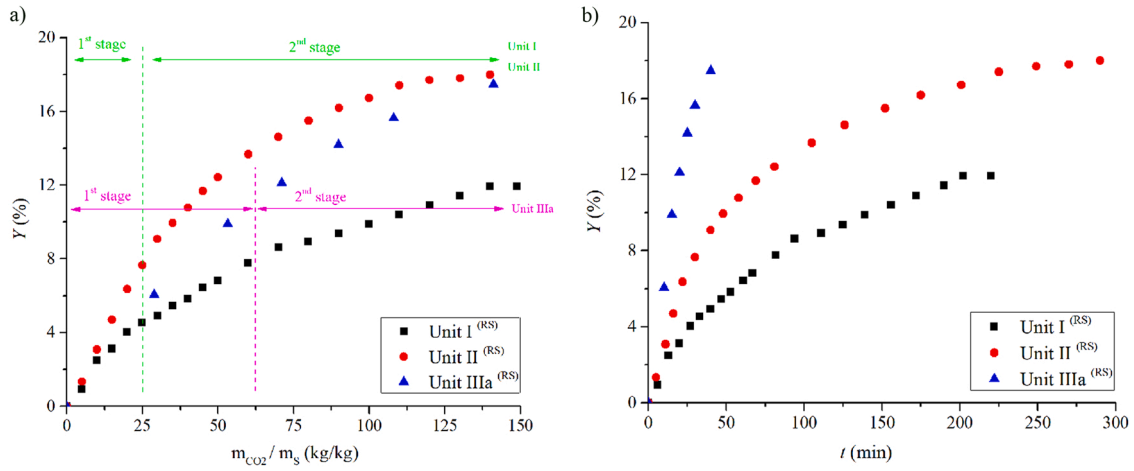

Fig. 3. Change of extraction yield with high-pressure units for *S. marianum* seeds grown in Serbia (RS): a) yield vs. solvent to feed ratio and b) yield vs. time.

pathway before the separator is much longer and amounts to 165 cm. Although pipe length could have had a dominant effect on extract separation in Units I and II, by comparing these findings with the results obtained using Unit III (pipe length of 354 cm), it can be further concluded that the pipe length has a negligible effect in case of high CO_2 flows. Salea et al. [10] also demonstrated that other factors such as the extractor geometry and plant material aggregation may restrict the performance of the SFE process. Additionally, longer $scCO_2$ residence time (t_{res}) in Unit II could have led to a higher extraction yield compared with Unit I (Table 3).

Parameters that differ based on the used unit are the superficial velocity and moreover significantly for Unit IIIa, the values for Reynolds number that are quite low in all cases and imply a laminar flow regime (Re_p <10) (Table 3). It is interesting to notice that, although used Units I and II are quite different, resulting in different solvent flow, flux, and residence time, the first stage of extraction was finished for a solvent to feed ratio of around 25 kg/kg (Fig. 3a), while in Unit III this happened at a ratio around 60 kg/kg. The first stage of extraction kinetics corresponds to the extraction of easily accessible solute from the surface of plant material particles, while the second stage of extraction kinetics is related to the extraction of solute from the inside of the particles [4,6,27,28]. The mentioned difference in the first stage of the extraction could be a consequence of a short solvent residence time of 0.45 min for Unit IIIa (Table 3). However, the final extraction yields in all tested units were comparable (Fig. 3a). Similar extraction yields were achieved using Units II and IIIa for a solvent to feed ratio of around 140 kg/kg, regardless of the significant differences in the SFE process operating time i.e. 250 min and 40 min, respectively (Fig. 3b). A similar decrease in extraction time with higher flows was previously reported for SFE from cocoa butter [47].

