# Sub- and supercritical fluid extraction of bioactive compounds from plants, food-by-products, seaweeds and microalgae – an update.

Rocío Gallego, Mónica Bueno, Miguel Herrero*

Laboratory of Foodomics, Institute of Food Science Research, CIAL, CSIC, Nicolás Cabrera 9, 28049 Madrid, Spain.

*Corresponding author:

M. Herrero, Laboratory of Foodomics, Institute of Food Science Research, CIAL, CSIC, Nicolás Cabrera 9, 28049 Madrid, Spain, e-mail: m.herrero@csic.es, Tel: +34 910 017 946.

## TABLE OF CONTENTS

**Abstract**

Following our previous reviews, this manuscript presents an updated perspective on the use of compressed fluids, mainly under sub- and supercritical conditions, for the extraction of bioactive components from natural matrices covering the period from 2015 to present. These extraction technologies might have an important role in the development of sustainable and efficient extraction processes to cope with the high demand of natural bioactive compounds. Moreover, more complex approaches based on process integration, intensification and the development of sequential valorization chains are being increasingly developed. Most recent and interesting applications grouped according to the type of natural material used (plants, seaweeds, microalgae and food-related by-products) are described and critically commented. Furthermore, we discuss the potential future outlooks related to this field in agreement with our own experience.

**Keywords:** Algae; Bioactive compounds; Compressed fluids; Food by-product; Green extraction; Microalgae; Nutraceutical; Plant; Subcritical water extraction; Supercritical fluid extraction

## 1. INTRODUCTION

Since we firstly reviewed the research performed on this field back in 2006 [1], a lot has changed and evolved. However, one thing still remains at the bottom of this topic: the interest on functional ingredients from natural sources that could be potentially used in the food industry in an effort to improve consumers' health and well-being. Indeed, the number of research projects and published papers focused on the relationship between food and food ingredients and health do not stop growing year after year [2-4]. As a consequence, the search for natural compounds that could provide with a biological activity is still a hot-topic.

There are important natural sources of bioactives that could be grouped into plants, food and agricultural-related by-products, and algae, including seaweeds and microalgae. During these last years, the interest in plants as potential natural sources is intact, as new species are being explored. However, the other two groups have increased their relative importance nowadays with respect to the past. One of them is considering agrifood by-products as sources of valuable compounds [5-7]. With the advance on environmental awareness, much effort is being centered on developments related to circular economy and bioeconomy. Under these perspectives, by-products, which were often underestimated and underused, are now valorized in order to obtain high added-value products at the same time that food wastes are reduced. As described in the present review, a good number of applications have been recently developed in order to produce an efficient valorization of food-related by-products, which are demonstrated to be important sources of valuable compounds.

The other group of sources is formed by algae, either seaweeds or microalgae [8]. Whereas the marine environment is an understudied source of bioactives, the use of these organisms is even more interesting considering that they can be cultivated and grown for a variety of uses. Among these uses, the attainment of high added-value compounds is found. Besides,

there are species that do not actually possess any commercial value that could be, consequently, better used by obtaining bioactive compounds from them.

At present, the use of the mentioned natural sources to obtain bioactive compounds cannot be separated from the use of appropriate, environmentally friendly, advanced extraction techniques and processes. In this regard, the extraction processes developed should comply with the Green Chemistry principles related to extraction [9]. This is an aspect that has also significantly evolved in the last 10 years. Compressed fluids-based extraction techniques are among those that may fulfill the criteria to be considered suitable under the mentioned perspective. Sub- and supercritical extraction methods, mainly characterized by pressurized liquid extraction (PLE), gas-expanded liquids extraction (GXL) and supercritical fluid extraction (SFE) are efficient tools to extract bioactives from natural sources. Besides, all these techniques may be scalable and provide interesting advantages over the conventional extraction protocols, while they have also the possibility to be coupled to other processes within a biorefinery approach. This latest characteristic is very interesting, as nowadays the efforts focused on the development of biorefineries in order to minimize or completely eliminate any wastes related to agri-food products are increasing. Readers interested on gaining deeper insight on the technical aspects of these extraction tools are referred to other previous reviews already published [10,11].

Having all these ideas in mind, the main goal of the present contribution is to provide an updated overview on the use of compressed fluids-based extraction techniques, mainly PLE and SFE to obtain bioactive compounds from natural sources from 2015 to present, following our previous review [11]. The most notable applications showing major technological and methodological advances are highlighted and critically discussed. Moreover, future needs and trends are commented.

## 2. PLANTS AS A SOURCE OF BIOACTIVES

Compressed fluids-based extraction techniques, including sub- and supercritical fluid approaches have been widely employed for the extraction of bioactive compounds from plants. These organisms contain a large amount of different metabolites, including phenols, essential oils, proteins, terpenoids and flavonoids, among others, that are considered bioactive components. In this section, recent and remarkable studies about the recovery of bioactive compounds from plant material will be highlighted. Other recent reviews can be consulted for the extraction of specific and non-specific compounds from different plant material, including polyphenols and phenolic compounds [12-14], essential oils [15], pigments [16], phyosterols [17], and other bioactives [18-22].

One of the most studied extraction techniques when using plant materials is SFE. Some of the most recent and remarkable applications of SFE in plants are listed in Table 1. As it can be observed, the vast majority of target compounds using this technique are non-polar or mid-polar compounds such as lipids, essential oils and carotenoids. This is obviously due to the fact that supercritical $CO_2$ ($scCO_2$) is the preferred solvent for the extractions, due to the advantages that it possesses [46]. The use of $CO_2$ is limited by its low polarity, although SFE processes can be aided by a co-solvent in order to extract more polar compounds.

In general, vegetable matrices are very complex and many techniques are usually performed before or during the extraction itself to allow a better recovery of the bioactives. One of the most useful pretreatments for the extraction of compounds is the use of enzymes, which are able to break the plant cell wall, producing an increase in mass transfer rate. As an example, Lenucci et al. [33] used glycosidases before $scCO_2$ extraction of lycopene from freeze-dried tomato, reaching up to 153% of this carotenoid and 137% of lipid concentration compared to the control process using only $scCO_2$ extraction. An interesting point of this work is the addition of hazelnuts seeds as a co-matrix of the raw material, which could improve the

113 $scCO_2$ diffusion and increased the total lycopene yield in the final extract. Another example
114 of the use of enzyme-assisted SFE (EAE-SFE) was performed by Krakowska et al. [31].
115 Here, a commercial enzyme preparation containing xylanase, β-glucanase, cellulase,
116 amylase and protease, responsible for the degradation of plant cell walls, was added to
117 *Medicago sativa* leaves. After optimization of the extraction parameters (68 °C, 20.5 MPa
118 and 15.5% of the ethanol as co-solvent), an increase of total phenols content and
119 antioxidants was reached, compared to the control (without enzymatic treatment) and the
120 conventional extraction method.
121 Furthermore, the use of a sub- or supercritical extraction step can also be used to improve a
122 subsequent extraction, as a combined extraction process. This concept was performed by
123 Babova et al. [23], who extracted anthocyanins and other phenolic compounds from
124 bilberries (*Vaccinium myrtillus*) using SFE before a PLE with aqueous ethanol as co-solvent.
125 In their work, a multistep supercritical/subcritical extraction was carried out at 2.5 MPa and
126 40 °C for a total of 5 h and they could selectively obtain specific compounds such as
127 cyanidin-3-O-glucoside or cyanidin-3-O-arabinoside, which were demonstrated to have a
128 high antioxidant activity.
129 It is well-known that the modification of the variables (pressure, time, feed and $CO_2$ flow
130 rate, use of co-solvent, among others) can dramatically affect the composition of the final
131 extracts [47]. As an example of this concept, Wei et al. [32] carried out a complete study of
132 the effects of modulating some extraction parameters such as dynamic extraction time, $CO_2$
133 flow rate, co-solvent proportion, and extraction pressure and temperature, in the recovery of
134 triterpenic acids from *Hedyotis diffusa* and *Hedyotis corymbosa*. Just to mention some of
135 them, in terms of dynamic time, a longer time increased the extraction yield of the extracts
136 although, after some point the increase of extraction yield was minimal since there is no
137 more compound to extract from the matrix. This behavior was also previously corroborated

138 in other vegetable materials [48,49]. Another important parameter that should be optimized
139 is $scCO_2$ flow, as it was comprehensively explained by the authors [32]. They showed that a
140 really low $scCO_2$ flow leads to an insufficient contact and thus, insufficient extraction of the
141 compounds whereas an extremely high $scCO_2$ flow can make the $scCO_2$ flows around the
142 matrix, limiting the contact between the solvent and the target compounds.
143 The modification of the extraction parameters affects not only the amount of extractable
144 compounds but also can alter the composition of the extracts, giving an extra selectivity
145 within the process. In this sense, Bayrak et al. [28] studied the addition of methanol as co-
146 solvent of a SFE process (35 °C, 24.7 MPa, 1.5 mL $min^{-1}$ $scCO_2$) in which colchicine and
147 other derived-compounds were extracted. After the incorporation of 3 % (v/v) of methanol
148 as co-solvent, they obtained an almost colchicine-pure extract from *Colchicum speciosum*,
149 although the extraction yield was lower than without using co-solvent. These results show
150 the potential and selectivity that can offer this extraction technique due to the different
151 extraction conditions that can be modulated depending on the target compound.
152 On the other hand, PLE has also been widely applied for the recovery of bioactives from
153 vegetable matrices. Some representative applications of this technique are shown in Table 1.
154 In comparison with SFE, pressurized liquid extraction is more flexible in the use of solvents.
155 The most common ones for the extraction of natural sources are water (which is named as
156 subcritical water extraction, SWE), ethanol, methanol or ethyl acetate, and their mixtures.
157 As these solvents have different polarities, this technique covers a great range of compounds
158 that can be extracted, from very polar components (such as sugars or proteins) to mid/non-
159 polar compounds (such as carotenoids and lipids).
160 The use of pretreatments is not limited to foster a weakening on cell wall structure but also
161 can be used to remove some components of the samples that hamper the extraction process
162 of the target components. For instance, Castejón et al. [35] achieved a great oil extraction

163 from chia (*Salvia hispanica* L.) seeds using PLE, after a pre-treatment based in ultrasounds,
164 in which a large amount of mucilage was removed from the seeds. This way, optimum
165 conditions for the PLE extraction using ethyl acetate or hexane as extracting solvent, 90 °C
166 and only ten minutes of static extraction time, were obtained, allowing the recovery of
167 interesting compounds such as α-linolenic acid, tocopherols and tocotrienols.
168 Many researches are not only focused on the extraction of plant components but also in the
169 biological activity and/or the application of those extracts as complex mixtures. For
170 instance, Švarc-Gajić et al. [37] characterized ginger (*Zingiber officinale*) extracts obtained
171 by SWE (150 °C, 5 MPa for 60 min), and both antimicrobial and cytotoxic activities were
172 observed for several cell lines in subcritical extracts. A cytoprotective activity against
173 oxidation was showed by several immature fruit extracts obtained by SWE using 100 °C as
174 extraction temperature and pressures up to 1.5 MPa [36]. Also, a great amount of
175 polyphenols was found in the aqueous extracts, which could be responsible of the mentioned
176 activity, with the highest content in grape fruit extract. Another example of application of
177 PLE extracts was given by López-Padilla et al. [40]. They studied the antioxidant activity of
178 some PLE extracts from *Vaccinium meridionale* Swartz in order to add it in beef burgers,
179 obtaining an optimum phenol-rich extract using a mixture of ethanol:water (1:1), 200 °C and
180 only 15 min static extraction time. Thus, the idea of introducing this natural extract to
181 control the oxidation of beef burgers could be an alternative to the use of synthetic
182 antioxidants which are commonly used by food industries.
183 Depending on the extraction conditions and the chemical characteristics of the target
184 compound, sometimes it is difficult to obtain pure extracts, and a subsequent fractionation or
185 purification steps must be done. Indeed, this is one of the most promising research lines in
186 extraction process design and application. Thus, the integration of extraction processes is
187 gaining more and more relevance. One of the most common techniques to purify extracts is

188 the coupling of a sub- or supercritical extraction (or another extraction technique) and the
189 fractionation using supercritical antisolvent fractionation (SAF). Using SAF, compounds
190 will precipitate depending on their polarity and the polarity of the system itself. The
191 continuous contact of a liquid extract (i.e PLE extract dissolved in ethanol/water) with
192 pressurized $CO_2$ dissolves the less polar compounds in the extracts and can be separated
193 from the more polar compounds, which precipitate within the extraction cell. Torres et al.
194 [50] reviewed some applications of SAF for the fractionation of plant extracts.
195 An example of this integrated process was given by Villanueva-Bermejo et al. [51] who
196 carried out a SAF process starting from an ultrasonic-assisted ethanolic extract from yarrow
197 (*Achillea millefolium*) L. Figure 1 shows a schematic diagram of the SAF precipitation cell
198 used. Within the range of 10 and 20 MPa, the fractions obtained were richer in terms of
199 phenolic compounds compared to the original extract. Going even further using the same
200 approach, Villalva et al. [52] studied different conditions of SAF process in order to
201 determinate the biological activities of the fractions. Interestingly, they obtained two well-
202 defined extracts, which presented different activities: the separator-fraction with higher anti-
203 inflammatory activity and the remaining fraction (precipitated within the vessel), rich in
204 phenolic compounds with higher antioxidant activity.
205 Another approach of integrated process was developed by Sánchez-Camargo et al. [39]; in
206 this case, PLE and SAF were integrated to obtain phenolic-rich extracts from rosemary in
207 order to increase the bioactivity of the extracts. After obtaining a PLE extract using optimum
208 conditions (150 °C, 10 MPa, ethanol/water (80:20) and 20 min as extraction time)
209 previously determined, a second optimization of SAF step was performed. Best results were
210 achieved using 10 MPa, 50% (v/v) of water in the feed solution (PLE extract) and a
211 feed/SC-$CO_2$ mass flow ratio of 0.025.

As there are many different products that can be extracted and valorized from a single matrix, the concept of biorefinery has emerged in the last years. As it is well-known, this concept relies on the application of a sequential process of extraction techniques, without the manipulation of the biomass, in which diverse compounds are effectively recovered. Table 1 can be consulted for some representative examples of biorefinery processes for plants. An interesting biorefinery approach was studied by Kraujalis et al. [45]. Here, a $scCO_2$ extraction of *Viburnum opulus* L. fruits was performed followed by a PLE using different solvents (acetone, ethanol and water) in order to obtain valuable compounds such as oleic and linoleic fatty acids, tocopherols, polyphenols and other antioxidants. Both steps were optimized to reach the highest concentration of those compounds. In the first case, at 57 MPa and 50 °C for 131 min and with a flow of 2.5 L $CO_2$ $min^{-1}$, extraction yields ranged from 6.6 to 19.1 %, depending on the raw material (whole berries, unwashed and washed berry pomace, respectively). The SFE residue was subsequently extracted using the mentioned solvents (at 70-120 °C, 10.3 MPa and three cycles of 5 min each) and all extracts presented strong antioxidant activity and a great amount of phenolic compounds.

A similar study was followed by Bendif et al. [44]. The Algerian *Thymus munbyanus* was extracted by SFE and then, by successive pressurized extractions using acetone, ethanol and water. In this case, the target compounds were phenolic compounds and antioxidants. As the matrix and target compounds are not similar, extraction parameters were also different. Thus, the SFE process was conducted at 70 °C and 45 MPa for 210 min, using 2 L $min^{-1}$ as $CO_2$ flow rate, whereas the second step were performed at 70 or 120 °C and 10.3 MPa for 15 min. Results showed that SFE extracts where rich in terpenoids, long chain hydrocarbons and tocopherols while PLE extracts contained a great amount of phenolic compounds and also a higher antioxidant activity in comparison with SFE extracts, being increased with solvent polarity.

Another example of fractionation was given by Santos et al. [42], who studied the antiproliferative activity of neem (*Azadirachta indica* A. Juss) extracts after a sequential PLE process. Here, they used hexane, ethyl acetate and, lastly, ethanol as solvents and a fixed temperature, pressure and solvent flow (25 °C, 10 MPa and 1 mL $min^{-1}$ respectively), obtaining extracts richer in terpenes when ethyl acetate was used as solvent. Furthermore, these extracts showed higher antiproliferative activity after several assays against human tumor cells, compared to the other extracts. A relevant issue was also accomplished in this study, since all neem extracts seemed to be more selective for malignant cell in comparison to normal cells. This fact could be a promising tool in further oncological studies.

