Green extraction processes, biorefineries and sustainability: recovery of high added-value products from natural sources

Miguel Herrero, Elena Ibañez

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

ABSTRACT

The role of compressed fluids-based extraction techniques for the sustainable recovery of valuable products from natural sources is described and discussed. Important aspects for green process design including the use of new solvents with novel interesting properties, the development of integrated and intensified multi-unit operation processes as well as scale-up and techno-economic and environmental assessment are emphasized. Within this important research field, some key aspects are identified for the future development of more efficient, environmentally friendly and sustainable processes for bioactives recovery from natural sources. The use of biorefinery platforms based on the use of supercritical and/or pressurized fluids should have a critical importance in the near future.

Keywords: Environmentally-friendly processes; compressed fluids; natural sources; bioactive compounds; valorization; green chemistry; biorefinery

INTRODUCTION.

In spite of the detrimental opinions of some important world leaders today, global environmental conscience and awareness continues to be on the rise. Terms like those included in the title of the present manuscript, *green*, *biorefineries* and *sustainability*, are more and more important in all the aspects of general development. Climate change, global warming, and the realistic threat of a lack of resources in the future for the rapidly growing world population have contributed to the push for process greenness and sustainability and not just to productivity. As a consequence, processes within different fields are being re-formulated to get an enhanced sustainability. Sustainability was brilliantly defined in 1987 by the UN World Commission on Environment and Development as “the development that meets the needs of the present without compromising the ability of future generations to meet their own needs” [1]. Thus, strictly speaking, to promote a sustainable development implies not to induce any harm to the environment, avoiding both damage and resources exhaustion. One of the key aspects of sustainable development is the reduction or even total elimination of wastes. The European Union, as well as other international organizations, is fostering actions in order to stimulate the transition towards circular economy, in which exhaustive recycling and re-use in every step of the production chain is sought [2]. This idea is in close association with the principles governing the concept of Green Chemistry, which are mainly aimed to reduce wastes and to promote a more efficient use of energy and resources [3]. Regarding exclusively the extraction of natural products, another six specific principles have been proposed [4]. These include innovation by i) selection of varieties and use of renewable plant resources, ii) use of alternative solvents and principally water or agro-solvents, iii) reduce energy consumption by energy recovery and using innovative technologies, iv) production of co-products instead of waste to

include the bio-and agro-refining industry, v) reduce unit operations and favour safe, robust and controlled processes, and vi) to aim for a non-denatured and biodegradable extract without contaminants. Most if not all the present and future trends on extraction of high-value compounds from natural matrices follow these principles, which are linked to the biorefinery concept. Biorefinery can be defined as the development of integrated processes for the conversion of biomass into energy and a variety of products, mainly biofuels and added-value co-products, in a sustainable approach [5].

Within the natural products extraction field, biorefinery implies the attainment of targeted compounds from the matrices as well as from the possible by-products generated. In particular, the extraction of bioactive compounds is of utmost interest, both for the functional foods industry as well as for the production of dietary supplements. From the functional foods containing health claims marketed worldwide at present, peptides, polyphenols, carotenoids, polyunsaturated fatty acids or sterols and stanol, just to name a few, are obtained from natural sources. Most common raw materials are plants, marine organisms, including microalgae and seaweeds, but also food- and agri-food related by-products. In order to be fully utilized, the bioactive compounds contained in those matrices should be selectively extracted, minimizing the co-extraction of unwanted materials while looking for high extraction efficiency. To achieve these requirements, advanced environmentally clean extraction techniques using green solvents are needed. Techniques based on the use of compressed fluids clearly fall within that category. Pressurized liquids extraction (PLE), supercritical fluids extraction (SFE) or gas-expanded liquids (GXLs) extraction are the most-widely employed. These techniques are characterized by the possibility of using appropriate green solvents, but keeping in mind the highest possible reduction in the total volume needed. The properties that an ideal green solvent should possess include: i) low

toxicity to humans and other organisms; ii) easily biodegradable in the environment without adverse effects; iii) naturally occurring; iv) produced from renewable sources; v) produced as a by-product, vi) low vapor pressure; vii) no need of a traditional evaporation step after extraction [6]. In any case, it is difficult to find a solvent matching all these properties. Additionally, sustainable extraction processes for the extraction of high-added value products from natural matrices should be assessed from a techno-economical point of view, including life cycle analysis (LCA). This way, even a perfectly green solvent providing low capability for the recovery of a particular compound shall be discarded.