In addition to mentioned parameters that can affect the extraction rate from the plant material, the relationship between different bed height (H_{BED}) and diameter (D_{BED}) can also have an effect as previously reported [5,8,48]. However, due to the considerably different construction of tested high-pressure units, the discussion of obtained results regarding their H_{BED}/D_{BED} ratio is not recommended. Namely, tested high-pressure units have different diameters (Table 1) and different entrances of the CO_2 inside extractors (Fig. 1), which leads to variations in CO_2 distribution/path through extractor and plant material.

The effect of high-pressure equipment design was further evaluated by comparing the composition of obtained extracts. For this purpose, the content of the most dominant compounds i.e. fatty acids [24] was determined by CG-MS and CG-FID analysis. Results indicate the presence of saturated fatty acids (palmitic, stearic, and behenic) with a content of 12.6 % ± 0.3 % and unsaturated fatty acids (oleic, linoleic, and eicosanoic) with a content of 87.4 % ± 0.3 % (Fig. 4a). Dominant

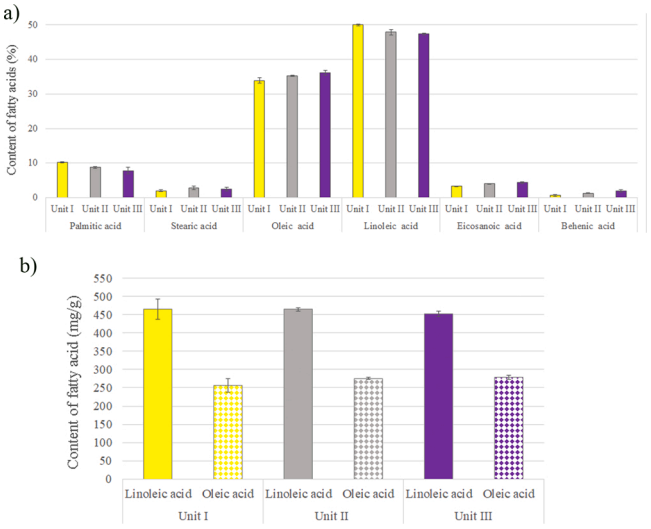

Fig. 4. Content of fatty acids in extracts from *S. marianum* seeds grown in Serbia: a) qualitative composition and b) quantitative composition.

fatty acid was linoleic acid (460.7 mg/g ± 13.5 mg/g) followed by oleic acid (270.1 mg/g ± 8.7 mg/g) (Fig. 4b).

By comparing the presented results, it can be concluded that although the design of high-pressure units had a significant effect on the kinetics of the SFE process, it had a negligible effect on the content of fatty acids in supercritical extracts obtained from *S. marianum* seeds.

4.3. The SFE process scale-up

For a process to reach an adequate scale-up level, it was reported that the SFE process should be previously assessed by optimization of operating conditions, selection of preferable extraction time, CO_2 consumption, and modeling of the same extraction curves to disclose extraction mechanisms that characterize the rate at which solutes are removed from plant material [3]. After assessing pressure, temperature, solvent to feed ratio, and literature models, the scale-up from 560 mL (Unit III) to 39.7 L high-pressure unit (Unit IV) was tested. Due to economic reasons, a scale-up was performed using *S. marianum* seeds grown in Poland. After the pressure of 300 bar, the temperature of 40 °C, and the solvent to feed ratio up to 140 kg/kg were selected, the first SFE was performed with an initial plant material mass of 40.0 g placed in the extractor (denoted as Unit IIIa $^{(PL)}$). Further, the initial mass of plant material placed in the extractor was increased to 211.5 g (denoted as

Unit IIIb (PL)) and the resulting change in extraction yields is presented in Fig. 5. It can be seen that about a 5-fold increase in the initial amount of plant material placed in the extractor of Unit III increased the extraction rate while final extraction yields were comparable (24.1 % and 26.0 %, respectively). Although the CO_2 flow and solvent to feed ratio were almost the same for both experiments, CO_2 consumption was around 6 and 26 kg/kg for Unit IIIa and IIIb, respectively, which could be the reason for slight discrepancies between final extraction yields. Considering that the SFE process performed with a higher initial amount of plant material enabled the separation of a higher amount of extract for a lower solvent to feed ratio, the ratio of extractor volume to plant material mass of 2.65 mL/g was added to the list of parameters that were maintained constant for the scale-up for Unit IV.