## 3. EXTRACTION OF BIOACTIVE COMPOUNDS FROM FOOD AND AGRICULTURAL BY-PRODUCTS

The reduction of agricultural processing wastes and residues generated by the industry is a topic of utmost importance for sustainability. Food processing by-products are often still rich in bioactive compounds which, if properly extracted and recovered, can be valorized into valuable food supplements or in nutraceutical formulations, mitigating their environmental impact and also adding economic benefits. To recover bioactives from food wastes, environment-friendly processes such as sub- and supercritical fluid technologies using green solvents, in single or combined ways, are preferred. In the period covered by the present review, different applications were developed to extract several kind of bioactive compounds from agricultural by-products. Generally, SFE is suitable for extracting non-polar compounds while PLE or SWE are capable to extract polar and semi-polar compounds, as for any other natural matrix. Table 2 summarizes the extraction conditions employed in the most remarkable applications. For more in-depth information on the role of sub- and supercritical fluids in the reutilization of wheat residues [83], winemaking-related

wastes [84,85], coffee by-products [86], fruit [87-89] or olive oil [90,91] industries by-products, among others [92-95], readers are referred to these excellent reviews.

As already mentioned, extraction solvent and temperature are parameters that can give an extra selectivity within the extraction process. As an example, an anthocyanin- rich fraction was obtained separately from other phenolic compounds present in grape marc using a sequential PLE process changing the solvent and increasing the temperature in the second step [70] and juçara residues [55]. In the latter example, the PLE optimized solvent for the extraction of anthocyanins was employed as co-solvent in SFE. By using this approach, extracts were further enriched in anthocyanins. Another example was given by Ersan et al. [79], who were able to produce a selective extraction of gallantannins and flavonols while anacardic acids, sensitizing and possible allergenic substances, remained in the residue. When using aqueous methanol for control extraction, large amounts of total anacardic acids (67.5 g/kg dry pistachio hulls) were found in the extract. By employing SWE, substantially lower amounts of anacardic acids (<3 g/kg dry pistachio hulls) were extracted.

Generation of compounds that could arguably pose a risk for food safety, such as hydroxymethylfurfural, has been observed during SWE processes. This is the case of the extraction of polyphenols from grape pomace carried out at high temperatures [96]. The addition of ethanol (up to 15%) could reduce the process temperatures, thus, decreasing the generation of some Maillard reaction products with known cytotoxicity in grape pomace [72] or spent coffee grounds [82]. In addition, a resin purification of the extract with 80% of ethanol maintained the overall polyphenols recovery at the same time as hydroxymethylfurfural was eliminated (95%) from the purified extract retaining the antioxidant capacity of the crude extract between 60% and 88%, depending on the assay employed (DPPH and ORAC) [82].

286 Omega-3 polyunsaturated fatty acids (PUFAs) represent a very important class of bioactives
287 present in fish processing residues. SFE carried out with neat $scCO_2$ is the preferred
288 technique for PUFAs extraction. In general, temperatures from 30 to 60 °C and pressures
289 between 20 and 35 MPa were used. The main advantages of PUFAs extraction using SFE
290 are: 1) the significant enrichment of eicosapentaenoic acid (EPA) and docosahexaenoic acid
291 (DHA) that are related to prevention of heart-related diseases, 2) the better sensory
292 parameters (color and viscosity) of the oil obtained, and 3) a significant reduction of toxic
293 heavy metals extraction in comparison with conventional methods [97,98].
294 As it is obvious that optimum extraction conditions will vary depending not only on the
295 matrix but also on the target components, optimization of the extraction parameters using
296 experimental designs is widely employed. Furthermore, compounds recovered from
297 agricultural processing wastes possess some interesting bioactivities such as antioxidant,
298 anti-proliferative or anti-inflammatory with obvious advantages from the health and
299 economical standpoints. However, their diverse chemical structure mean that the extraction
300 conditions should be properly tuned. For example, one remarkable application of extracts
301 from by-products which combines both antibacterial and antioxidant activities could be their
302 addition in new food products as natural preservatives for reducing food spoilage and
303 therefore, prolonging food shelf life. Thus, new multi-analytical platforms and bio-based
304 directed methodologies have been developed to this aim. For instance, Ballesteros-Vivas et
305 al. [58] combined PLE, liquid chromatography and gas chromatography quadrupole time-of-
306 flight mass spectrometry, *in vitro* antioxidant assays and mathematical modelling tools for
307 guiding extraction optimization of withanolides from goldenberry calyces.
308 Regarding the anti-inflammatory activity showed by winemaking by-products extracts
309 obtained by PLE, Nieto et al. [73] reported that these phenolic-rich extracts act as effective
310 inhibitors of pro-inflammatory cytokines. Therefore, these PLE extracts could have a great

311 potential to be used as natural ingredients in the development of anti-atherogenic products.
312 Another interesting example was given by Ndayishimiye et al. [61] who studied the use of
313 citrus seeds oils as co-solvent for $scCO_2$ to enhance the carotenoids extraction from citrus
314 peels. However, the relevant fact was that the combination of both by-products has a
315 synergistic effect in the antioxidant activity of resulting oils.
316 In order to make the whole extraction more efficient, new approaches have been developed
317 coupling processes or integration of procedures within the same process. One example is the
318 coupling of ultrasound treatment and extraction in sequence or simultaneously. Sumere et al.
319 [63] corroborated that the simultaneous combination of ultrasound and pressurized liquid
320 extraction (UAE+PLE, Figure 2) is able not only to improve the extraction of phenolic
321 compounds from pomegranate peels but also to recover these faster (requires less cycles).
322 Different parameters including the ultrasound power and particle size, important to
323 determine the influence of the application of ultrasounds to assist the extraction process,
324 were optimized. Interestingly, they found that ultrasound power had no effect on the
325 extraction using small particles (0.68 mm) samples. In contrast, the effect was evident and
326 positive applying 480 and 640W ultrasound powers to large average particle size (1.05 mm)
327 samples.
328 There are other interesting published works on the extraction of polyphenols using
329 ultrasounds as pretreatment showing its versatility at the time of coupling to any technique
330 of pressurized fluids, for instance, from grape marc by UAE+SFE [71], from different
331 berries by UAE+PLE [74], or spent coffee grounds by UAE+SWH [81].
332 Nevertheless, sometimes the strong cell walls of the samples hamper to a certain extent the
333 efficiency of extraction. For this reason, the use of enzyme treatments, very high pressures
334 (>300 MPa) or the combination of both, provide better results in terms of recovery of
335 bioactive compounds [62]. However, enzymatic assisted extraction is not the only

biotransformation that enhances the release of bioactives from agricultural by-products. Recently, the fermentation process of orange pomace using the fungus *Paecilomyces variotii* was evaluated [60]. When the orange pomace was biotransformed, phenols extracted increased more than twice in SFE with $CO_2$ + 6% ethanol/water (9:1 v/v) and thus promoted the functional activity of antioxidants comparing with the non-fermented pomace.

The low stability of some bioactive compounds during their extraction, purification and storage has been increasingly a subject of interest. Under this topic, research is focused on new forms of processing with minimal degradation. A typical example in this regard is the coupling of compressed fluids extraction and drying processes. Firstly, a proper optimization of the PLE or SFE processes towards the extraction of target compounds should be done. Later on, the extracts attained are dried using Supercritical AntiSolvent (SAS). The technique is based in putting into contact an organic solution with $scCO_2$ in the same way as it was explained before for SAF. SAS method can also be used to encapsulate or co-precipitate target compounds by super saturation of the polymer/solute, leading to sub-micrometric particles with controlled size. Oliveira et al. [67] produced passion fruit seed oil particles encapsulated with the biopolymer, PLGA (poly(lactic-co-glycolic) acid). By using the selected SAS encapsulation conditions (35°C, $CO_2$ mass fraction between 92.5 and 95%, and a pressure of 9 MPa), they obtained spherical shape particles with an encapsulation efficiency from 67.8 to 91%. After an initial burst, the oil released raised gradually (until 24 h), followed by a uniform release up to 72 h, reaching up to 88% of entrapped oil released. These approaches are doubly valuable since they preserve the biological activities of the extracted compounds at the same time that are presented on an interesting form from an energetic point of view, considering that the drying step is usually regarded as very energy-demanding. There is even a trend to use the same equipment for PLE and SAS as the one

360 described by Zabot et al. [57] to extract flavonoids from onion wastes. In this way, wastes
361 and energy consumption are even more reduced.
362 Taking into account the industrial scale proportion of agricultural by-products, the scale-up
363 [59] and the economic evaluation [99] of the compressed fluid extractions should be studied
364 to assess the economic feasibility of the processes. For example, the software SuperPro
365 Design can be used to perform material and energy balance calculations for all process
366 streams, as well as to perform a project cost analysis, including capital and manufacturing
367 costs. In this sense, a PLE technique using ethanol for carotenoids extraction from pressed
368 palm fibers was evaluated [54]. The economic analysis showed that the cost of
369 manufacturing for this technique was 29.2 US$ $kg^{-1}$ extract for a 0.5 $m^3$ vessel capacity
370 while its selling price is higher than 667 US$ $kg^{-1}$ extract. These values can be obtained due
371 to its faster extraction time and higher extract productivity in comparison to conventional
372 techniques (45.1 US$ for Soxhlet extraction). The use of this kind of estimations is
373 interesting to know if an extraction is competitive compared to the selling price.
374 Another expensive procedure is the removal of water from by—products before extraction;
375 thus, an interesting approach is to find out which matrices can be processed in their native
376 state. In this sense, Ferrentino et al. [65] compared the phenol recovery and antioxidant
377 activity of freeze-dried, oven dried and fresh apple pomace. Total phenol content were
378 higher in dried samples (66-70%) in comparison to fresh pomace (58%); however, antioxant
379 values were significantly higher in fresh samples. This fact makes the extraction of fresh
380 apple pomace an industrial viable process since both time and money are reduced (avoiding
381 drying steps).
382 Considering the intrinsic nature of agro-industrial by-products, these have gained a special
383 attention of the scientific community in a circular economy perspective, and different
384 biorefinery approaches based on integrated processes have been developed [53,75,77]. For

385 instance, the combined used of high pressure extractions and hydrolysis with or without
386 enzymatic assistance has been studied to obtain value added fractions from olive pomace
387 [78], namely, oil, proteins, fermentable sugars and lignin (Figure 3). Moreover, the obtained
388 sugars were used to produce bioethanol.
389 Another interesting example dealing with a biorefinery approach is a two-step extraction
390 conducted to evaluate a sequential SFE process base on the use of neat $scCO_2$ and addition
391 of co-solvents (ethanol+ water) to extract lipids and phenolic compounds consecutively from
392 cranberry pomace [76]. Different compositions of ternary mixtures ($CO_2$ + ethanol + water)
393 were systematically evaluated in this work. The final molar ratio chosen was $CO_2$ + ethanol
394 + water 0.312:0.048:0.640. The inclusion of water had several advantages: fast and
395 quantitative recovery of the phenolic compounds and high anthocyanin concentration and
396 antioxidant capacity. The possibility of using low amounts of ethanol also reduces the cost
397 and environmental impact of the process. This work shows that the presence of water in
398 ternary compressed fluids leads to the *in situ* formation of carbonic acid which provokes a
399 decrease in pH. This decrease in turn, might have a stabilizing effect on the target
400 compounds and might also lead to higher diffusivities due to increased cell membrane
401 permeability resulting from the effect of low pH on cell membrane proteins.
402 Many of the above described examples are based on process integration achieved by the
403 combination of different unit operations, whereas process intensification is based on the use
404 of the same equipment, as described for the biorefinery of cocoa bean hulls [80] or mango
405 peel [66]. A nice example of a multipurpose equipment has been used to consecutively
406 extract different passion fruits seeds compounds using SFE and PLE. Several sequential
407 SFE processes were studied based on the use of neat $scCO_2$ with different densities by
408 changing temperatures and pressures (see Table 2) to produce fractions enriched on tocols
409 (tocopherols and tocotrienols), fatty acids and carotenoids [68], followed by a PLE to

recover phenols [69]. The use of this kind of approach shows how, by tuning the extraction parameters and coupling different techniques, a complete biorefiery of by-products can be obtained using the same system. Therefore, process intensification can be considered a way to optimize systematically the use of energy, capital or other benefits through the development of efficient techno-economical systems [100].

## 4. EXTRACTION OF BIOACTIVE COMPOUNDS FROM SEAWEEDS AND MICROALGAE

Marine sources, especially seaweeds and microalgae are still an untapped reservoir of bioactive compounds, since there are still thousands of different species that have not been studied yet, which have considerable potential to supply novel ingredients towards food and pharmaceutical industries. Other strains might also have potential for other uses, such as biodiesel production.

In addition, most micro- and macroalgae produce highly valuable metabolites such as fatty acids, proteins, pigments or polysaccharides with biological activities (antioxidant, anti-inflammatory, neuroprotective or antimicrobial activities) due to their adaptation to the extreme environments of light, salinity, and temperature [101]. That is why, during the last years, extraction of compounds from seaweeds and microalgae was a subject of growing interest. There are several updated reviews which can be consulted for the green extraction of these bioactives from seaweeds [102-105] and microalgae [106-108]. More compound-specific ones can also be found, i.e. lipids [109] carotenoids [110] or phenols [8].

A list of remarkable applications of compressed fluid extraction applied to these matrices are shown in Table 3. Some of them involve the use of $scCO_2$ as extraction solvent, or $CO_2$-expanded ethanol (CXE). In general, these techniques are commonly used for the extraction of non-polar or mid-polar compounds such as lipids, carotenoids and chlorophylls, since these matrices are rich in those compounds, as it happens for the rest of natural sources

436 described in the present review. On the other hand, pressurized liquid extraction in
437 microalgae is mainly focused on the recovery of carotenoids and lipids, since these bioactive
438 compounds are very appreciated in many industries such as oil, pharmaceutical or
439 cosmetics, while in macroalgae, research is mainly focused on phenolic compounds and
440 polysaccharides. A selection of the most remarkable studies about the recovery of bioactive
441 compounds from marine material are highlighted in this section.
442 Castro-Puyana et al. [126] studied the potential of the microalga *Neochloris oleoabundans*
443 as a natural source of bioactives. For this goal, they evaluated extracts obtained by PLE in
444 terms of *in vitro* antiproliferative activity using different colon cancer cell lines.
445 Interestingly, extracts with highest content of carotenoids (obtained at 100 °C, 10.3 MPa
446 during 20 min and ethanol as extracting solvent) showed also the highest antiproliferative
447 activity, specifically when carotenoids monoesters were in a higher concentration in the
448 extracts. These results leave the door open to new *in vivo* studies about the possible potential
449 of this microalga as a functional food ingredient or nutraceutical and the prevention of colon
450 cancer development. Another interesting example relating extraction and bioactivity was
451 given by Heavisides et al. [122], where the application of a definitive screening design-
452 based optimized PLE extraction combined with an untargeted metabolomics approach was
453 used for the identification of seasonal variations in both metabolome and bioactivity of the
454 macroalgae *Fucus vesiculosus*. The extracts were simultaneously screened for their *in vitro*
455 methicillin-resistant *Staphylococcus aureus* inhibitory activity, caspase-induced Panc1
456 cancer cell apoptosis and free radical scavenging activities. The greatest radical scavenging
457 and apoptotic activities against pancreas cancer cells were observed in the summer months,
458 which were attributed to high phlorotannin content, while antimicrobial activity was
459 produced year-round without a clear seasonal trend. This study highlights the significant

effect of the sampling month on the chemical composition and, therefore, the possibility to design different approaches to maximize the yield of specific bioactive compounds.

In light of the health and safety risks posed by commonly used organic solvents, nowadays, the use of green solvents is preferred for different reasons already mentioned here and comprehensively described elsewhere [135]. Even though the use of carbon dioxide in SFE is unquestionable, the use of other new green emerging solvents has been increased in PLE approaches. Deep eutectic solvents (DES) are obtained by mixing two or more organic compounds and the new solvent present a melting point lower than that of either individual components. DES are cheaper to produce than ionic liquids (ILs) but they have similar characteristics such as high thermal and chemical stabilities, negligible vapor pressure and wide solvating range, which make DES and ILs suitable as catalysts to enhance the yield and increase dissolution of polysaccharides [124,127] or phenolic compounds [128] from different seaweed matrices. Regarding biodegradation and sustainability of the extraction process, some researchers are investigating the use of bio-based solvents such as ethyl acetate or ethyl lactate for compressed fluid extractions of bioactives from microalgae [136], among other natural sources [35,38,137,138] since these solvents can be prepared from renewable sources (Figure 4). Another upcoming solvent is 2-methyltetrahydrofuran (MTHF), which was studied for the first time by Damergi et al. [120] as a new alternative solvent for the extraction of carotenoids from *Chlorella vulgaris*. MTHF is a green solvent derived from renewable resources (lignocellulosic biomass) and has the advantages to be biodegradable and easy recyclable. Using PLE and a mixture of ethanol/MTHF (1:1) as extraction solvent (at 110 °C for 30 min), they obtained promising results in terms of total carotenoids. Thus, MTHF appears to have the potential to be an alternative to n-hexane for the extraction of carotenoids due to its unique properties.