In the present Perspective article, a description of the current state of this topic is included, as well as some interesting examples illustrating the latest advancements made in the field in recent years. Moreover, the future knowledge needs are identified and critically assessed.

2. CURRENT STATE

In our previous manuscript [7] published in 2015, we identified some needs that were still missing to favor the widespread use of compressed fluids technologies; in this section, those needs are discussed, highlighting their evolution along these last two years; as mentioned, some examples will be presented in more detail considering their key interest in the field and as a way to introduce us to the new challenges for the future.

1) the need for designing new processes based on green solvents such as pressurized fluids, GXLs, organic aqueous tunable solvents (OATS), switchable

solvents, deep eutectic solvents (DES), ionic liquids, etc. and new tools for solvent modelling and design under pressurized conditions.

In the published literature in the last two years there has been an increase in the contributions related to “green solvents AND supercrit*” (based on Scopus search, September 2017) with around 400 manuscripts, from which half correspond to “green solvents AND supercrit* AND design”. This large increase has to do not only with the applications of green solvents in different high pressure conditions but also on new tools for solvent modelling; for instance using molecular dynamics (MD) simulations [8] and Monte Carlo simulations it has been possible to investigate, among others, the phase equilibria in CO₂-expanded systems and to predict their physicochemical properties as media for engineering processes [9]. On the other hand, new solvents, with interesting properties have been studied with the goal of improving the coverage of supercritical CO₂ for the solubilization of “insoluble” substances: for example, Ingrosso et al. [9,10] synthesized and characterized a supramolecular complex in scCO₂ to act as “solubilizer” (systems able to transport insoluble substances into the solvent owing to their emulsifying or dispersion properties) based on a polar aromatic molecule (benzoic acid) and peracetylated β -cyclodextrin, which is soluble in the supercritical medium. In this study, authors demonstrated that a polar guest with hydrogen-bond donor capacity was able to force the opening of the cavity and to form a stable inclusion complex. The properties and behavior of the complex was predicted by simulation and experimentally confirmed, opening the door for more applications of scCO₂ in different areas, including supramolecular synthesis, reactivity and catalysis, micro and nano-particle formation, and extraction processes with increased selectivity.

In the search for new solvents appropriate for designing new sustainable and green processes for the recovery of bioactive compounds from natural sources, deep eutectic

solvents (DES) have emerged [11]. A DES is usually composed of two or three different components that are able to interact with each other establishing hydrogen-bond interactions. The possibilities are huge, although, typically, a mix between a quaternary ammonium salt and a hydrogen-bond donor is used. Consequently, these new solvents are described as cheap, non-flammable, possessing low vapor pressure and involving easy steps for their preparation and purification. Although the “greenness” of each DES should be carefully assessed looking into their biodegradation potential, in principle, they are able to solve some of the issues related to the use of ionic liquids, such as avoiding the generation of by-products during their preparation, and improving the biodegradability potential, thus, minimizing bioaccumulation. Although the mentioned characteristics are advantageous for the recovery of valuable compounds, some of them also imply diverse shortcomings for the final recovery of the targeted compounds, as DES will essentially be impossible to evaporate. This topic shall be investigated further, although some approaches have been already employed, such as liquid-liquid extraction using another solvent, solid-liquid extraction using some adsorbents, or precipitation by addition of antisolvents [12]. In any case, as new applications of these solvents are explored, new separation procedures will be also developed, depending on the particular application. The use of antisolvent or precipitation procedures would arguably be more advantageous from a sustainability perspective, as would allow the purification or separation of the extracted compounds without using significant amounts of organic solvents.