Previously it was determined that the moisture content present in *S. marianum* seeds grown in Poland was 5.77 %. A part of this moisture was collected in a single separator of Unit III with extract at 50 bar and 20 °C and it was necessary to remove it using vacuum evaporation to determine the amount of separated extract presented in Fig. 5. On the other hand, the additional step of moisture removal was not necessary for the SFE process performed in Unit IV operated with a high CO_2 flow of 131.5 kg/h due to two built-in separators that enable in situ moisture separation from the desired extract by variation in collection pressure and temperature. In this way, the extract was collected in S1 (Fig. 1) at 65 bar and 50 °C and moisture in S2 at 56 bar and 20 °C.

By comparing the results of SFE processes performed in Units IIIb and IV, presented in Fig. 5, it can be seen that the final extraction yield was almost the same (25.6 % and 26.0 %, respectively). In addition, it can be seen that, similarly to the extraction of seeds grown in Serbia using Units I, II, and IIIa (Fig. 3), the first stage of extraction from seeds grown in Poland using Units IIIb and IV (Fig. 5) was finished when around 25 kg of CO_2 was consumed per kg of the plant material while for Unit IIIa was around 60 kg/kg. Again, the reason for this could be found in a shorter solvent residence time, which was 0.45 min, 2.38 min, and 11.30 min in Units IIIa, IIIb, and IV, respectively.

The separation of the extract was slower in Unit IV with a lower solvent to feed ratio. Unit IV enabled the exhaustion of the plant material with a solvent to feed ratio of around 50.0 kg/kg and CO_2 consumption of ca. 750 kg, while Unit III enabled the exhaustion with a solvent to feed ratio of around 80.0 kg/kg. If the process of extraction from *S. marianum* seeds in Unit IV was performed until solvent to feed ratio was 150 kg/kg it would last for 1080 min and consume 2250 kg of CO_2 but it would not significantly contribute to an increase in extraction yield.

According to the presented results and the final extraction yields achieved in the laboratory-scale Unit (IIIb) and semi-industrial scale Unit (IV), it can be concluded that the extraction process based on the parameters determined in the lab-scale, was successfully transferred to a semi-industrial scale. These results are in agreement with the scale-up study reported by Prado et al. [49], who observed a similar shape of extraction curves, with yields being slightly higher for the pilot-scale compared with the laboratory scale. Besides extractor volume to plant material mass ratio [40], there are several parameters reported in the literature that should be maintained constant for the SFE process scale-up [4–14]. In general, there is not a single criterion for scale-up of the SFE process that can be effectively applied to all systems. Scale-up data can have big variations and sometimes there is no easy way to find a generalized conclusion between them. Therefore, more studies are required to get information about the applicability of SFE scale-up criteria for different types of raw materials [14].

4.4. Estimation of costs for industrial production of extracts

High manufacturing costs associated with SFE, resulting primarily from high initial investment costs (due to high-pressure operation/equipment costs) used to be a major obstacle to its wide use in industry. Since there have been significant developments in industrial-scale units, high-pressure equipment costs are lowering [28]. Still, it is important to estimate the cost of supercritical extract manufacturing. In order to estimate manufacturing cost (C_{OM}), the SFE process performed in Unit IV (ca. 40 L volume) was extrapolated to a high-pressure unit consisting of two extractor vessels of 500 L volume, each operated by 2 workers for an 8-hour shift (i.e. 8 workers for three shifts per day and one additional shift). Table 4 shows the calculated costs divided into fractions for different extraction times for the first year of extract production.