To illustrate the effect of the solvent in PLE processes, Otero et al. [123] investigated the selectivity of five solvents of different polarities (hexane, ethyl acetate, acetone, ethanol and ethanol:water 50:50) towards the extraction of lipids from *Fucus vesiculosus* by PLE. They observed that ethyl acetate is a selective solvent to enhance the extraction of long chain fatty acids including oleic, arachidonic and eicosapentaenoic acids (EPA), producing extracts that at least double the fatty acids quantity in comparison to the other solvents. However, the lowest ω-6/ ω-3 ratio was achieved with the most polar solvent (ethanol:water 50:50) with a value of 1.92, much lower than those recommended by FAO (ω-6/ ω-3 = 10) [139].

Parameters involving solvent-solute behavior are also studied by several researchers. In this way, Kwan et al. [130] studied the influence of some parameters related to solvatochromism (consult Maiwald and Schneider work [140] for more information about this concept) in order to select the best conditions to extract triacylglycerides (TG) and astaxanthin from *Haematococcus pluvialis* using SFE. Interestingly, results showed that it was possible to separately extract these compounds by changing the density of the $scCO_2$ with pressure: at low densities, TG were recovered (up to 78 %) with only 1 % of astaxanthin and, at high densities, over 70 % of astaxanthin were extracted whereas the amount of TG were less than 5 % of total TG in the microalga. This fractionation process can be also considered among the biorefinery platform, since different fractions are obtained by coupling diverse procedures.

Astaxanthin recovery from *H. pluvialis* have been widely studied using all kind of compressed fluid extraction techniques, since this carotenoid is a high-value compound and its purification is not easily achieved. In contrast to the study mentioned before, Cheng et al. [114] achieved a great recovery of astaxanthin using low pressures (8 MPa in comparison to 48 MPa) in SFE. In this case, the addition of ethanol as co-solvent notably reduced

508 extraction time from 15 h to 30 s, showing once again, the huge importance of the
509 optimization of extraction parameters for the recovery of bioactives.
510 In the search for an appropriate solvent or bio-solvent for obtaining good selectivity, Hansen
511 Solubility Parameters (HSP) help to predict an estimation of the solubility of the solute in
512 the solvent, as it was already set by many authors [141,142]. In this sense, Sánchez-
513 Camargo et al. [121] compared several green solvents in subcritical (water, ethanol and ethyl
514 lactate) and supercritical ($scCO_2$ and $scCO_2$ with different proportions of ethanol) conditions
515 to extract phlorotannins from *Cystoseira abies-marina* seaweeds. Theoretically, pure ethanol
516 at low temperature (25 °C) was shown to be the most suitable solvent. Nevertheless, it was
517 experimentally demonstrated using a comprehensive two-dimensional liquid
518 chromatography (LC×LC-MS/MS) method, that pure ethanol at 100 °C in subcritical state
519 (10.3 MPa) showed the highest selectivity to extract phlorotannins among different solvents
520 studied. Similarly, a recent study for the selective extraction of β-carotene from *Dunaliella*
521 *salina* was carried out by Tirado et al. [112]. Using HSP, ethanol (with 5 % mass fraction)
522 was predicted as the best co-solvent for SFE to achieve this goal (up to 25 mg of β-carotene
523 per g microalgae, in comparison to 6 mg per g microalgae that was obtained using only
524 $scCO_2$).
525 The vast majority of studies for the recovery of bioactives from macro- and microalgae
526 involve a drying pre-treatment of the raw material prior extraction in order to increase the
527 direct contact between solvent and sample, although this step highly increases costs and
528 sometimes can damage the sample. To avoid this situation, some researchers studied the
529 influence of the water content during extraction process. For instance, Mouahid et al. [113]
530 investigated not only the influence of the water content but the drying mode applied in
531 *Dunaliella salina* for the recovery of carotenoids by SFE, concluding that at certain
532 conditions (60 °C and 20-40 MPa) a water content of 23 wt.% helped to recover a higher

533 content of β-carotene (major carotenoid in *D. salina*) without affecting the extraction
534 process. Another curious approach was performed by Reyes et al. [116], who effectively
535 extracted carotenoids from *Neochloris oleoabundans* paste (containing around 70-80 %
536 water) mixing this paste with adsorbents as supporting media. After comparing different
537 adsorbents with diverse adsorbent capacities, results showed that chitosan allowed the
538 higher recovery of carotenoids.
539 As discussed in the previous sections, novel technologies such as ultrasound, and enzyme-
540 aided extraction are used as powerful tools in providing high extraction of bioactive
541 compounds. Although not all the examples are successful, they leave the way open for
542 future practical applications. For instance, EAE process using either proteases or
543 carbohydrases before PLE did not improve the attainable results in terms of total
544 polyphenols and phlorotannins recoveries from the seaweed *Sargassum muticum* [129],
545 suggesting that more selective enzymes directed to algal polysaccharides from the cell wall
546 would be required to selectively release these compounds. Another interesting study using
547 enzymes was carried out by Shomal et al. [118]. Here, they used immobilized lipases during
548 the supercritical $CO_2$ extraction of microalga *Scenedesmus* sp. for a simultaneous extraction
549 and reaction of the oils to produce biodiesel. After the optimization of some parameters, a
550 maximum recovery of biodiesel (up to 19.3 % of yield) was achieved at 35 °C and 40 MPa
551 during 6 h, using a specific amount methanol for the catalytic reaction (methanol:oil molar
552 ratio of 8:1). Unfortunately, this yield is lower than the one obtained with separate extraction
553 and reaction processes, but further studies and optimization of this one-step process could
554 simplify the overall biodiesel production by microalgae.
555 In general, this type of studies also involves a comprehensive characterization of the extracts
556 using modern techniques for the identification and quantification of the bioactive
557 compounds such as high performance liquid chromatography (HPLC) or gas

chromatography (GC) coupled to mass spectrometry (MS). However, new and more sophisticated equipment, which allow a simultaneous extraction and characterization of compounds, are emerging in the last years. As an example, Abrahamsson et al. [111] developed a SFE-UV/Vis-ELSD equipment (Figure 5) capable of detecting carotenoids, chlorophyll A, ergosterol and total lipids from a microalgae extract obtained by SFE. This approach not only simplifies the whole extraction-identification-quantification process but also avoid the possible damage that extracts can suffer during these steps.

Besides, common one-step extraction procedures, SFE and PLE are being studied as potential unit operations to be employed in biorefinery processes involving algae. As can be observed in Table 3, microalgae are among the organisms with higher potential in this regard. In order to increase, even further, the economic competitiveness of these processes, some researchers have applied the innovative concept of $CO_2$ as a switchable solvent for the biorefinery valorization of algae biomass [119]. A switchable solvent is a solvent that can be reversibly converted from one form to another, where the two forms differ in one or more physical properties [143]. In this regard, carbon dioxide-expanded liquids (CXLs) was defined as a type of switchable solvent that is half way between pressurized liquids and supercritical fluids by increasing the amount of compressed $CO_2$ [144]. Just to highlight some recent examples, Gilbert-López et al. [134] achieved the fractionation of the microalga *Scenedesmus obliquus* into several high-value compounds such as total phenols, carotenoids, proteins and sugars. The process began with pure $scCO_2$, the next step involved gas expanded liquids (75 % ethanol and 25 % $scCO_2$) and after that, a PLE was performed using water as solvent. Thus, non-polar compounds (such as TG) were extracted in the first step whereas mid-polar compounds and polar compounds (almost pigments) were extracted in the following steps. A similar approach was carried out by Sánchez-Camargo et al. [132]. In this study, previous high-pressure homogenization (HPH) prior extraction was performed to

583 *Nannochloropsis gaditana* biomass in order to break or weaken the cell wall and to foster a
584 better extraction of its components. After that, a two-step extraction was carried out: firstly,
585 a SFE using neat $scCO_2$ was performed and non-polar lipids and pigments were recovered.
586 In a second step, a PLE process was optimized in order to obtain extracts with antioxidant
587 activity. Optimum extracts were obtained using pure ethanol at 170 °C for 20 min,
588 containing carotenoids, chlorophylls and polar lipids.
589

590 **5. CONCLUSIONS AND FURTHER PERSPECTIVES**

591 As shown in the previous sections, the use of compressed fluids-based extraction
592 technologies still retains a lot of potential for the efficient extraction of bioactive compounds
593 from very different natural matrices. Although some important leaps forward have been
594 produced in the last years and the use of these techniques is mature, there is still room for
595 improvement in different aspects. One of them is linked to the knowledge about the natural
596 materials. In fact, the attainment of new relevant information on the chemical composition
597 of the natural sources is of utmost importance. As a previous step to process design, to
598 precisely know which components and in which amount are present in the different matrices
599 help to increase the efficiency of the later on applied extraction process. Different
600 parameters directly related to sample composition affect to the extraction, as shown in
601 sections 2-4, such as moisture, carbohydrate or lipid content to name a few. For this reason,
602 it is always interesting to acquire as much as possible information about the sample
603 chemical composition in order to be able to propose the most suitable extraction approach in
604 order to not only maximize the extraction of the target bioactive compounds, but also to
605 produce a recovery of other components in parallel that could also be of interest.
606 It is clear that the natural matrices described in this review have been demonstrated to be
607 feasible alternatives for the production of bioactive compounds. However, further search for

608 new natural sources (plant and algae species, other underexploited by-products) is foreseen
609 in the future research on this field. The marine environment can still provide with new
610 relevant discoveries. Moreover, microalgae culture conditions could be further fine-tuned in
611 order to increase the amount of particular bioactive compounds within their chemical
612 composition. At the same time, new interesting species could be cultured under controlled
613 conditions at an industrial level. These advances, although not directly related to compressed
614 fluids, will have an impact on the design of processes. Likewise, multiple agri-food by-
615 products are still valorizable should the correct approaches are applied. Thus, further
616 development in these areas will significantly influence the appearance of new applications
617 of compressed fluids-based extraction technologies.
618 Concerning new designs of processes, novel green solvents will have a lot to say in the
619 future. Green solvents already proposed, such as subcritical water, some ionic liquids, as
620 well as other solvents less used, such as DES, switchable solvents should be further studied
621 in order to perfectly understand how they could be efficiently applied to the extraction of
622 bioactive substances in a high-pressure environment. This is also the case of other food-
623 grade solvents, such as ethyl lactate or d-limonene, which use could be of great interest in
624 some applications. Moreover, it could be also interesting to fully study how these can be
625 combined with supercritical $CO_2$ in order to foster the extraction and purification of
626 bioactives. In fact, the combination of process unit operations into more complex combined
627 processes can be considered as an important future line of research. There are a wide array
628 of possibilities going from combination of extraction processes to produce purification of
629 bioactive compounds as well as generating valuable co-products from the natural material
630 extracted, to the use of other technologies in parallel. Among them, the use of enzymes has
631 already been explored as above described [31,33,62,78,118], although their potential has not
632 been fully established yet. The use of enzymes at pressurized conditions could theoretically

help to combine extraction and modification processes in order to produce a particular compound in higher extent. Ultrasounds could be also employed to increase the extraction rate in sub- and supercritical extraction processes. The effect that ultrasounds may infer in the samples is well-known. Their coupling during a particular extraction protocol could effectively help to weaken the matrix structure favoring and increasing the mass transfer rate, thus, improving the extraction efficiency, as some applications have already shown.

Other combined processes that are worth to be further studied are related to the coupling of drying steps to the extraction protocols. Some methods based on the use of compressed fluids have been developed and applied to this field, including supercritical antisolvent (SAS), rapid expansion of a supercritical solution (RESS) or solution-enhanced dispersion by supercritical fluids (SEDS) [38,39,57,67,145]. Moreover, other alternatives combining the extraction with subcritical water and particle formation on-line have been presented [146-148], although their wider used could be expected considering the benefits of applying those approaches. Moreover, these developments could be important from the ever more relevant field of biorefinery since some of them have the potential to be scaled up and applied in combination with other technologies in order to establish complete valorization chains. In fact, all the mentioned future advances could be applied to biorefineries, although the combination of different unit operations into wider platforms that operate in a continuous or semi-continuous mode is still an important challenge.

Lastly, aspects related to scale-up of these developments should be further studied. Indeed, most of the processes published covered by this review are at a lab or relatively small scale. Once the concept is demonstrated, scale-up and integration has to be performed, also including techno-economical assessment and life-cycle analysis. At the end, any promising process or alternative based on the use of compressed fluids for the attainment of bioactive compounds from natural matrices has to demonstrate its feasibility at a larger scale in order

to transfer these technologies to the industry. Only by doing this, the environmental and efficiency-related advantages that compressed fluids may provide will effectively achieved in a context in which circular economy may accomplish a decisive leap forward.

**ACKNOWLEDGEMENTS**

M.B. acknowledges MINECO for the "Juan de La Cierva-Formación" postdoctoral grant FJCI-2016-30902. Authors thank projects ABACUS (Algae for a Biomass Applied to the produCtion of added value compounds - funded by the Bio Based Industries Joint Undertaking under the European Union's Horizon 2020 research and innovation programme under grant agreement No 745668), AGL2017-89417-R (MINECO, Spain) and i-LINK+ 1096 (CSIC, Spain) for financial support.

## 6. REFERENCES


[1] M. Herrero, A. Cifuentes, E. Ibañez, Sub- and supercritical fluid extraction of functional ingredients from different natural sources: Plants, food-by-products, algae and microalgae: A review, Food Chem. 98 (2006) 136–148. doi:10.1016/j.foodchem.2005.05.058.

[2] R. Perez-Gregorio, J. Simal-Gandara, A Critical Review of Bioactive Food Components, and of their Functional Mechanisms, Biological Effects and Health Outcomes, Curr. Pharm. Des. 23 (2017) 2731–2741. doi:10.2174/1381612823666170317122913.

[3] J. Premkumar, R. Thottiam Vasudevan, Bioingredients: functional properties and health impacts, Curr. Opin. Food Sci. 19 (2018) 120–128. doi:10.1016/j.cofs.2018.03.016.

[4] C. Caleja, A. Ribeiro, M.F. Barreiro, I.C.F.R. Ferreira, Phenolic Compounds as Nutraceuticals or Functional Food Ingredients, Curr. Pharm. Des. 23 (2017) 2787–2806. doi:10.2174/1381612822666161227153906.

[5] M. Atef, S. Mahdi Ojagh, Health benefits and food applications of bioactive compounds from fish byproducts: A review, J. Funct. Foods. 35 (2017) 673–681. doi:10.1016/j.jff.2017.06.034.

[6] H. Kowalska, K. Czajkowska, J. Cichowska, A. Lenart, What's new in biopotential of fruit and vegetable by-products applied in the food processing industry, Trends Food Sci. Technol. 67 (2017) 150–159. doi:10.1016/j.tifs.2017.06.016.

[7] K. Kumar, A.N. Yadav, V. Kumar, P. Vyas, H.S. Dhaliwal, Food waste: a potential bioresource for extraction of nutraceuticals and bioactive compounds, Bioresour. Bioprocess. 4 (2017) 18. doi:10.1186/s40643-017-0148-6.

[8] L. Montero, A. del Pilar Sánchez-Camargo, E. Ibáñez, B. Gilbert-López, Phenolic Compounds from Edible Algae: Bioactivity and Health Benefits, Curr. Med. Chem. 25 (2019) 4808–4826. doi:10.2174/0929867324666170523120101.

[9] F. Chemat, M.A. Vian, G. Cravotto, Green Extraction of Natural Products: Concept and Principles, Int. J. Mol. Sci. 13 (2012) 8615–8627. doi:10.3390/ijms13078615.

[10] M. Herrero, M. Castro-Puyana, J.A. Mendiola, E. Ibañez, Compressed fluids for the extraction of bioactive compounds, TrAC Trends Anal. Chem. 43 (2013) 67–83. doi:10.1016/j.trac.2012.12.008.