A clear example of the application of these solvents is the systematic production and study of 20 DESs including choline chloride and several hydrogen-bond donors to extract rutin from *Sophora japonica* tree [13] in order to avoid the use of traditional low efficiency extraction methods based on hot water, methanol or ethanol. All the tested

DESs showed good biodegradability rates, by far higher than most common ionic liquids, and presented low toxicity. From the studied DESs, 9 of them provided higher extraction yield for rutin than conventional solvents such as 60% methanol or 60% ethanol [13]. This work shows the good possibilities of DESs for the extraction of bioactive compounds from natural sources, and opens the door to future applications of these solvents under pressurized conditions, where their characteristics could favor even further the recovery of interesting compounds. Up to now, this field is greatly underexplored and, thus, their application together with advanced extraction techniques could result in with efficient and sustainable new processes for the recovery of bioactives from natural sources.

Other interesting applications have been developed in the last few years showing the importance of solvent selection in the development of processes for the extraction of bioactive compounds from natural sources, here we are going to highlight those based on solubility parameter theory. Several examples can be found recently in which the estimation of the Hansen Solubility Parameters (HSP) is employed as a tool to narrow the selection of the most appropriate green solvents to selectively extract bioactive metabolites from natural sources [14,15]. For instance, Srinivas and King [16] estimated HSP of some carotenoids (e.g. β -carotene, curcumin, lutein, violaxanthin and zeaxanthin) present in spices (e.g. black pepper, cayenne, cinnamon, garlic, ginger) in supercritical carbon dioxide (SC-CO₂) at different temperatures and pressures, while Chemat et al. [17] also employed the HSP to evaluate the performance of several alternative solvents to extract valuable compounds (aroma, fat and oils, carotenoids, etc.) from different food matrices to substitute petroleum based solvents (such as hexane and dichloromethane). Key aspects to consider in this approach are the need for estimating individual HSP of the target molecule and the predictions needed for

obtaining HSP for both, solutes and solvents under compressed fluids conditions. In a recent work by Sánchez-Camargo et al. [18], HSP were employed to identify the most convenient bio-based solvents for the selective extraction of a valuable carotenoid (fucoxanthin) from *Phaeodactylum tricornutum*, using pressurized technologies. The application of HSP reduced the list of candidate solvents for PLE to the following four solvents: ethyl acetate, ethyl lactate, d-limonene and ethanol (Figure 1). Among all of them, the bio-based solvent d-limonene was the most selective, although only a 50% of recovery of fucoxanthin from the biomass was obtained when working under static PLE conditions; in order to increase the recovery, a dynamic extraction using a mixture of SC-CO₂/d-limonene under CXL (Carbon dioxide-expanded liquids) conditions was proposed reaching, in this case, 90% of recovery. The other three solvents tested showed good recoveries of fucoxanthin, but were less selective, following the decreasing order: ethyl acetate>ethyl lactate>ethanol. Total extraction of fucoxanthin from the biomass, together with other co-extractants, was achieved using static PLE with ethyl acetate.

Therefore, it can be concluded that Hansen solubility parameter approach can be exploited in the development of greener selective processes for the extraction of valuable compounds from natural sources, since the use of a theoretical approach reduces the number of experiments, thus minimizing the use of resources and waste generation and making the processes more environmentally friendly and sustainable. More applications and new approaches towards the use of HSP on our way to a “bio-based world” are expected in the near future.

2) the need for a real scaling up of the integrated processes and for an improvement of our knowledge on scalability principles and on the application of

environmental assessment tools (LCA, etc.) and economic studies to offer better and safer (and clean) alternatives to more conventional processes.

Process integration and intensification are interesting concepts while designing sustainable natural products extraction processes. Although somewhat similar, process integration is based on the efficient coupling of different unit operations involving the best conditions for each one, while process intensification implies performing different unit operations within the same equipment [19]. In any case, both alternatives permit reducing energy consumption, cost as well as waste and by-products. In the last few years there has been also an increasing contribution of manuscripts related to process integration and intensification and supercritical fluids; in a search done in Scopus (September, 2017), more than 400 manuscripts have been published between 2014 and October 2017 but only a few deal with scaling up, economic and life cycle assessments. Although some of them have been associated with a more broad approach to bio refinery (that will be discussed in more detail in the following section), most of them deal with the integration (or intensification) of different unit operations for extraction, separation, reaction, particle formation, etc.