It can be seen that, under proposed conditions, the *S. marianum* extract production can reach 63.3–152.5 tons/year. Estimated fixed capital investment costs (F_{CI}) are constant regardless of extraction times due to the fixed cost of equipment and spent CO_2. In addition, if the unit is operated for 24 h at the same pressure and temperature conditions, utility costs (C_{UT}) will also remain constant. The cost that is also constant is labor price (C_{OL}) due to the assumption that the number of employees is not changing during one year. The duration of the extraction cycle has a crucial influence on productivity and consequently on economic viability. When SFE is performed for a relatively short time of 60 min (Table 4), only a small amount of the solute can be extracted and the influence of the raw material cost (C_{RM}) on C_{OM} is high. On the other hand, if the SFE process is performed for a relatively long time of 360 min, the impact of the C_{RM} on C_{OM} significantly decreases but the amount of produced extract per year is also decreasing.

The variation of the specific cost (*SC*) for the first year of extract production plotted vs. operating time for a unit consisting of 2 extractors having a volume of 500 L (denoted as Unit 2 ×500 L) is presented in

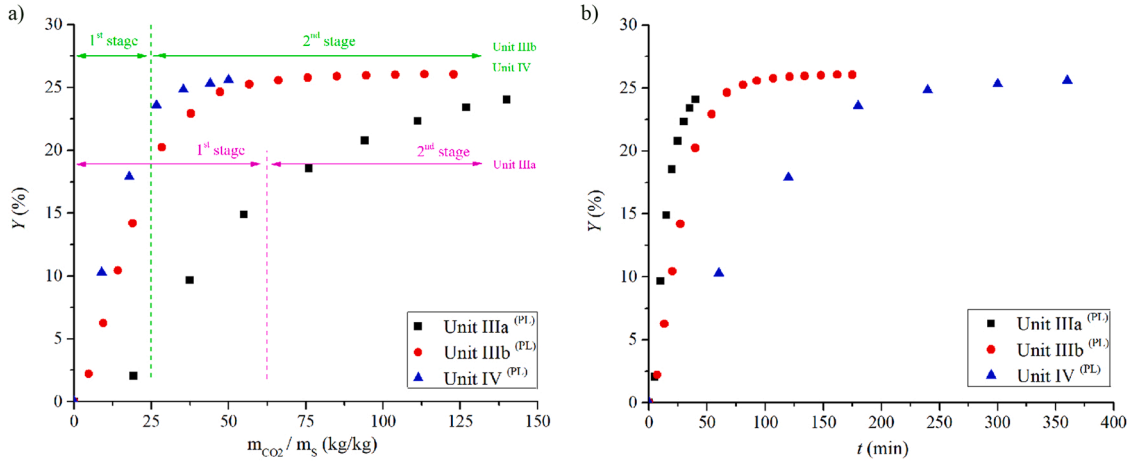

Fig. 5. Change of extraction yield for *S. marianum* seeds grown in Poland (PL): a) yield vs. solvent to feed ratio and b) yield vs. time.

Table 4
Values of estimated costs for a SFE industrial plant based on literature data for the first year of extract production.