[11] M. Herrero, A. del P. Sánchez-Camargo, Plants, seaweeds, microalgae and food by-products as natural sources of functional ingredients obtained using pressurized liquid extraction and supercritical fluid extraction, TrAC Trends Anal. Chem. 71 (2015) 26–38. doi:10.1016/j.trac.2015.01.018.

[12] K. Ameer, H.M. Shahbaz, J.H. Kwon, Green Extraction Methods for Polyphenols from Plant Matrices and Their Byproducts: A Review, Compr. Rev. Food Sci. Food Saf. 16 (2017) 295–315. doi:10.1111/1541-4337.12253.

[13] V. V. Milevskaya, S. Prasad, Z.A. Temerdashev, Extraction and chromatographic determination of phenolic compounds from medicinal herbs in the Lamiaceae and Hypericaceae families: A review, Microchem. J. 145 (2019) 1036–1049. doi:10.1016/j.microc.2018.11.041.

[14] G.-I. Hidalgo, M. Almajano, Red Fruits: Extraction of Antioxidants, Phenolic Content, and Radical Scavenging Determination: A Review, Antioxidants. 6 (2017) 7. doi:10.3390/antiox6010007.

[15] Z.A.A. Aziz, A. Ahmad, S.H.M. Setapar, A. Karakucuk, M.M. Azim, D. Lokhat, M. Rafatullah, M. Ganash, M.A. Kamal, G.M. Ashraf, Essential Oils: Extraction

719 Techniques, Pharmaceutical And Therapeutic Potential - A Review, Curr. Drug
720 Metab. 19 (2018) 1100–1110. doi:10.2174/1389200219666180723144850.
721 [16] L. Ngamwonglumlert, S. Devahastin, N. Chiewchan, Natural colorants: Pigment
722 stability and extraction yield enhancement via utilization of appropriate pretreatment
723 and extraction methods, Crit. Rev. Food Sci. Nutr. 57 (2017) 3243–3259.
724 doi:10.1080/10408398.2015.1109498.
725 [17] M.S. Uddin, S. Ferdosh, M.J. Haque Akanda, K. Ghafoor, A.H. Rukshana, M.E. Ali,
726 B.Y. Kamaruzzaman, M.B. Fauzi, S. Hadijah, S. Shaarani, M.Z. Islam Sarker,
727 Techniques for the extraction of phytosterols and their benefits in human health: a
728 review, Sep. Sci. Technol. 53 (2018) 2206–2223.
729 doi:10.1080/01496395.2018.1454472.
730 [18] N.A. Yahya, N. Attan, R.A. Wahab, An overview of cosmeceutically relevant plant
731 extracts and strategies for extraction of plant-based bioactive compounds, Food
732 Bioprod. Process. 112 (2018) 69–85. doi:10.1016/j.fbp.2018.09.002.
733 [19] J. Duval, V. Pecher, M. Poujol, E. Lesellier, Research advances for the extraction,
734 analysis and uses of anthraquinones: A review, Ind. Crops Prod. 94 (2016) 812–833.
735 doi:10.1016/j.indcrop.2016.09.056.
736 [20] M. Knez Hrnčič, E. Španinger, I.J. Košir, Ž. Knez, U. Bren, Hop Compounds:
737 Extraction Techniques, Chemical Analyses, Antioxidative, Antimicrobial, and
738 Anticarcinogenic Effects, Nutrients. 11 (2019) 1–37. doi:10.3390/nu11020257.
739 [21] D. Bursać Kovačević, M. Maras, F.J. Barba, D. Granato, S. Roohinejad, K.
740 Mallikarjunan, D. Montesano, J.M. Lorenzo, P. Putnik, Innovative technologies for
741 the recovery of phytochemicals from Stevia rebaudiana Bertoni leaves: A review,
742 Food Chem. 268 (2018) 513–521. doi:10.1016/j.foodchem.2018.06.091.

743 [22] V. Raks, H. Al-Suod, B. Buszewski, Isolation, Separation, and Preconcentration of
744 Biologically Active Compounds from Plant Matrices by Extraction Techniques,
745 Chromatographia. 81 (2018) 189–202. doi:10.1007/s10337-017-3405-0
746 [23] O. Babova, A. Occhipinti, A. Capuzzo, M.E. Maffei, Extraction of bilberry
747 (Vaccinium myrtillus) antioxidants using supercritical/subcritical CO2 and ethanol
748 as co-solvent, J. Supercrit. Fluids. 107 (2016) 358–363.
749 doi:10.1016/j.supflu.2015.09.029.
750 [24] K.S. Andrade, G. Trivellin, S.R.S. Ferreira, Piperine-rich extracts obtained by high
751 pressure methods, J. Supercrit. Fluids. 128 (2017) 370–377.
752 doi:10.1016/j.supflu.2017.05.001.
753 [25] D.R. Grijó, I.A. Vieitez Osorio, L. Cardozo-Filho, Supercritical extraction strategies
754 using CO2 and ethanol to obtain cannabinoid compounds from Cannabis hybrid
755 flowers, J. CO2 Util. 28 (2018) 174–180. doi:10.1016/j.jcou.2018.09.022.
756 [26] T. Hatami, J.C.F. Johner, G.L. Zabot, M.A.A. Meireles, Supercritical fluid extraction
757 assisted by cold pressing from clove buds: Extraction performance, volatile oil
758 composition, and economic evaluation, J. Supercrit. Fluids. 144 (2019) 39–47.
759 doi:10.1016/j.supflu.2018.10.003.
760 [27] P.C. Frohlich, K.A. Santos, F. Palú, L. Cardozo-Filho, C. da Silva, E.A. da Silva,
761 Evaluation of the effects of temperature and pressure on the extraction of eugenol
762 from clove (Syzygium aromaticum) leaves using supercritical CO2, J. Supercrit.
763 Fluids. 143 (2019) 313–320. doi:10.1016/j.supflu.2018.09.009.
764 [28] S. Bayrak, M. Sökmen, E. Aytaç, A. Sökmen, Conventional and supercritical fluid
765 extraction (SFE) of colchicine from Colchicum speciosum, Ind. Crops Prod. 128
766 (2019) 80–84. doi:10.1016/j.indcrop.2018.10.060.

[29] B.W. Bin Kueh, S. Yusup, N. Osman, Supercritical carbon dioxide extraction of Melaleuca cajuputi leaves for herbicides allelopathy: Optimization and kinetics modelling, J. CO2 Util. 24 (2018) 220–227. doi:10.1016/j.jcou.2018.01.005.

[30] B.W. Bin Kueh, S. Yusup, N. Osman, N.H. Ramli, Analysis of Melaleuca cajuputi extract as the potential herbicides for paddy weeds, Sustain. Chem. Pharm. 11 (2019) 36–40. doi:10.1016/j.scp.2018.12.004.

[31] A. Krakowska, K. Rafińska, J. Walczak, B. Buszewski, Enzyme-assisted optimized supercritical fluid extraction to improve Medicago sativa polyphenolics isolation, Ind. Crops Prod. 124 (2018) 931–940. doi:10.1016/j.indcrop.2018.08.004.

[32] M.C. Wei, Y.C. Yang, Kinetic studies for ultrasound-assisted supercritical carbon dioxide extraction of triterpenic acids from healthy tea ingredient Hedyotis diffusa and Hedyotis corymbosa, Sep. Purif. Technol. 142 (2015) 316–325. doi:10.1016/j.seppur.2015.01.008.

[33] M.S. Lenucci, M. De Caroli, P.P. Marrese, A. Iurlaro, L. Rescio, V. Böhm, G. Dalessandro, G. Piro, Enzyme-aided extraction of lycopene from high-pigment tomato cultivars by supercritical carbon dioxide, Food Chem. 170 (2015) 193–202. doi:10.1016/j.foodchem.2014.08.081.

[34] C.-I. Cheigh, S.-Y. Yoo, M.-J. Ko, P.-S. Chang, M.-S. Chung, Extraction characteristics of subcritical water depending on the number of hydroxyl group in flavonols, Food Chem. 168 (2015) 21–26. doi:10.1016/j.foodchem.2014.07.047.

[35] N. Castejón, P. Luna, F.J. Señorans, Ultrasonic removal of mucilage for pressurized liquid extraction of omega-3 rich oil from chia seeds (Salvia Hispanica L.), J. Agric. Food Chem. 65 (2017) 2572–2579. doi:10.1021/acs.jafc.6b05726.

790 [36] M.Y. Heng, S. Katayama, T. Mitani, E.S. Ong, S. Nakamura, Solventless extraction
791 methods for immature fruits: Evaluation of their antioxidant and cytoprotective
792 activities, Food Chem. 221 (2017) 1388–1393. doi:10.1016/j.foodchem.2016.11.015.
793 [37] J. Švarc-Gajić, A. Cvetanović, A. Segura-Carretero, I.B. Linares, P. Mašković,
794 Characterisation of ginger extracts obtained by subcritical water, J. Supercrit. Fluids.
795 123 (2017) 92–100. doi:10.1016/j.supflu.2016.12.019.
796 [38] D. Villanueva Bermejo, E. Ibáñez, G. Reglero, C. Turner, T. Fornari, I. Rodriguez-
797 Meizoso, High catechins/low caffeine powder from green tea leaves by pressurized
798 liquid extraction and supercritical antisolvent precipitation, Sep. Purif. Technol. 148
799 (2015) 49–56. doi:10.1016/j.seppur.2015.04.037.
800 [39] A.P. Sánchez-Camargo, J.A. Mendiola, A. Valdés, M. Castro-Puyana, V. García-
801 Cañas, A. Cifuentes, M. Herrero, E. Ibáñez, Supercritical antisolvent fractionation of
802 rosemary extracts obtained by pressurized liquid extraction to enhance their
803 antiproliferative activity, J. Supercrit. Fluids. 107 (2016) 581–589.
804 doi:10.1016/j.supflu.2015.07.019.
805 [40] A. López-Padilla, D. Martín, D. Villanueva Bermejo, L. Jaime, A. Ruiz-Rodriguez,
806 C.E. Restrepo Flórez, D.M. Rivero Barrios, T. Fornari, Vaccinium meridionale
807 Swartz extracts and their addition in beef burgers as antioxidant ingredient, J. Sci.
808 Food Agric. 98 (2018) 377–383. doi:10.1002/jsfa.8483.
809 [41] E. Clain, R. Baranauskienė, P. Kraujalis, A. Šipailienė, R. Maždžierienė, R.
810 Kazernavičiūtė, C. El Kalamouni, P.R. Venskutonis, Biorefining of Cymbopogon
811 nardus from Reunion Island into essential oil and antioxidant fractions by
812 conventional and high pressure extraction methods, Ind. Crops Prod. 126 (2018)
813 158–167. doi:10.1016/J.INDCROP.2018.10.015.

814 [42] K.S. Santos, A.M. Barbosa, V. Freitas, A.V.C.S. Muniz, M.C. Mendonça, R.C.
815 Calhelha, I.C.F.R. Ferreira, E. Franceschi, F.F. Padilha, M.B.P.P. Oliveira, C.
816 Dariva, Antiproliferative Activity of Neem Leaf Extracts Obtained by a Sequential
817 Pressurized Liquid Extraction., Pharmaceuticals (Basel). 11 (2018).
818 doi:10.3390/ph11030076.
819 [43] D. Grauzdytė, A. Pukalskas, C. El Kalamouni, P.R. Venskutonis, Antioxidant
820 potential and phytochemical composition of extracts obtained from Phyllanthus
821 phillyreifolius by different extraction methods, Nat. Prod. Res. (2018) 1–4.
822 doi:10.1080/14786419.2018.1493586.
823 [44] H. Bendif, K. Adouni, M.D. Miara, R. Baranauskienė, P. Kraujalis, P.R.
824 Venskutonis, S.M. Nabavi, F. Maggi, Essential oils (EOs), pressurized liquid extracts
825 (PLE) and carbon dioxide supercritical fluid extracts (SFE-CO2) from Algerian
826 Thymus munbyanus as valuable sources of antioxidants to be used on an industrial
827 level, Food Chem. 260 (2018) 289–298. doi:10.1016/j.foodchem.2018.03.108.
828 [45] P. Kraujalis, V. Kraujalienė, R. Kazernavičiūtė, P.R. Venskutonis, Supercritical
829 carbon dioxide and pressurized liquid extraction of valuable ingredients from
830 Viburnum opulus pomace and berries and evaluation of product characteristics, J.
831 Supercrit. Fluids. 122 (2017) 99–108. doi:10.1016/j.supflu.2016.12.008.
832 [46] R.P.F.F. da Silva, T.A.P. Rocha-Santos, A.C. Duarte, Supercritical fluid extraction
833 of bioactive compounds, TrAC Trends Anal. Chem. 76 (2016) 40–51.
834 doi:10.1016/j.trac.2015.11.013.
835 [47] P. Kraujalis, P.R. Venskutonis, Optimisation of supercritical carbon dioxide
836 extraction of amaranth seeds by response surface methodology and characterization
837 of extracts isolated from different plant cultivars, J. Supercrit. Fluids. 73 (2013) 80–
838 86. doi:10.1016/j.supflu.2012.11.009.

839 [48] Y. Gao, B. Nagy, X. Liu, B. Simándi, Q. Wang, Supercritical CO2 extraction of
840 lutein esters from marigold (Tagetes erecta L.) enhanced by ultrasound, J. Supercrit.
841 Fluids. 49 (2009) 345–350. doi:10.1016/j.supflu.2009.02.006.
842 [49] K.W. Chan, M. Ismail, Supercritical carbon dioxide fluid extraction of Hibiscus
843 cannabinus L. seed oil: A potential solvent-free and high antioxidative edible oil,
844 Food Chem. 114 (2009) 970–975. doi:10.1016/j.foodchem.2008.10.055.
845 [50] A.R.C. Torres, A.L. Santana, D.T. Santos, M.A. A. Meireles, Perspectives on the
846 Application of Supercritical Antisolvent Fractionation Process for the Purification of
847 Plant Extracts: Effects of Operating Parameters and Patent Survey, Recent Patents
848 Eng. 10 (2016) 88–97. doi:10.2174/1872212110666160311201756.
849 [51] D. Villanueva-Bermejo, F. Zahran, D. Troconis, M. Villalva, G. Reglero, T. Fornari,
850 Selective precipitation of phenolic compounds from Achillea millefolium L. extracts
851 by supercritical anti-solvent technique, J. Supercrit. Fluids. 120 (2017) 52–58.
852 doi:10.1016/j.supflu.2016.10.011.
853 [52] M. Villalva, L. Jaime, D. Villanueva-Bermejo, B. Lara, T. Fornari, G. Reglero, S.
854 Santoyo, Supercritical anti-solvent fractionation for improving antioxidant and anti-
855 inflammatory activities of an Achillea millefolium L. extract, Food Res. Int. 115
856 (2019) 128–134. doi:10.1016/j.foodres.2018.08.027.
857 [53] V. Kitrytė, D. Bagdonaitė, P. Rimantas Venskutonis, Biorefining of industrial hemp
858 (Cannabis sativa L.) threshing residues into cannabinoid and antioxidant fractions by
859 supercritical carbon dioxide, pressurized liquid and enzyme-assisted extractions,
860 Food Chem. 267 (2018) 420–429. doi:10.1016/j.foodchem.2017.09.080.
861 [54] F.P. Cardenas-Toro, S.C. Alcázar-Alay, J.P. Coutinho, H.T. Godoy, T. Forster-
862 Carneiro, M.A.A. Meireles, Pressurized liquid extraction and low-pressure solvent
863 extraction of carotenoids from pressed palm fiber: Experimental and economical

evaluation, Food Bioprod. Process. 94 (2015) 90–100. doi:10.1016/j.fbp.2015.01.006.

[55] M. del P. Garcia-Mendoza, F.A. Espinosa-Pardo, A.M. Baseggio, G.F. Barbero, M.R. Maróstica Junior, M.A. Rostagno, J. Martínez, Extraction of phenolic compounds and anthocyanins from juçara (Euterpe edulis Mart.) residues using pressurized liquids and supercritical fluids, J. Supercrit. Fluids. 119 (2017) 9–16. doi:10.1016/j.supflu.2016.08.014.

[56] H. Chen, X. Fu, Z. Luo, Properties and extraction of pectin-enriched materials from sugar beet pulp by ultrasonic-assisted treatment combined with subcritical water, Food Chem. 168 (2015) 302–310. doi:10.1016/j.foodchem.2014.07.078.

[57] G.L. Zabot, M.A.A. Meireles, On-line process for pressurized ethanol extraction of onion peels extract and particle formation using supercritical antisolvent, J. Supercrit. Fluids. 110 (2016) 230–239. doi:10.1016/j.supflu.2015.11.024.