One of the possible alternatives with high interest is the simultaneous or sequential extraction and modification of a compound to yield a more interesting substance. Some approaches have been already presented, for instance for the pressurized extraction and subsequent enzymatic hydrolysis of quercetin glucosides from onions [20]. Other possibility is based on tuning the extraction conditions in order to produce a concurrent extraction and modification of the compounds contained in the natural matrix in a single process. A recent example of this approach is illustrated in the simultaneous extraction of sinapoylcholine (sinapine), sinapic acid and canolol from rapeseed meal [21]. Sinapine, a choline ester of sinapic acid, is the main phenolic compound in rapeseed.

Under proper circumstances, sinapine can be chemically hydrolyzed to sinapic acid, which in turn, could be transformed into canolol under high temperature. Canolol has been described as a good radical scavenger, and it is believed to possess anticarcinogenic and antimutagenic activities. Thus, this compound could be interesting for the production of functional foods and supplements.

Thus, thanks to these particular properties, authors developed a one-step integrated method for the concurrent extraction and conversion of sinapine into canolol. Firstly, the ability of PLE to recover a bioactive compound such as sinapine was further demonstrated, since using 60% methanol for 20 min, 200 °C, it was possible to extract more than 300% the amount extractable using Soxhlet extraction for 12 h (using 100% methanol at 100 °C, employed as a reference method). Subsequently, it was shown that with the addition of 1% NaOH to methanol and using this mixture as extracting solvent at 200 °C was possible to obtain up to 7.23 mg canolol/g rapeseed in just 5 min. This yield of conversion was significantly higher than those reported previously based on classical processes involving different steps such as transformation, extraction and hydrolysis. The idea behind this approach could be further exploited in other applications in which a simultaneous extraction and modification of bioactive natural compounds could be obtained in a shorter period of time, thus, reducing energy and solvent consumption while increasing process efficiency and sustainability. A field in which this approach may have tremendous success is the valorization of food-related by-products. Thus, in the coming years more applications following this line to obtain high added-value natural compounds are expected.

Supercritical (or compressed) fluids technologies have been always associated to high investments costs but most of time, no real economic evaluation of the processes (including simulation at large scale) has been carried out. In order to address these

important issues, readers are referred to a basic and fundamental text of Brunner [22], dealing with the process design and scaling up of separation processes based on supercritical fluids. Two very interesting examples have been published recently involving the economic assessment of integrated [23] and intensified processes [24] based on compressed fluid technologies. For instance, Viganó et al. [23], carried out the economic evaluation of two scale-up processes to obtain different phytonutrients, such as fatty acids, carotenoids, tocopherols, and phenolic compounds from passion fruit by-products (bagasse and rinds). Processes developed consisted of a) a sequential multi-stage process comprising three steps of SFE and one step of PLE to obtain four different fractions from passion fruit bagasse and b) a single-stage PLE process to obtain one extract rich in phenolic compounds from passion fruit rinds. Authors carried out simulations of the extraction processes using the SuperPro Designer 9.0 software. Figure 2 shows, as an example, the flowsheet of the extraction process developed for the simulation of the sequential multistage process. Economic simulation and sensitivity study were performed for plants containing two extraction vessels of 1, 5, 50 and 500 L. Results demonstrated that both processes seem to be economically applicable at large production scale since scaling up increased the process productivity and decreased the cost of manufacturing (COM); in particular, when the system capacity increased from $2 \times 1 \text{ L}$ to $2 \times 500 \text{ L}$ COMs of extracts from sequential multi-stage and single-stage processes decreased, respectively, from US\$ 220.51/kg to US\$ 26.33/kg and US\$ 71.03/kg. This work is a good example on the economic viability of compressed fluid technologies when bioactive extracts are produced in large scale and sold at the current market price.