	No	*t** (min)	*No*** (SFE/day)	$m_{EXTRACT}$ (kg/year)	F_{CI} (EUR/year)	C_{OL} (EUR/year)	C_{UT} (EUR/year)	C_{RM} (EUR/year)	C_{OM} (EUR/year)
2 extractors of 500 L 8 workers	*1*	60	24	152,509.50	1,276,567.50	93,440.00	1,649,904.02	3,712,500.00	7,238,924.66
	2	120	12	132,833.25	1,276,567.50	93,440.00	1,649,904.02	1,856,250.00	4,955,741.72
	3	180	8	116,721.00	1,276,567.50	93,440.00	1,649,904.02	1,237,500.00	4,194,677.70
	4	240	6	92,144.25	1,276,567.50	93,440.00	1,649,904.02	928,125.00	3,814,138.85
	5	300	4.8	75,200.40	1,276,567.50	93,440.00	1,649,904.02	742,500.00	3,585,815.54
	6	360	4	63,335.25	1,276,567.50	93,440.00	1,649,904.02	618,750.00	3,433,539.20
3 extractors of 1000 L 20 workers	*1*	60	24	305,019.00	3,207,980.00	262,800.00	3,299,808.03	7,425,000.00	14,884,183.80
	2	120	12	265,666.50	3,208,010.00	262,800.00	3,299,808.03	3,712,500.00	10,317,817.92
	3	180	8	233,442.00	3,208,000.00	262,800.00	3,299,808.03	2,475,000.00	8,795,689.88
	4	240	6	184,288.50	3,207,950.00	262,800.00	3,299,808.03	1,856,250.00	8,034,612.18
	5	300	4.8	150,400.80	3,207,920.00	262,800.00	3,299,808.03	1,485,000.00	7,577,965.56
	6	360	4	126,670.50	3,207,500.00	262,800.00	3,299,808.03	1,237,500.00	7,273,412.88

* t – operating time per one extraction
** No – theoretical number of extractions performed per day for one plant material loading

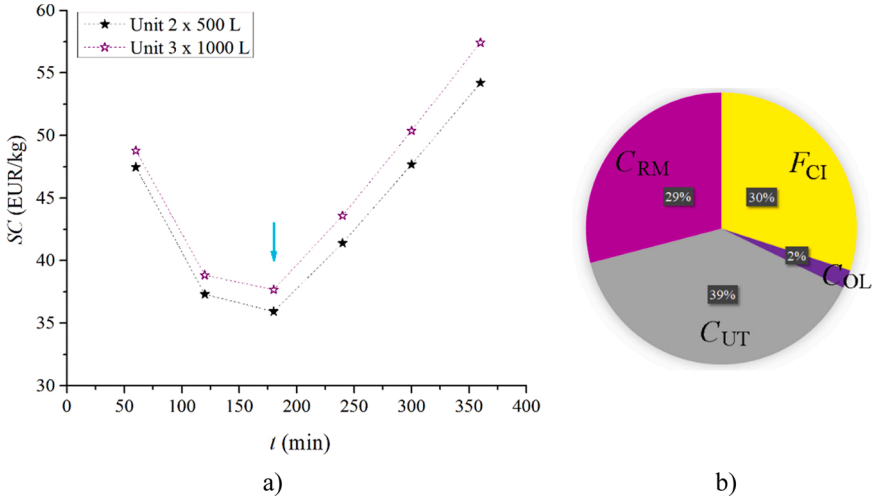

Fig. 6. Estimated costs for SFE from *S. marianum* seeds performed at 300 bar 40 °C: a) variation of specific cost with operating time and b) partition of estimated costs for the optimal SFE process in 2 × 500 L unit.

Fig. 6a. It can be seen that the estimated minimum value of *SC* for extract manufacturing is 35.94 EUR/kg. The industrial production of *S. marianum* extract, as proposed in this study, should be discontinued after 180 min to optimize the extraction process in terms of *SC*. The proposed model for cost estimation for industrial production of supercritical extracts was reported in the literature for different plant materials. Paula et al. [8] estimated C_{OM} of *B. dracunculifolia* operating at 300 bar and 50 °C to be in the range of 2.1–23.7 million EUR/year and calculated *SC* to be in the range of 155–544 EUR/kg. Aydi et al. [29] reported that the manufacturing cost of *Pistacia lentiscus* leaves supercritical extract is around 764 EUR/kg. Significantly lower *SC* values obtained in this study can be attributed to the higher extraction yields from *S. marianum* seeds.