[58] D. Ballesteros-Vivas, G. Álvarez-Rivera, A. del Pilar Sánchez-Camargo, E. Ibáñez, F. Parada-Alfonso, A. Cifuentes, A multi-analytical platform based on pressurized-liquid extraction, in vitro assays and liquid chromatography/gas chromatography coupled to high resolution mass spectrometry for food by-products valorisation. Part 1: Withanolides-rich fractions from goldenberry (Physalis peruviana L.) calyces obtained after extraction optimization as case study, J. Chromatogr. A. 1584 (2019) 155–164. doi:10.1016/j.chroma.2018.11.055.

[59] M.-J. Ko, H.-L. Kwon, M.-S. Chung, Pilot-scale subcritical water extraction of flavonoids from satsuma mandarin (Citrus unshiu Markovich) peel, Innov. Food Sci. Emerg. Technol. 38 (2016) 175–181. doi:10.1016/j.ifset.2016.10.008.

[60] F.A. Espinosa-Pardo, V.M. Nakajima, G.A. Macedo, J.A. Macedo, J. Martínez, Extraction of phenolic compounds from dry and fermented orange pomace using

889 supercritical CO2 and cosolvents, Food Bioprod. Process. 101 (2017) 1–10.
890 doi:10.1016/j.fbp.2016.10.002.
891 [61] J. Ndayishimiye, B.S. Chun, Optimization of carotenoids and antioxidant activity of
892 oils obtained from a co-extraction of citrus (Yuzu ichandrin) by-products using
893 supercritical carbon dioxide, Biomass and Bioenergy. 106 (2017) 1–7.
894 doi:10.1016/j.biombioe.2017.08.014.
895 [62] E.M.C. Alexandre, S. Silva, S.A.O. Santos, A.J.D. Silvestre, M.F. Duarte, J.A.
896 Saraiva, M. Pintado, Antimicrobial activity of pomegranate peel extracts performed
897 by high pressure and enzymatic assisted extraction, Food Res. Int. 115 (2019) 167–
898 176. doi:10.1016/j.foodres.2018.08.044.
899 [63] B.R. Sumere, M.C. de Souza, M.P. dos Santos, R.M.N. Bezerra, D.T. da Cunha, J.
900 Martinez, M.A. Rostagno, Combining pressurized liquids with ultrasound to improve
901 the extraction of phenolic compounds from pomegranate peel (Punica granatum L.),
902 Ultrason. Sonochem. 48 (2018) 151–162. doi:10.1016/J.ultsonch.2018.05.028.
903 [64] F. Montañés, O.J. Catchpole, S. Tallon, K.A. Mitchell, D. Scott, R.F. Webby,
904 Extraction of apple seed oil by supercritical carbon dioxide at pressures up to
905 1300 bar, J. Supercrit. Fluids. 141 (2018) 128–136.
906 doi:10.1016/j.supflu.2018.02.002.
907 [65] G. Ferrentino, K. Morozova, O.K. Mosibo, M. Ramezani, M. Scampicchio,
908 Biorecovery of antioxidants from apple pomace by supercritical fluid extraction, J.
909 Clean. Prod. 186 (2018) 253–261. doi:10.1016/j.jclepro.2018.03.165.
910 [66] M.P. Garcia-Mendoza, J.T. Paula, L.C. Paviani, F.A. Cabral, H.A. Martinez-Correa,
911 Extracts from mango peel by-product obtained by supercritical CO2 and pressurized
912 solvent processes, LWT - Food Sci. Technol. 62 (2015) 131–137.
913 doi:10.1016/j.lwt.2015.01.026.

914 [67] D.A. Oliveira, N. Mezzomo, C. Gomes, S.R.S. Ferreira, Encapsulation of passion
915 fruit seed oil by means of supercritical antisolvent process, J. Supercrit. Fluids. 129
916 (2017) 96–105. doi:10.1016/j.supflu.2017.02.011.
917 [68] J. Viganó, J.P. Coutinho, D.S. Souza, N.A.F. Baroni, H.T. Godoy, J.A. Macedo, J.
918 Martínez, Exploring the selectivity of supercritical CO2 to obtain nonpolar fractions
919 of passion fruit bagasse extracts, J. Supercrit. Fluids. 110 (2016) 1–10.
920 doi:10.1016/j.supflu.2015.12.001.
921 [69] J. Viganó, A.C. Aguiar, D.R. Moraes, J.L.P. Jara, M.N. Eberlin, C.B.B. Cazarin,
922 M.R. Maróstica, J. Martínez, Sequential high pressure extractions applied to recover
923 piceatannol and scirpusin B from passion fruit bagasse, Food Res. Int. 85 (2016) 51–
924 58. doi:10.1016/j.foodres.2016.04.015.
925 [70] D.T.V. Pereira, A.G. Tarone, C.B.B. Cazarin, G.F. Barbero, J. Martínez, Pressurized
926 liquid extraction of bioactive compounds from grape marc, J. Food Eng. 240 (2019)
927 105–113. doi:10.1016/j.jfoodeng.2018.07.019.
928 [71] C. Da Porto, A. Natolino, D. Decorti, The combined extraction of polyphenols from
929 grape marc: Ultrasound assisted extraction followed by supercritical CO2 extraction
930 of ultrasound-raffinate, LWT - Food Sci. Technol. 61 (2015) 98–104.
931 doi:10.1016/j.lwt.2014.11.027.
932 [72] M.S. Mariotti-Celis, M. Martínez-Cifuentes, N. Huamán-Castilla, F. Pedreschi, N.
933 Iglesias-Rebolledo, J.R. Pérez-Correa, Impact of an integrated process of hot
934 pressurised liquid extraction-macroporous resin purification over the polyphenols,
935 hydroxymethylfurfural and reducing sugars content of Vitis vinifera ‘Carménère’
936 pomace extracts, Int. J. Food Sci. Technol. 53 (2018) 1072–1078.
937 doi:10.1111/ijfs.13684.

938 [73] J.A. Nieto, L. Jaime, E. Arranz, G. Reglero, S. Santoyo, Winemaking by-products as
939 anti-inflammatory food ingredients, Food Agric. Immunol. 28 (2017) 1507–1518.
940 doi:10.1080/09540105.2017.1350832.
941 [74] A.P.D.F. Machado, A.L.D. Pereira, G.F. Barbero, J. Martínez, Recovery of
942 anthocyanins from residues of Rubus fruticosus , Vaccinium myrtillus and Eugenia
943 brasiliensis by ultrasound assisted extraction, pressurized liquid extraction and their
944 combination, Food Chem. 231 (2017) 1–10. doi:10.1016/j.foodchem.2017.03.060.
945 [75] N. Kryževičiūtė, P. Kraujalis, P.R. Venskutonis, Optimization of high pressure
946 extraction processes for the separation of raspberry pomace into lipophilic and
947 hydrophilic fractions, J. Supercrit. Fluids. 108 (2016) 61–68.
948 doi:10.1016/j.supflu.2015.10.025.
949 [76] S. Kühn, F. Temelli, Recovery of bioactive compounds from cranberry pomace using
950 ternary mixtures of CO2 + ethanol + water, J. Supercrit. Fluids. 130 (2017) 147–155.
951 doi:10.1016/j.supflu.2017.07.028.
952 [77] A. Schievano, F. Adani, L. Buessing, A. Botto, E.N. Casoliba, M. Rossoni, J.L.
953 Goldfarb, An integrated biorefinery concept for olive mill waste management:
954 supercritical CO2 extraction and energy recovery, Green Chem. 17 (2015) 2874–
955 2887. doi:10.1039/c5gc00076a.
956 [78] A. Kazan, M.S. Celiktas, S. Sargin, O. Yesil-Celiktas, Bio-based fractions by
957 hydrothermal treatment of olive pomace: Process optimization and evaluation,
958 Energy Convers. Manag. 103 (2015) 366–373. doi:10.1016/j.enconman.2015.06.084.
959 [79] S. Erşan, Ö. Güçlü Üstündağ, R. Carle, R.M. Schweiggert, Subcritical water
960 extraction of phenolic and antioxidant constituents from pistachio (Pistacia vera L.)
961 hulls, Food Chem. 253 (2018) 46–54. doi:10.1016/j.foodchem.2018.01.116.

962 [80] S. Mazzutti, L.G.G. Rodrigues, N. Mezzomo, V. Venturi, S.R.S. Ferreira, Integrated
963 green-based processes using supercritical CO2 and pressurized ethanol applied to
964 recover antioxidant compouds from cocoa (Theobroma cacao) bean hulls, J.
965 Supercrit. Fluids. 135 (2018) 52–59. doi:10.1016/j.supflu.2017.12.039.
966 [81] A.T. Getachew, B.S. Chun, Influence of pretreatment and modifiers on subcritical
967 water liquefaction of spent coffee grounds: A green waste valorization approach, J.
968 Clean. Prod. 142 (2017) 3719–3727. doi:10.1016/j.jclepro.2016.10.096.
969 [82] M.S. Mariotti-Celis, M. Martínez-Cifuentes, N. Huamán-Castilla, M. Vargas-
970 González, F. Pedreschi, J.R. Pérez-Correa, The Antioxidant and Safety Properties of
971 Spent Coffee Ground Extracts Impacted by the Combined Hot Pressurized Liquid
972 Extraction-Resin Purification Process., Molecules. 23 (2017).
973 doi:10.3390/molecules23010021.
974 [83] E. Alonso, The role of supercritical fluids in the fractionation pretreatments of a
975 wheat bran-based biorefinery, J. Supercrit. Fluids. 133 (2018) 603–614.
976 doi:10.1016/j.supflu.2017.09.010.
977 [84] F.J. Barba, Z. Zhu, M. Koubaa, A.S. Sant'Ana, V. Orlien, Green alternative methods
978 for the extraction of antioxidant bioactive compounds from winery wastes and by-
979 products: A review, Trends Food Sci. Technol. 49 (2016) 96–109.
980 doi:10.1016/j.tifs.2016.01.006.
981 [85] S. Yammine, S. Brianceau, S. Manteau, M. Turk, R. Ghidossi, E. Vorobiev, M.
982 Mietton-Peuchot, Extraction and purification of high added value compounds from
983 by-products of the winemaking chain using alternative/nonconventional
984 processes/technologies, Crit. Rev. Food Sci. Nutr. 58 (2018) 1375–1390.
985 doi:10.1080/10408398.2016.1259982.

[86] A. Kovalcik, S. Obruca, I. Marova, Valorization of spent coffee grounds: A review, Food Bioprod. Process. 110 (2018) 104–119. doi:10.1016/j.fbp.2018.05.002.

[87] N. M'hiri, I. Ioannou, M. Ghoul, N. Mihoubi Boudhrioua, Phytochemical characteristics of citrus peel and effect of conventional and nonconventional processing on phenolic compounds: A review, Food Rev. Int. 33 (2017) 587–619. doi:10.1080/87559129.2016.1196489.

[88] P. Putnik, D. Bursać Kovačević, A. Režek Jambrak, F. Barba, G. Cravotto, A. Binello, J. Lorenzo, A. Shpigelman, Innovative "Green" and Novel Strategies for the Extraction of Bioactive Added Value Compounds from Citrus Wastes—A Review, Molecules. 22 (2017) 680. doi:10.3390/molecules22050680.

[89] C.A. Perussello, Z. Zhang, A. Marzocchella, B.K. Tiwari, Valorization of Apple Pomace by Extraction of Valuable Compounds, Compr. Rev. Food Sci. Food Saf. 16 (2017) 776–796. doi:10.1111/1541-4337.12290.

[90] E. Roselló-Soto, M. Koubaa, A. Moubarik, R.P. Lopes, J.A. Saraiva, N. Boussetta, N. Grimi, F.J. Barba, Emerging opportunities for the effective valorization of wastes and by-products generated during olive oil production process: Non-conventional methods for the recovery of high-added value compounds, Trends Food Sci. Technol. 45 (2015) 296–310. doi:10.1016/j.tifs.2015.07.003.

[91] T. Žugčić, R. Abdelkebir, C. Alcantara, M.C. Collado, J.V. García-Pérez, A.J. Meléndez-Martínez, A. Režek Jambrak, J.M. Lorenzo, F.J. Barba, From extraction of valuable compounds to health promoting benefits of olive leaves through bioaccessibility, bioavailability and impact on gut microbiota, Trends Food Sci. Technol. 83 (2019) 63–77. doi:10.1016/j.tifs.2018.11.005.

1009 [92] K.S. Duba, L. Fiori, Extraction of bioactives from food processing residues using
1010 techniques performed at high pressures, Curr. Opin. Food Sci. 5 (2015) 14–22.
1011 doi:10.1016/j.cofs.2015.06.009.
1012 [93] R. Vardanega, J.M. Prado, M.A.A. Meireles, Adding value to agri-food residues by
1013 means of supercritical technology, J. Supercrit. Fluids. 96 (2015) 217–227.
1014 doi:10.1016/j.supflu.2014.09.029.
1015 [94] J. Viganó, A.P. da F. Machado, J. Martínez, Sub- and supercritical fluid technology
1016 applied to food waste processing, J. Supercrit. Fluids. 96 (2015) 272–286.
1017 doi:10.1016/j.supflu.2014.09.026.
1018 [95] T.T. Nguyen, A.R. Barber, K. Corbin, W. Zhang, Lobster processing by-products as
1019 valuable bioresource of marine functional ingredients, nutraceuticals, and
1020 pharmaceuticals, Bioresour. Bioprocess. 4 (2017) 27. doi:10.1186/s40643-017-0157-
1021 5.
1022 [96] J.R. Vergara-Salinas, M. Vergara, C. Altamirano, Á. Gonzalez, J.R. Pérez-Correa,
1023 Characterization of pressurized hot water extracts of grape pomace: Chemical and
1024 biological antioxidant activity, Food Chem. 171 (2015) 62–69.
1025 doi:10.1016/j.foodchem.2014.08.094.
1026 [97] A. Raju, H. Monjurul, C. Yeon-Jin, B.-S. Chun, Quality Evaluation of Oil Recovered
1027 from By-products of Bigeye Tuna Using Supercritical Carbon Dioxide Extraction,
1028 Turkish J. Fish. Aquat. Sci. 17 (2017) 663–672. doi:10.4194/1303-2712-v17_4_02.
1029 [98] T.T. Nguyen, W. Zhang, A.R. Barber, P. Su, S. He, Significant Enrichment of
1030 Polyunsaturated Fatty Acids (PUFAs) in the Lipids Extracted by Supercritical CO2
1031 from the Livers of Australian Rock Lobsters (Jasus edwardsii), J. Agric. Food Chem.
1032 63 (2015) 4621–4628. doi:10.1021/jf5059396.

[99] J. Viganó, G.L. Zabot, J. Martínez, Supercritical fluid and pressurized liquid extractions of phytonutrients from passion fruit by-products: Economic evaluation of sequential multi-stage and single-stage processes, J. Supercrit. Fluids. 122 (2017) 88–98. doi:10.1016/j.supflu.2016.12.006.

[100] A.P. Sánchez-Camargo, M. Herrero, Bioactives Obtained From Plants, Seaweeds, Microalgae and Food By-Products Using Pressurized Liquid Extraction and Supercritical Fluid Extraction, in: Compr. Anal. Chem., Elsevier, 2017: pp. 27–51. doi:10.1016/bs.coac.2017.01.001.

[101] E. Ibañez, M. Herrero, J.A. Mendiola, M. Castro-Puyana, Extraction and Characterization of Bioactive Compounds with Health Benefits from Marine Resources: Macro and Micro Algae, Cyanobacteria, and Invertebrates, in: Mar. Bioact. Compd., Springer US, Boston, MA, 2012: pp. 55–98. doi:10.1007/978-1-4614-1247-2_2.

[102] A.-M. Cikoš, S. Jokić, D. Šubarić, I. Jerković, Overview on the Application of Modern Methods for the Extraction of Bioactive Compounds from Marine Macroalgae, Mar. Drugs. 16 (2018) 348. doi:10.3390/md16100348.

[103] D.A. Esquivel-Hernández, I.P. Ibarra-Garza, J. Rodríguez-Rodríguez, S.P. Cuéllar-Bermúdez, M. de J. Rostro-Alanis, G.S. Alemán-Nava, J.S. García-Pérez, R. Parra-Saldívar, Green extraction technologies for high-value metabolites from algae: a review, Biofuels, Bioprod. Biorefining. 11 (2017) 215–231. doi:10.1002/bbb.1735.

[104] S. Machmudah, W. Diono, H. Kanda, M. Goto, Supercritical Fluids Extraction of Valuable Compounds from Algae: Future Perspectives and Challenges, Eng. J. 22 (2018) 13–30. doi:10.4186/ej.2018.22.5.13.