As mentioned, another example involving economic evaluation of, in this case, an intensified process including in sequential mode PLE (at 40°C, 12 MPa with ethanol) +

supercritical antisolvent (SAS) precipitation (at 40°C, 10 MPa with supercritical CO₂) to produce quercetin-rich powdered extracts from onion peels was recently published by Zabot et al. [24]. The sequential process was able to produce around 4 grams of microparticles per 100 g of onion peels with 26 wt% of quercetin; the microparticles had a mean particle diameter of 119 µm. Different scenarios for techno-economic evaluation of the process were selected. As in the above mentioned example, the best scenario was obtained using a larger plant capacity, with vessels of 500 L. Results showed that for a productivity of 17.7 ton/year, the COM of the microparticles was quite low, US\$ 63.98/kg. Other parameters, such as the return on investment, the payback time, and the gross margin were also positive. In this case, process intensification is economically viable since the energy required to pressurize the extraction vessel can be later used for spraying and producing microparticles in the precipitation vessel.

It is worth to mention that in both examples, an agricultural by-product was employed, which clearly can help reducing the overall costs of the process since the price of the raw material employed is almost zero. Moreover, this approach is in line with the sustainability concept through the revalorization of biowastes for the manufacture of co-products of high added-value.

On the other hand, it is important to mention that sometimes evaluation of economic viability does not consider amortization costs, which are undoubtedly higher at large scales, nor leverage levels required for bank loans for large scale plants. In cases in which these factors make unacceptable large scale production, low to medium scales of specialty products with improved characteristic can be profitable if the process is optimized and justified for certain applications.

Other interesting examples dealing with the techno-economic and environmental assessment of different processes based on the use of compressed fluids technologies are suggested in order to guide readers and researchers in the field [25,26].

3) the need for developing multi-unit operation systems and integrated/intensified processes as the right track towards a biorefinery platform.

As already mentioned in the introduction, biorefinery can be defined as the development of integrated and/or multi-unit operation processes for the conversion of biomass (biowastes, microalgae, algae, plants, forest biomass, etc.) into energy and a variety of products, mainly biofuels and high added-value co-products and chemicals, in a sustainable approach [5]. In this area of research, important advancements have been produced in the last 3 years in which publications (143) accounting for “biorefinery and supercrit*” (Scopus, September, 2017) correspond to more than 70% of the total publications considering all years. These publications deal with the integration of a variety of separation and conversion processes to produce multiple product streams from renewable feedstocks with little or no waste. Production of energy, biofuels, multiple products and, more importantly, high added-value products can help promoting the viability of the biorefinery as a whole and the growth of a sustainable bioeconomy. It is important to highlight that, among the 143 manuscripts published, 35 of them address the issue of economic analysis but only 4 of them include also the scale-up study of the process and 4 contain environmental assessment of the processes through LCA studies. Undoubtedly, economic analysis can be considered as the first step for industrial establishment of these technologies; therefore, an important progress is observed in the last few years, although there is a real need for a more integrative approach that considers together process scalability, economic analysis and

environmental issues in order to make biorefineries based on compressed fluid platforms a reality.

In a very interesting review paper from Temelli and Ciftci [27], different biorefining approaches (or ideas) for lipid-rich grains using SC-CO₂ are presented and discussed, together with the technical and economic challenges identified for developing an integrated SC-CO₂ biorefinery (considering also integration of supercritical operations with conventional technologies) for the processing of grains. Among the different processes described, the supercritical biorefinery of grains and of dried distillers' grains with solubles (DDGS), a by-product of the bio-ethanol industry, are especially interesting.

Supercritical biorefinery of grains targets utilization of all components to produce high added-value products. A process chain is proposed including 1) extraction of lipids with SC-CO₂; 2) fractionation of the extracted lipid mixture into high-value minor lipids (carotenoids, tocopherols and phytosterols); 3) separation of the residue, containing proteins and carbohydrates using conventional techniques or subcritical water extraction. The proposal of using this last fraction as the coating material or the matrix for particle formation to encapsulate the minor lipid components (using SC-CO₂ for particle formation) is especially attractive. Moreover, the lipid fraction (mainly triacylglycerides, TAGs) remaining after separation of minor lipids can be also employed to produce biodiesel in a SC-CO₂ bioreactor. Figure 3 shows a scheme of the proposed integrated supercritical biorefinery for the processing of grains.

On the other hand, the re-use of DDGS for a biorefinery is also suggested; in this case, it is important to highlight the great interest of processing a material which is rich in proteins, lipids and carbohydrates and that is, as mentioned, a by-product of the bio-ethanol industry. An integration of supercritical operations with bio-ethanol production

is presented as an advantageous economic situation in which minor lipids and biodiesel were obtained.