A partition of estimated costs for the optimal industrial SFE process (when a single SFE lasts 180 min) conducted during the first year is presented in Fig. 6b. It can be seen that the highest partition in production costs of 39 % has the C_{UT}, followed by the F_{CI} (30 %). The investment fraction for the next years of production can be calculated by multiplying the total investment by the depreciation rate (assumed to be 10 % per year) [3,8,27–31]. This would result in a decrease in estimated costs of supercritical extracts production on a yearly basis.

Despite the fact that the literature model (Eq. 5) can be useful for the estimation of some production costs, there are some restrictions that the model does not consider such as leverage and bank expenses. In addition, at an industrial level, the time needed to unload, reload and pressurize an extractor may not be negligible if dealing with processes involving short extraction times. This is a key factor that should be correctly tackled to boost the productivity and profitability of SFE units [3]. It is not possible to perform a 24/7 continuous SFE process with large-scale units consisting of two extractors that last shorter than 2 h. The reason for this is the time necessary for loading/removing/re-loading of tones of plant material in an extractor, as well as heating, pressurizing, and depressurizing of the extractor. The time necessary for this handling of plant material can be around 1 h per extractor or even longer. In addition, the calculation of labor cost based on 2 workers for 8-hour shifts (in three shifts) considers minimal demands. The ideal number of workers for operating the proposed industrial scale unit could be 15 (2 workers per shift, 5 teams of 2 workers, and 5 supervisors of teams). Calculation of this cost should also include necessary holidays, sick leaves, as well as supervisors' salaries. Besides mentioned, the waste treatment cost is questionable. Although it can be neglected due to the possible reusability of exhausted plant material, still cost of workers and vehicles necessary for the transport of exhausted plant material should be also considered. Therefore, to improve estimation, costs were also calculated for a high-pressure unit consisting of three extractors with a volume of 1000 L (having a price of 3,200,000 EUR [31]) operated by 20 workers (15 manual workers and 5 supervisors working in 5 teams). C_{OM} was calculated taking into account that high-pressure units work 330 days. In addition, C_{OL} was calculated for 365 days taking into account holidays for workers and that 3 teams/-shifts will operate the SFE process during one day, as well as higher wages for supervisors (6 EUR/h). It can be seen that estimated C_{OM} was

around 2-fold higher compared with the smaller unit operated by fewer workers (Table 4). However, *SC* values are comparable (Fig. 6a) due to the larger amount of produced extract. In addition, a partition of estimated costs for the optimal SFE process in 3×1000 L unit was not significantly different compared with 2 × 500 L unit.

5. Conclusion

This study presented for the first time the scale-up of the SFE process from *S. marianum* seeds by in situ study (extractor vessels ranging from 0.28 to 40 L) as well as by theoretical model (for two 500 L extractor vessels). First, it was determined at the laboratory scale that the extraction yield increases significantly with increasing pressure from 100 to 300 bar for the SFE process performed at 40 °C and 80 °C. Further, it was shown that the construction of a high-pressure unit on a laboratory scale has a significant effect on the SFE process. It determined the packing of plant material in the extractor, CO_2 flow, and conditions for extract collection, leading to variation in extraction yield from 11.9 % to 18.0 % for *S. marianum* seeds grown in Serbia. Although the design of a high-pressure unit had a significant effect on the kinetics of the SFE process, its effect on the content of dominant compounds (fatty acids) in extracts was negligible. Selected pressure, temperature, ratio of extractor volume to plant material mass, and solvent to feed ratio, were applied for scale-up from 0.56 L to 40 L unit using *S. marianum* seeds grown in Poland. Scale-up study for selected criteria showed a good agreement between laboratory and semi-industrial scale units resulting in extraction yields up to 26 %. Finally, the literature model for estimation of production costs on an industrial scale, based on the results of the semi-industrial scale unit, showed that the optimal SFE process from *S. marianum* seeds should last 3 h and will result in a price of 35.9 EUR for 1 kg of extract. This study provided valuable data that could be used for SFE processes optimization and scale-up to industrial-level production.

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

Data will be made available on request. The data presented in this study are available on request from the corresponding author.

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