[105] I. Michalak, K. Chojnacka, Algae as production systems of bioactive compounds, Eng. Life Sci. 15 (2015) 160–176. doi:10.1002/elsc.201400191.

1058 [106] R. Gallego, L. Montero, A. Cifuentes, E. Ibáñez, M. Herrero, Green Extraction of
1059 Bioactive Compounds from Microalgae, J. Anal. Test. 2 (2018) 109–123.
1060 doi:10.1007/s41664-018-0061-9.
1061 [107] C. Grosso, P. Valentão, F. Ferreres, P. Andrade, Alternative and Efficient Extraction
1062 Methods for Marine-Derived Compounds, Mar. Drugs. 13 (2015) 3182–3230.
1063 doi:10.3390/md13053182.
1064 [108] J.E. Sosa-Hernández, Z. Escobedo-Avellaneda, H.M.N. Iqbal, J. Welti-Chanes,
1065 State-of-the-Art Extraction Methodologies for Bioactive Compounds from Algal
1066 Biome to Meet Bio-Economy Challenges and Opportunities, Molecules. 23 (2018)
1067 2953. doi:10.3390/molecules23112953.
1068 [109] M. Mubarak, A. Shaija, T.V. Suchithra, A review on the extraction of lipid from
1069 microalgae for biodiesel production, Algal Res. 7 (2015) 117–123.
1070 doi:10.1016/j.algal.2014.10.008.
1071 [110] M. Poojary, F. Barba, B. Aliakbarian, F. Donsì, G. Pataro, D. Dias, P. Juliano,
1072 Innovative Alternative Technologies to Extract Carotenoids from Microalgae and
1073 Seaweeds, Mar. Drugs. 14 (2016) 214. doi:10.3390/md14110214.
1074 [111] V. Abrahamsson, F. Jumaah, C. Turner, Continuous multicomponent quantification
1075 during supercritical fluid extraction applied to microalgae using in-line UV/Vis
1076 absorption spectroscopy and on-line evaporative light scattering detection, J.
1077 Supercrit. Fluids. 131 (2018) 157–165. doi:10.1016/j.supflu.2017.09.014.
1078 [112] D.F. Tirado, L. Calvo, The Hansen theory to choose the best cosolvent for
1079 supercritical CO2 extraction of β-carotene from Dunaliella salina, J. Supercrit.
1080 Fluids. 145 (2019) 211–218. doi:10.1016/j.supflu.2018.12.013.
1081 [113] A. Mouahid, C. Crampon, S.-A.A. Toudji, E. Badens, Effects of high water content
1082 and drying pre-treatment on supercritical CO2 extraction from Dunaliella salina

microalgae: Experiments and modelling, J. Supercrit. Fluids. 116 (2016) 271–280. doi:10.1016/j.supflu.2016.06.007.

[114] X. Cheng, Z. Qi, T. Burdyny, T. Kong, D. Sinton, Low pressure supercritical CO2 extraction of astaxanthin from Haematococcus pluvialis demonstrated on a microfluidic chip, Bioresour. Technol. 250 (2018) 481–485. doi:10.1016/j.biortech.2017.11.070.

[115] M. Becerra, S. Boutefnouchet, O. Córdoba, G.P. Vitorino, L. Brehu, I. Lamour, F. Laimay, A. Efstathiou, D. Smirlis, S. Michel, M. Kritsanida, M.L. Flores, R. Grougnet, Antileishmanial activity of fucosterol recovered from Lessonia vadosa Searles (Lessoniaceae) by SFE, PSE and CPC, Phytochem. Lett. 11 (2015) 418–423. doi:10.1016/j.phytol.2014.12.019.

[116] F.A. Reyes, J.A. Mendiola, S. Suárez-Alvarez, E. Ibañez, J.M. del Valle, Adsorbent-assisted supercritical CO2 extraction of carotenoids from Neochloris oleoabundans paste, J. Supercrit. Fluids. 112 (2016) 7–13. doi:10.1016/j.supflu.2016.02.005.

[117] E. Balboa, A. Moure, H. Domínguez, Valorization of Sargassum muticum Biomass According to the Biorefinery Concept, Mar. Drugs. 13 (2015) 3745–3760. doi:10.3390/md13063745.

[118] R. Shomal, H. Hisham, A. Mlhem, R. Hassan, S. Al-Zuhair, Simultaneous extraction–reaction process for biodiesel production from microalgae, Energy Reports. 5 (2019) 37–40. doi:10.1016/j.egyr.2018.11.003.

[119] H.-C. Wang, W. Klinthong, Y.-H. Yang, C.-S. Tan, Continuous extraction of lipids from Schizochytrium sp. by CO2-expanded ethanol, Bioresour. Technol. 189 (2015) 162–168. doi:10.1016/j.biortech.2015.04.011.

[120] E. Damergi, J.-P. Schwitzguébel, D. Refardt, S. Sharma, C. Holliger, C. Ludwig, Extraction of carotenoids from Chlorella vulgaris using green solvents and syngas

production from residual biomass, Algal Res. 25 (2017) 488–495. doi:10.1016/j.algal.2017.05.003.

[121] A.P. Sánchez-Camargo, L. Montero, A. Cifuentes, M. Herrero, E. Ibáñez, Application of Hansen solubility approach for the subcritical and supercritical selective extraction of phlorotannins from Cystoseira abies-marina, RSC Adv. 6 (2016) 94884–94895. doi:10.1039/c6ra16862k.

[122] E. Heavisides, C. Rouger, A.F. Reichel, C. Ulrich, A. Wenzel-Storjohann, S. Sebens, D. Tasdemir, Seasonal Variations in the Metabolome and Bioactivity Profile of Fucus vesiculosus Extracted by an Optimised, Pressurised Liquid Extraction Protocol., Mar. Drugs. 16 (2018). doi:10.3390/md16120503.

[123] P. Otero, S. Quintana, G. Reglero, T. Fornari, M. García-Risco, Pressurized Liquid Extraction (PLE) as an Innovative Green Technology for the Effective Enrichment of Galician Algae Extracts with High Quality Fatty Acids and Antimicrobial and Antioxidant Properties, Mar. Drugs. 16 (2018) 156. doi:10.3390/md16050156.

[124] C.R.N. Gereniu, P.S. Saravana, B.-S. Chun, Recovery of carrageenan from Solomon Islands red seaweed using ionic liquid-assisted subcritical water extraction, Sep. Purif. Technol. 196 (2018) 309–317. doi:10.1016/j.seppur.2017.06.055.

[125] M.H. Eikani, N. Khandan, E. Feyzi, Increased bio-oil yield from Nannochloropsis salina through tuning the polarity of subcritical water, J. Mol. Liq. 277 (2019) 163–169. doi:10.1016/j.molliq.2018.12.110.

[126] M. Castro-Puyana, A. Pérez-Sánchez, A. Valdés, O.H.M. Ibrahim, S. Suarez-Álvarez, J.A. Ferragut, V. Micol, A. Cifuentes, E. Ibáñez, V. García-Cañas, Pressurized liquid extraction of Neochloris oleoabundans for the recovery of bioactive carotenoids with anti-proliferative activity against human colon cancer cells, Food Res. Int. 99 (2017) 1048–1055. doi:10.1016/J.FOODRES.2016.05.021.

[127] P.S. Saravana, Y.-N. Cho, H.-C. Woo, B.-S. Chun, Green and efficient extraction of polysaccharides from brown seaweed by adding deep eutectic solvent in subcritical water hydrolysis, J. Clean. Prod. 198 (2018) 1474–1484. doi:10.1016/J.JCLEPRO.2018.07.151.

[128] T. Vo Dinh, P.S. Saravana, H.C. Woo, B.S. Chun, Ionic liquid-assisted subcritical water enhances the extraction of phenolics from brown seaweed and its antioxidant activity, Sep. Purif. Technol. 196 (2018) 287–299. doi:10.1016/J.SEPPUR.2017.06.009.

[129] A.P. Sánchez-Camargo, L. Montero, V. Stiger-Pouvreau, A. Tanniou, A. Cifuentes, M. Herrero, E. Ibáñez, Considerations on the use of enzyme-assisted extraction in combination with pressurized liquids to recover bioactive compounds from algae, Food Chem. 192 (2016) 67–74. doi:10.1016/j.foodchem.2015.06.098.

[130] T.A. Kwan, S.E. Kwan, J. Peccia, J.B. Zimmerman, Selectively biorefining astaxanthin and triacylglycerol co-products from microalgae with supercritical carbon dioxide extraction, Bioresour. Technol. 269 (2018) 81–88. doi:10.1016/J.biortech.2018.08.081.

[131] B. Gilbert-López, J.A. Mendiola, J. Fontecha, L.A.M. van den Broek, L. Sijtsma, A. Cifuentes, M. Herrero, E. Ibáñez, Downstream processing of Isochrysis galbana: a step towards microalgal biorefinery, Green Chem. 17 (2015) 4599–4609. doi:10.1039/c5gc01256b.

[132] A.P. Sánchez-Camargo, N. Pleite, J.A. Mendiola, A. Cifuentes, M. Herrero, B. Gilbert-López, E. Ibáñez, Development of green extraction processes for Nannochloropsis gaditana biomass valorization, Electrophoresis. 39 (2018) 1875–1883. doi:10.1002/elps.201800122.

[133] H. Harrysson, M. Hayes, F. Eimer, N.-G. Carlsson, G.B. Toth, I. Undeland, Production of protein extracts from Swedish red, green, and brown seaweeds, Porphyra umbilicalis Kützing, Ulva lactuca Linnaeus, and Saccharina latissima (Linnaeus) J. V. Lamouroux using three different methods, J. Appl. Phycol. 30 (2018) 3565–3580. doi:10.1007/s10811-018-1481-7.

[134] B. Gilbert-López, J.A. Mendiola, L.A.M. van den Broek, B. Houweling-Tan, L. Sijtsma, A. Cifuentes, M. Herrero, E. Ibáñez, Green compressed fluid technologies for downstream processing of Scenedesmus obliquus in a biorefinery approach, Algal Res. 24 (2017) 111–121. doi:10.1016/j.algal.2017.03.011.

[135] M. Herrero, E. Ibañez, Green extraction processes, biorefineries and sustainability: Recovery of high added-value products from natural sources, J. Supercrit. Fluids. 134 (2018) 252–259. doi:10.1016/j.supflu.2017.12.002.

[136] F. Derwenskus, F. Metz, A. Gille, U. Schmid-Staiger, K. Briviba, U. Schließmann, T. Hirth, Pressurized extraction of unsaturated fatty acids and carotenoids from wet Chlorella vulgaris and Phaeodactylum tricornutum biomass using subcritical liquids, GCB Bioenergy. 11 (2019) 335–344. doi:10.1111/gcbb.12563.

[137] K.A. Santos, J.E. Gonçalves, L. Cardozo-Filho, E.A. da Silva, Pressurized liquid and ultrasound-assisted extraction of α-bisabolol from candeia (Eremanthus erythropappus) wood, ind. crops prod. 130 (2019) 428–435. doi:10.1016/j.indcrop.2019.01.013.

[138] Y.L. Kua, S. Gan, A. Morris, H.K. Ng, Ethyl lactate as a potential green solvent to extract hydrophilic (polar) and lipophilic (non-polar) phytonutrients simultaneously from fruit and vegetable by-products, Sustain. Chem. Pharm. 4 (2016) 21–31. doi:10.1016/j.scp.2016.07.003.

[139] Food and Agriculture Organization of the United Nations (FAO), Fats and fatty acids in human nutrition - Report of an expert consultation, (2010) 91, 1–166. http://www.fao.org/3/a-i1953e.pdf

[140] M. Maiwald, G.M. Schneider, Solvatochromism in supercritical fluids, Berichte Der Bunsengesellschaft Für Phys. Chemie. 102 (1998) 960–964. doi:10.1002/bbpc.19981020708.

[141] A.P. Sánchez-Camargo, N. Pleite, M. Herrero, A. Cifuentes, E. Ibáñez, B. Gilbert-López, New approaches for the selective extraction of bioactive compounds employing bio-based solvents and pressurized green processes, J. Supercrit. Fluids. 128 (2017) 112–120. doi:10.1016/j.supflu.2017.05.016.

[142] Z. Li, K.H. Smith, G.W. Stevens, The use of environmentally sustainable bio-derived solvents in solvent extraction applications—A review, Chinese J. Chem. Eng. 24 (2016) 215–220. doi:10.1016/j.cjche.2015.07.021.

[143] P.G. Jessop, S. Bala, Gas-Expanded Liquids, Chem. Rev. 107 (2007) 2666–2694. doi:10.1021/cr040199o.

[144] M. Herrero, J.A. Mendiola, E. Ibáñez, Gas expanded liquids and switchable solvents, Curr. Opin. Green Sustain. Chem. 5 (2017) 24–30. doi:10.1016/j.cogsc.2017.03.008.

[145] I. Rodríguez-Meizoso, M. Plaza, Particle Formation of Food Ingredients by Supercritical Fluid Technology, in: S.R. Fornari T. (Ed.), High Press. Fluid Technol. Green Food Process., Springer, Cham, 2015: pp. 155–183. doi:10.1007/978-3-319-10611-3_5.

[146] J.M. Andersson, S. Lindahl, C. Turner, I. Rodriguez-Meizoso, Pressurised hot water extraction with on-line particle formation by supercritical fluid technology, Food Chem. 134 (2012) 1724–1731. doi:10.1016/j.foodchem.2012.03.123.

[147] M. Herrero, M. Plaza, A. Cifuentes, E. Ibáñez, Green processes for the extraction of bioactives from Rosemary: Chemical and functional characterization via ultra-performance liquid chromatography-tandem mass spectrometry and in-vitro assays, J. Chromatogr. A. 1217 (2010) 2512–2520. doi:10.1016/j.chroma.2009.11.032.

[148] I. Rodríguez-Meizoso, M. Castro-Puyana, P. Börjesson, J.A. Mendiola, C. Turner, E. Ibáñez, Life cycle assessment of green pilot-scale extraction processes to obtain potent antioxidants from rosemary leaves, J. Supercrit. Fluids. 72 (2012) 205–212. doi:10.1016/j.supflu.2012.09.005.

## FIGURES

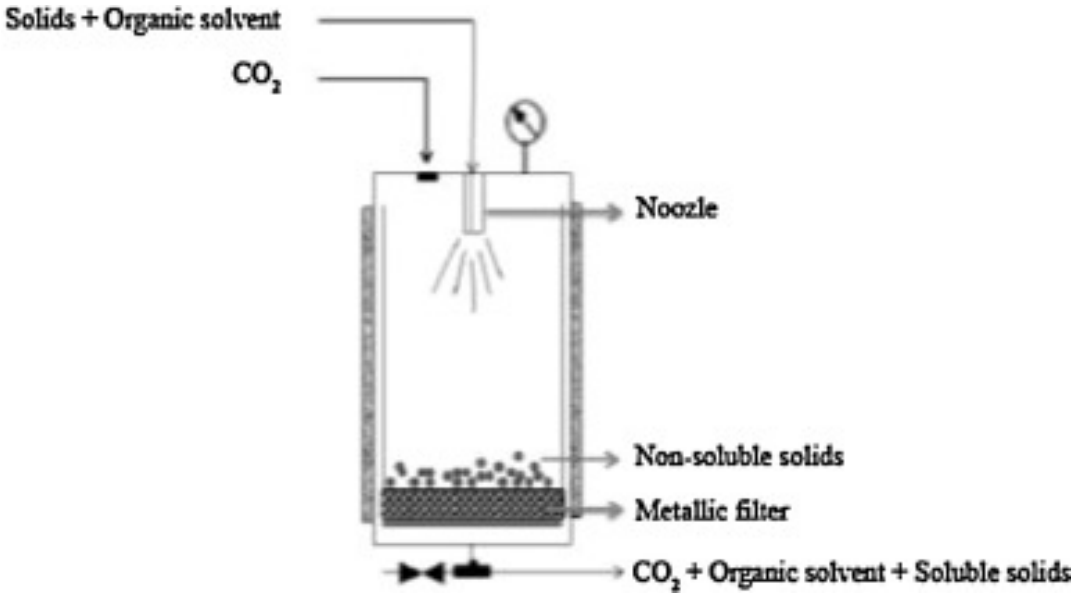
**Figure 1.** Schematic diagram of the SAF precipitation cell of the equipment. Reprinted with permission from Villanueva-Bermejo et al [51].

**Figure 2.** Integrated EXTRACT-US diagram system. P1: Liquid pump; P2: $CO_2$ pump; PRV: Pressure Regulating Valve; EC: Extraction Cell; USG: Ultrasound Generator; SPE: Solid Phase Extraction; USP: Ultrasound Probe; P1-5: Pressure transducer; V1-5: Automatic Valve 2-position/10-port; CV1-6: Check Valve; Vinj: Manual injection valve; MV1-2: Micrometric valve. *Dotted section represents the chromatographic oven. Reprinted with permission from Sumere et al. [63].

**Figure 3.** Biorefinery cascade processing of olive pomace. Adapted from Kazan et al. [78].

**Figure 4.** Cycle of sustainable production of ethyl lactate. Reprinted with permission from Kua et al. [138].

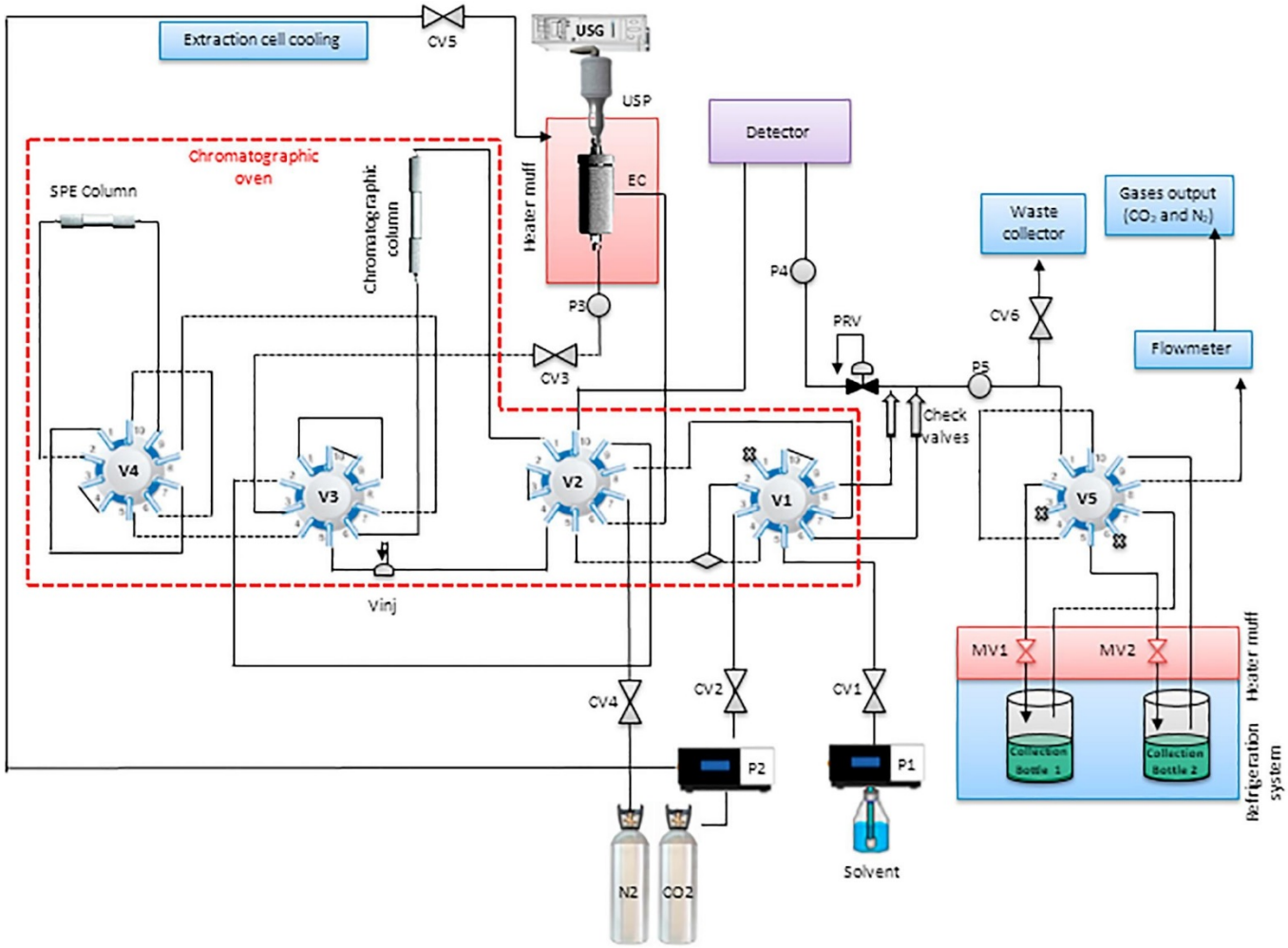
**Figure 5.** Instrumental setup of the SFE-UV/Vis-ELSD equipment. Reprinted with permission from Abrahamsson et al. [111].




1234

1235 Figure 1.

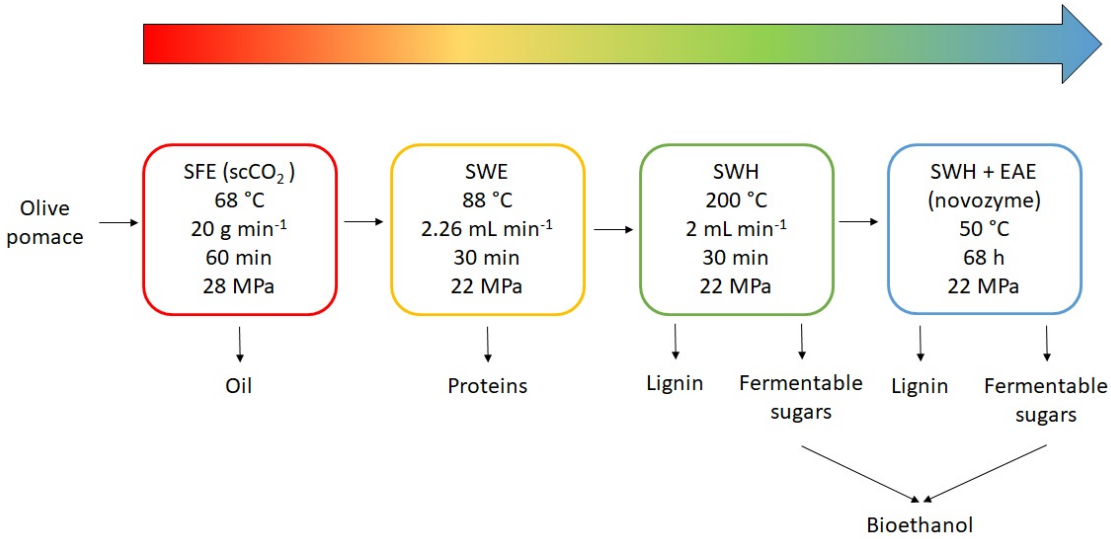
1236




1237

1238 Figure 2.

1239




1240

1241 Figure 3.

1242

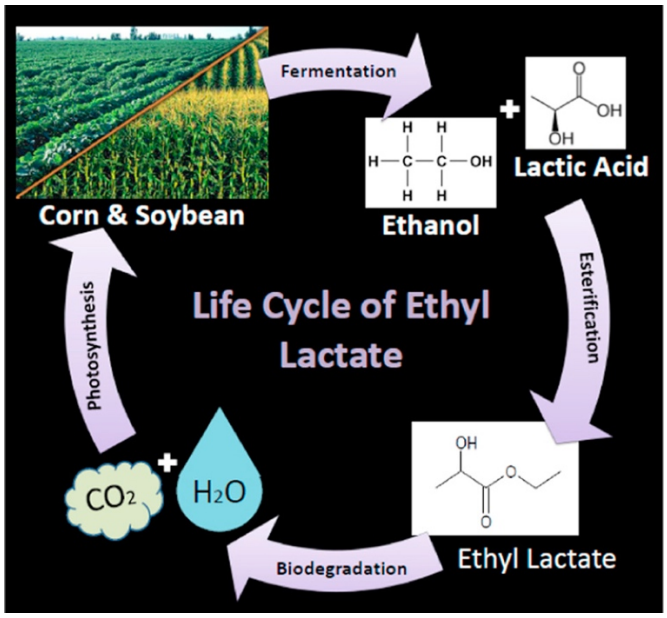

Fermentation
Corn & Soybean
Ethanol
Lactic Acid
Esterification
Life Cycle of Ethyl Lactate
Photosynthesis
CO2
H2O
Biodegradation
Ethyl Lactate

Figure 4.

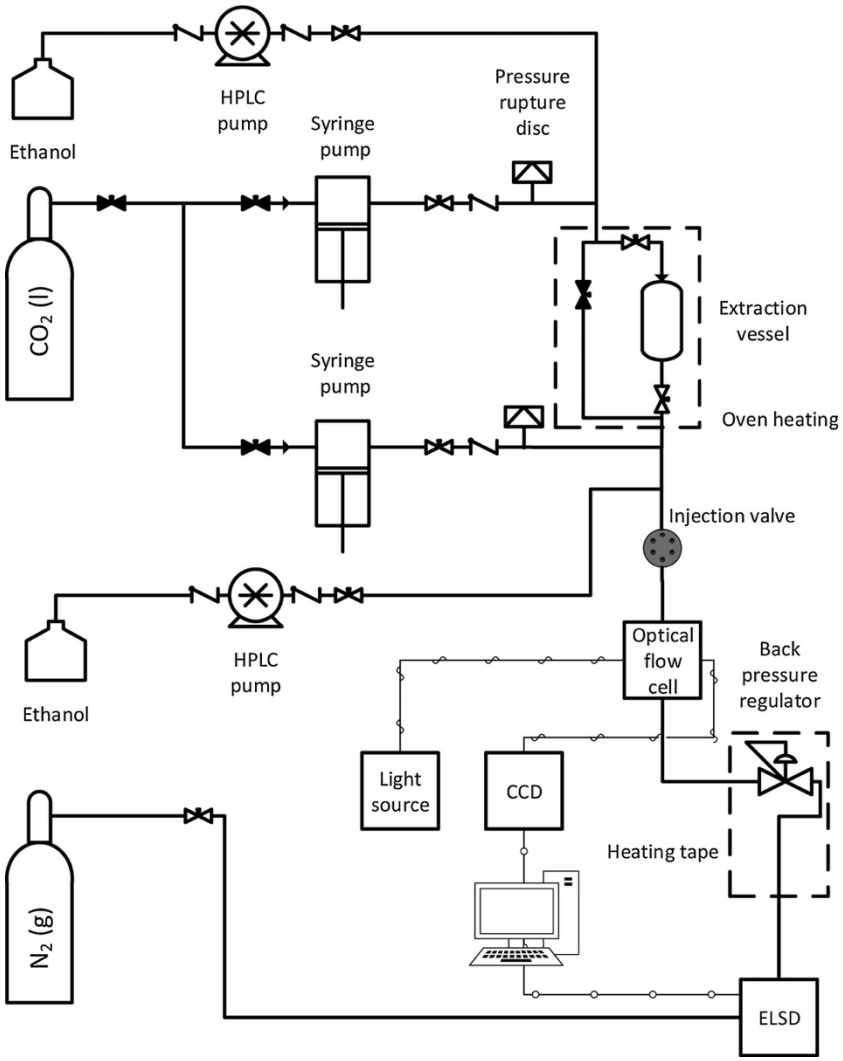

Ethanol
HPLC pump
Syringe pump
Pressure rupture disc
$CO_2$ (l)
Extraction vessel
Syringe pump
Oven heating
Injection valve
Ethanol
HPLC pump
Optical flow cell
Back pressure regulator
Light source
CCD
Heating tape
$N_2$ (g)
ELSD

Figure 5.

**Table 1.**
Some representative applications involving the use of sub- and supercritical fluid extractions for bioactive compounds from plants published during the period 2015–19

| **Matrix** | Compounds of interest | Extraction method | Extraction solvent | T (ºC) / P (MPa) | Extraction time (min) | Flow $CO_2$ rate (mL $min^{-1}$) | Ref. |
|---|---|---|---|---|---|---|---|
| Bilberry (Vaccinium myrtillus) | Anthocyanins and other phenolic compounds | SFE | $CO_2$ (+ 6 % ethanol/water 70:30) | 45 / 25 | 60 | 133.3 # | [23] |
| | | SubFE | $CO_2$ (+ 6 % ethanol/water 50:50) | | 60 | 100 # | |
| | | SubFE | $CO_2$ (+ 9 % ethanol/water 10:90) | | 180 | 100 # | |
| Black pepper (*Piper nigrum*) | Piperine | SFE | $CO_2$ (+5 % ethanol) | 40 / 20-30 | 240 | 8 ± 2 * | [24] |
| *Cannabis* hybrid flowers | Cannabinoids | SFE | $CO_2$ | 50-70 / 12.8-24.9 | | 2.5 | [25] |
| | | SFE | $CO_2$ (+ 6 % ethanol) | 50 / 16.5-24.0 | | 2.5 | |
| Clove (*Syzygium aromaticum*) | Sesquiterpenes and phenols | SFE / SFEAP | $CO_2$ | 40 / 15 | 20 + 14 | - | [26] |
| | Monoterpenes and vitamin E | SFE | $CO_2$ | 40 / 15-22 | 30 + 50 | - | [27] |
| *Colchicum speciosum* | Colchicine | SFE | $CO_2$ (+3 % methanol) | 35 / 24.7 | 25 + 30 | 1.5 | [28] |
| *Melaleuca cajuputi* | Sesquiterpenes and phenolics | SFE | $CO_2$ | 43 / 25 | 120 | 6 | [29,30] |
| *Medicago sativa* | Polyphenolics | EAE + SFE | $CO_2$ (+ 15 % ethanol) | 68 / 20.5 | - | 4 | [31] |
| Tea (*Hedyotis diffusa* and *Hedyotis corymbosa*) | Oleanolic and ursolic acids | SFE | $CO_2$ | 55 / 24.5 | 84 | 2.1 | [32] |
| Tomato (*Solanum lycopersicum*) | Lycopene | SFE | $CO_2$ | 86 / 50 | 15 + 270 | 4 | [33] |
| Black tea, celery, and ginseng leaf | Flavonoids | SWE | Water | 170–200 / 10 | 15 | | [34] |
| Chia (*Salvia hispanica* L.) | Omega-3 oil | UAE + PLE | Ethyl acetate | 90 / - | 10 | | [35] |
| Fruits | Polyphenols | SWE | Water | 100 / 1-1.5 | 40–45 | | [36] |
| Ginger (*Zingiber officinale*) | Sugars, diols, phenolic compounds, terpenoids, and other compounds. | SWE | Water | 150 / 5 | 60 | | [37] |
| Green tea leaves (*Camellia sinensis*) | Catechins | PLE + SAF | Ethyl lactate | 100 / 10 | 20 | | [38] |
| Rosemary (*Rosmarinus officinalis*) | Carnosic acid, carnosol and rosmarinic acid | PLE + SAF | Ethanol/water 80:20 | 150 / 10 | 20 | | [39] |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| *Stevia rebaudiana* | Antioxidants and steviol glycosides | PLE | Water | 100-160 /10.34 | 10 *** | | [21] |
| *Vaccinium meridionale* Swartz | Phenolic compounds | PLE | Ethanol/water 50:50 | 200 / 10.3 | 15 | | [40] |
| | | | | | | | |
| **Biorefinery approaches** | | | | | | | |
| *Cymbopogon nardus* | Essential oil and antioxidant fractions | SFE | $CO_2$ | 40-50 / 50 | 210 | 2–3 | [41] |
| | | PLE | Acetone | 40 / 10 | 5 *** | | |
| | | | Ethanol | | | | |
| | | | Water | | | | |
| Neem (*Azadirachta indica* A. Juss) | Terpenes and phenolic compounds | PLE | Hexane | 25/10 | 60 | 0.001 | [42] |
| | | | Ethyl acetate | | | | |
| | | | Ethanol/water 80:20 | | | | |
| *Phyllanthus phillyreifolius* | Lipids (tocopherol) | SFE | $CO_2$ | 45/ 47.5 | 10 + 120 | 2-3 | [43] |
| | Antioxidants | PLE | Acetone | 70 / 10 | 5 *** | | |
| | | | Ethanol/water 70:30 | | | | |
| *Thymus munbyanus* | Phenolic compounds and antioxidants | SFE | $CO_2$ | 70 / 45 | 30 + 180 | 2 | [44] |
| | | PLE | Acetone | 70 / 10.3 | 15 | | |
| | | | Ethanol | | | | |
| | | | Water | 120 / 10.3 | | | |
| *Viburnum opulus* L. fruits | Oleic and linoleic acids and tocopherols | SFE | $CO_2$ | 50 / 57 | 131 | 2.5 | [45] |
| | | PLE | Acetone | 70 / 10.3 | 5 *** | | |
| | | | Ethanol | | | | |
| | Phenolic compounds | | Water | 120 / 10.3 | | | |

$CO_2$ flow rate: # means g $min^{-1}$; extraction time: n. of * means no. cycles; extraction time: static + dynamic. EAE: enzyme-assisted extraction; PLE: pressurized liquid extraction; SAF: supercritical antisolvent fractionation; SFE: supercritical fluid extraction; SubFE: subcritical fluid extraction; SWE: subcritical water extraction; UAE: ultrasound-assisted extraction.

**Table 2.**
Some representative applications involving the use of sub- and supercritical fluid extractions for bioactive compounds from by-products published during the period 2015–19

| Matrix | Compounds of interest | Extraction method | Extraction solvent | T (ºC) / P (MPa) | Extraction time (min) | Flow $CO_2$ rate (mL $min^{-1}$) | Ref. |
|---|---|---|---|---|---|---|---|
| Hemp residue | Cannabinoids<br>Flavonoids<br>Flavonoids<br>Mono and disaccharides | SFE<br>PLE<br>PLE<br>EAE | $CO_2$<br>Acetone<br>Ethanol/water (80:20) | 70 / 46.5<br>100 / 10.3<br>100 / 10.3 | 10 + 120<br>15***<br>15*** | 2000-3000 | [53] |
| Pressed palm fibers | Carotenoids | PLE | Ethanol | 35 / 4 | 17 | 2.4 # | [54] |
| Juçara residues | Anthocyanins<br>Non-anthocyanic phenolic compounds | SWE<br>PLE | Acidified water<br>Acidified ethanol/water (50:50) | 40 / 10<br>80 / 10 | -<br>- | 1.5<br>1.5 | [55] |
| Juçara residues | Anthocyanins | SFE | $CO_2$ + 10% acidified ethanol/water (50:50) | 60 / 20 | 7 + 39 | 12.48 # | |
| Sugar beet pulp | Pectin | UAE + SWE | Water | 120.72 / 10.70 | 30.49 | | [56] |
| Onion peels | Quercetin | PLE + SAS | Ethanol | 40 / 12 | 20 | | [57] |
| Goldenberry calyces | Withanolides | PLE | Ethanol/ethyl acetate (75:25) | 125 / 10 | 20 | | [58] |
| Mandarin peel | Flavonoids | SWE | Water | 130 / 3 | 15 | 1000 | [59] |
| Orange pomace | Phenolic compounds | FAE + SFE | $CO_2$ + 6% ethanol/water (90:10) | 60 / 25 | 20+75 | 16.02 # | [60] |
| Citrus peels and seeds | Catotenoid and antioxidant compounds | SFE | $CO_2$ + seeds' oil | 41-45 / 25-30 | 120 | 27 # | [61] |
| Pomegranate peels | Phenolic compounds | EAE-HPE | Water | -/300 | 15 | | [62] |
| | Polyphenols | UAPLE | Water | 70 / 10 | 10* | | [63] |
| Apple seed | Lipids | UHSFE | $CO_2$ | 63 / 130 | 300 | 6-10 | [64] |
| Fresh apple pomace | Polyphenols | SFE | $CO_2$ + 5% ethanol | 45 / 30 | 120 | 33 | [65] |
| Mango peel | Nonpolar flavonoids and carotenoids<br>Polyphenols | SFE<br>PLE | $CO_2$<br>Ethanol | 40 / 30<br>40 / 30 | 450<br>330 | 1100<br>1100 | [66] |
| Passion fruit seeds | Antioxidants | SFE + SAS | $CO_2$ | 40 / 15 | 150 | 8.33 # | [67] |
| Passion fruit seeds | Tocols<br>FAs<br>Carotenoids<br>Phenols (piceatamol and scirpusin B) | SFE<br>SFE<br>SFE<br>PLE | $CO_2$<br>$CO_2$<br>$CO_2$<br>Ethanol/water (50:50) | 60 / 17<br>50 / 17<br>60 / 26<br>70 / 10 | -<br>-<br>-<br>120 | 20.64 #<br>20.64 #<br>20.64 #<br>30 # | [68,69] |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Grape marc | Monomeric anthocyanins<br>Other phenolic compounds | PLE<br>PLE | Acidified ethanol/water (50:50)<br>Ethanol/water (50:50) | 40 / 10<br>100 / 10 | 40<br>180 | 5 # | [70] |
| | Lipids<br>Polyphenols (proanthocyanidins) | SFE<br>UAE + SFE | $CO_2$<br>$CO_2$ + 10% ethanol | 45 / 28<br>40 / 8 | 180<br>300 | 167 #<br>100 # | [71] |
| Grape pomace | Polyphenols | PLE-RP | Water/ethanol (85:15) | 90 / 10.3 | - | | [72] |
| Grape stem<br>Grape seeds | Phenolic and anti-inflammatory compounds | PLE<br>PLE | Ethanol/water (70:30)<br>Ethanol/water (75:25) | 120 / -<br>20 / - | 10<br>11 | | [73] |
| Blackberry, blueberry and grumixama residues | Polyphenols (anthocyanins) | UAE + PLE | Ethanol/water (70:30) | 80 / 10 | 30 | | [74] |
| Raspberry pomace | Lipids<br>Polyphenols | SFE<br>PLE | $CO_2$<br>Ethanol/water (50:50) | 60 / 45<br>80 / 10.3 | 10 + 110<br>5*** | 2000 | [75] |
| Cranberry pomace | Lipids<br>Phenolic compounds | SFE<br>SFE | $CO_2$<br>$CO_2$/ethanol/water | | 90<br>90 | 1000 | [76] |
| Olive mill waste | Squalene, mono and polyunsaturated FAs<br>Polyphenols, squalene, mono and polyunsaturated FAs | SFE<br>SFE | $CO_2$<br>$CO_2$ + 0.25% ethanol | 70 / 25<br>70 / 25 | 420<br>480 | 1.33 #<br>1.33 # | [77] |
| Olive pomace | Oil<br>Proteins<br>Lignin and fermentable sugars<br>Lignin and fermentable sugars | SFE<br>SWE<br>SWH<br>SWH + EAE | $CO_2$<br>Water<br>Water<br>Water | 68 / 28<br>88 / 22<br>200 / 22<br>50 /22 | 60<br>30<br>30<br>4080 | 20 #<br>2.26<br>2 | [78] |
| Pistachio hulls | Phenolic compounds (gallantannins and flavonols) | SWE | Water | 110-190 / 6.9 | 30 | 4 | [79] |
| Cocoa bean hulls | FAs and phenolic compounds<br>Phenolic compounds and alcaloids | SFE<br>PLE | $CO_2$<br>Ethanol | 40 /20<br>70 / 10 | 120<br>20 | 11 # | [80] |
| Spent coffee ground | Phenols, flavonids, reducing sugars and proteins | UAS/MAE + SWH | Water + $CO_2$ or $N_2$ | 180-240 / 20-60 | 10 | | [81] |
| | Polyphenols | PLE-RP | Water/ethanol (84:16) | 90 / 10.3 | - | | [82] |

1262

1263 $CO_2$ flow rate: # means g $min^{-1}$; extraction time: n. of * means no. cycles; extraction time: static + dynamic. EAE: enzyme-assisted extraction; FAs: Fatty acids; FAE :fermented assited
1264 extraction; GXL: gas expanded liquids; HPE: high pressure extraction; MAE: Microwave-assisted extraction; PLE: pressurized liquid extraction; RP: resin purification; SAF: supercritical
1265 antisolvent fractionation; SAS: superctitical antisolvent; SFE: supercritical fluid extraction; SubFE: subcritical fluid extraction; SWE: subcritical water extraction; SWH: subcritical water
1266 hydrolysis; UAE: ultrasound-assisted extraction; UAPLE: ultrasound and pressurized liquid extraction; UHSFE: ultra-high pressure supercritical fluid extraction.

**Table 3.**
Some representative applications involving the use of sub- and supercritical fluid extractions for bioactive compounds from seaweeds and microalgae (period 2015–19).

| Matrix | Compounds of interest | Extraction method | Extraction solvent | T (ºC) / P (MPa) | Extraction time min) | Flow $CO_2$ rate (mL $min^{-1}$) | Ref. |
|---|---|---|---|---|---|---|---|
| *Chlorella* sp., and *Scenedesmus* sp. | Carotenoids, chlorophyll A, ergosterol | SFE | $CO_2$ (+ ethanol) | 40-60 / 15-30 | - | 0.5 - 4 # | [111] |
| *Dunaliella salina* | Carotenoids | SFE | $CO_2$ (+5 % ethanol) | 45 / 20 | 180 | - | [112] |
| *Dunaliella salina* | Carotenoids | SFE | $CO_2$ | 60 / 20-40 | - | 6.7 - 8.3 # | [113] |
| *Haematococcus pluvialis* | Carotenoids (astaxanthin) | SFE | $CO_2$ (+20 % ethanol) | 55 / 8 | 0.5 | - | [114] |
| *Lessonia vadosa*[BM] | Fucosterol | SFE | $CO_2$ (+1.5 % ethanol) | 50 / 18 | 100 | 100 # | [115] |
| *Neochloris oleoabundans* | Carotenoids | SFE | $CO_2$ (+10 % ethanol) | 40 / 40 | 120 | 0.6 # | [116] |
| *Sargassum muticum*[BM] | Fucoxanthin | SFE | $CO_2$ | 45 / 10 | 60 | 25 # | [117] |
| *Scenedesmus* sp. | Lipids | SFE | $CO_2$ | 35 / 40 | 360 | | [118] |
| *Schizochytrium* sp. | Lipids | GXL | $CO_2$ (+14 % ethanol) | 40 /6.9 | 120 | 6 | [119] |
| *Chlorella vulgaris* | Carotenoids | PLE | Ethanol/MTHF (50:50) | 110 / 10.3 | 30 | | [120] |
| *Cystoseira abies-marina*[BM] | Phlorotannins | PLE | Ethanol | 100 / 10 | 20 | | [121] |
| *Fucus vesiculosus*[BM] | Phlorotannins, chlorophylls, carotenoids and lipids | PLE | Methanol + DCM | 40 / 10 | 5+5 | | [122] |
| *Fucus vesiculosus*[BM] | Long chain Fas | PLE | Ethyl acetate | 120 / 10 | 10 | | [123] |
| *Kappaphycus alvarezii*[RM] | $_K$-Carrageenan | SWE (IL) | Water + 1% $C_4C_1$im | 150 / 5 | 30-40 | | [124] |
| *Nannochloropsis salina* | Lipids | SWE | Ethanol/water (75:25) | 90 | 120 | | [125] |
| *Neochloris oleoabundans* | Carotenoids | PLE | Ethanol | 100 / 10.34 | 20 | | [126] |
| *Saccharina japonica*[BM] | Polysaccharides (alginate and fucoidan) | SWE (DES) | Water/(ChCl: G, 1:2 mol/mol) (70:30) | 150 / 2 | - | | [127] |
| *Saccharina japonica*[BM] | Phenolic compounds | SWE (IL) | Water + 0.25M $[C_4C_1im][BF_4]$ | 175 / 5 | 5 | | [128] |
| *Sargassum muticum*[BM] | Phlorotannins | PLE | Ethanol/water (95:5) | 160 / 10 | 20 | | [129] |

**Biorefinery approaches**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| *Haematococcus pluvialis* | TG | SFE | $CO_2$ | 45 / 11.7 | 20+240 | 2700 ± 300 | [130] |
| | Carotenoids (astaxanthin) | SFE | $CO_2$ | 45 / 48.2 | 20+240 | 2700 ± 300 | |
| *Isochrysis galbana* | Carotenoids and non-polar lipids | SFE | $CO_2$ | 50 / 30 | 60 | 5000 | [131] |
| | Carotenoids, chlorophylls and mid/polar lipids | GXL | $CO_2$ (+45 % ethanol) | 50 / 7 | 60 | 5000 | |
| | Carbohydrates and proteins | PLE | Ethanol and water | 80 / 10 | 30 | - | |
| *Nannochloropsis gaditana* | Non-polar lipids and pigments | SFE | $CO_2$ | 55 / 40 | 270 | 10000 | [132] |
| | Carotenoids, chlorophylls and polar lipids | PLE | Ethanol | 170 / 10 | 20 | - | |
| *Porphyra umbilicalis*$^{RM}$*, Ulva lactuca*$^{GM}$ *and Saccharina latissima*$^{BM}$ | Phlorotannins and carbohydrates | PLE | Acetone/water (70:30) | 0 / 7 | 7 | | [133] |
| | Proteins | PLE | Methanol/water (50:50) | 37 / 10 | 5** | | |
| *Scenedesmus obliquus* | Lipids | SFE | $CO_2$ | 50/36 | 120 | 7000 | [134] |
| | Carotenoids | GXL | $CO_2$ (+75 % ethanol) | 50/7 | 150 | 7000 | |
| | Carbohydrates and proteins | PLE | Water | 50/10 | 45 | - | |

$CO_2$ flow rate: # means g $min^{-1}$; extraction time: n. of * means no. cycles; extraction time: static + dynamic. DES: deep eutectic solvents; IL: ionic liquids; FAs: fatty acids; FAMEs: fatty acids methyl esters; PUFAs: polyunsaturated fatty acids; TG: triacylglicerides. BF4: tetrafluoroborate; C4C1im: 1-butyl-3-methylimidazolium; ChCl: Choline chloride; DCM: Dichloromethane; G: glycerol; MTHF: 2-methyltetrahydrofuran. Brown macroalgae ($^{BM}$); red macroalgae ($^{RM}$); green macroalgae ($^{GM}$). GXL: gas expanded liquids; HPE: high pressure extraction; PLE: pressurized liquid extraction; SFE: supercritical fluid extraction; SWE: subcritical water extraction.

**TrAC-*Trends in* Analytical Chemistry**
www.elsevier.com/locate/trac

| | |
|---|---|
| To:<br>Dr. Miguel Herrero | Special Issue: **"Green Extraction Techniques"**<br><br>Guest Editor:<br>**Prof. Elena Ibáñez**<br>Laboratory of Foodomics, CIAL, CSIC<br>Nicolas Cabrera 9, 28049 Madrid, Spain<br>elena.ibanez@csic.es<br>http://www.cial.uam-csic.es/pagperso/foodomics<br>Overseeing Editor:<br>**Prof. Alejandro Cifuentes**<br>Laboratory of Foodomics, CIAL, CSIC<br>Nicolas Cabrera 9, 28049 Madrid, Spain<br>a.cifuentes@csic.es<br>http://www.cial.uam-csic.es/pagperso/foodomics |

Madrid, May, 14th, 2018

Dear Dr. Herrero,

As you definitely know, *TrAC-Trends in Analytical Chemistry* is an indexed journal with an impact factor of 8.442 (2016-JCR Science Edition) that covers relevant developments in analytical methodology, instrumentation, computation and interpretation as well as their application in many different fields of research.

After the success of the previous special issue on *"Green extraction techniques"* Edited by Elena Ibañez and Alejandro Cifuentes in September 2015 (Volume 71), and with the aim of providing the scientific community with up-to-date information on technologically and methodologically innovative strategies, together with the current trends and applications of advanced analytical techniques and methods in Green Extraction Techniques, we are preparing a *TrAC Special Issue* devoted to this topic. This special issue on "*Green Extraction Techniques"* will include top of the line **review papers** from experts in the field. Therefore, it is our pleasure to invite you to contribute with your recognized experience to this *TrAC Special Issue* with a review paper tentatively titled:

**Plants, food-by-products, algae and microalgae as natural source of functional ingredients obtained using sub- and supercritical fluid extraction**

Please feel free to contact Prof. Ibañez (elena.ibanez@csic.es) if you have any questions about the special issue or on your contribution.

The whole submission and editorial process are entirely managed via the journal's online system EVISE. Please see below submission instructions:

Submission link: https://www.evise.com/profile/#/TRAC/login

- First-time user will need to register first;
- Please select special issue short title "VSI: Green extraction techniq" during submission process;
- Please follow step-by-step guide in completing the submission procedures
- Submission deadline: 1st February 2019

You are kindly requested to send, by e-mail to, an answer (positive or negative) on this invitation providing a tentative title of your contribution ideally together with a brief scope and section headings **within three weeks**.
Thank you in advance for your interest and your cooperation. Looking forward to hearing from you soon.
Sincerely,
Elena Ibáñez and Alejandro Cifuentes