Readers are encouraged to carefully read the mentioned review for more information about possibilities offered by this biorefinery approach, together with an in depth explanation about fundamentals and challenges to be met.

A nice example of an economic, environmental and energetic evaluation of a supercritical biorefinery of sugarcane has been recently published [28]. In this paper, nanocellulose production based on four different lignocellulosic fractionation (pretreatments) processes were explored; two of them based on supercritical fluid processes (SC-CO₂ explosion or organosolv assisted by CO₂) and two based on conventional processes such as SO₂-catalyzed steam explosion and organosolv processes. These pretreatment processes were compared in terms of environmental (amount of reagent, water, and CO₂ emissions per kilogram of nanocellulose produced), energetic and economic aspects. A commercial simulator, Aspen Plus, was employed for this purpose. Moreover, the integration of nanocellulose production in the process of ethanol manufacturing from lignocellulosic materials was also tested as a way to revalorize the residual cellulose after enzymatic hydrolysis to produce ethanol. Results demonstrated that the integration of explosion-based methods (SO₂-catalyzed steam explosion and supercritical CO₂ explosion) as a pretreatment step, ethanol production through enzymatic hydrolysis and production of nanocellulose from the residue of hydrolysis was very attractive economically, energetically and environmentally. Authors point out that one of the advantages of including a supercritical fluid-based lignocellulosic biomass fractionation process (supercritical CO₂ explosion and supercritical CO₂ organosolv fractionation) inside an alcoholic fermentation facility comes from the recycling of the CO₂ produced as a by-product during fermentation thus

reducing the overall CO₂ emissions; these processes turn out to be very encouraging in terms of environmental aspects.

4) the need for more efficient processes for bioactive compounds recovery.

In this area of research, there is always a need for improved processes that can provide advantages over conventional processes in terms of efficiency, energy consumption and the ability to reduce or eliminate the use and generation of hazardous substances.

In this sense, an interesting alternative for the extraction of bioactive compounds might be the use of ultrahigh pressure extraction (UPE) [29]. UPE is based on the hydrostatic application of pressure typically up to 500 MPa. This is a batch operation in which the sample and the solvent are introduced in a plastic bag and then sealed. Although the operation may differ from conventional automatic extraction procedures, the application of super-high pressures has been demonstrated to produce substantial cell structure damage during the extraction of plant samples, thus, facilitating the recovery of the contained compounds. Moreover, it is performed at low temperature, although it can yield similar or better extraction yields than other extraction techniques such as reflux, ultrasonic or microwave-assisted extraction. Even if the integration of this technique in a coupled process may present some difficulties, the exploration of the use of new green solvents, as well as other intensification approaches may be worthwhile in the future. For more information about this promising process, readers are referred to an interesting review from Xi [29].

3. PERSPECTIVES AND FUTURE DIRECTIONS

Although throughout this article we have been identifying the future needs in the different fields of the development of green extraction processes for the recovery of

high added-value products and bioactive molecules from natural sources, in this section we are going to summarize all of them while suggesting new future directions or challenges in the field.

- Design of new processes based on green solvents: although, as mentioned, important advancements have been observed in the last few years in terms of tools for modelling and designing green solvents, there is still a long way to go until we are able to understand the interactions between the new types of solvents (subcritical water, GXLs, OATS, switchable solvents, DES, etc.) with bioactive molecules under pressurized conditions. This is mainly due to the change in the physicochemical properties of the solvents under high pressure conditions that can lead to modified interactions and, therefore, to a non-predictable behavior when designing green pressurized processes. In this sense, a wider application of simulation tools is expected to understand these interactions together with more accurate predictive tools to obtain, for example, HSP for both, solutes and solvents under compressed fluids conditions.

- scaling up of integrated and intensified processes and economic and environmental evaluation: we have shown with several examples that process integration/intensification, including, for example, extraction and modification of bioactive natural compounds can help reducing energy and solvent consumption, thus increasing the efficiency of the process and its sustainability. Moreover, if these processes are based on the use of biowastes or agricultural/food by-products they have more possibilities of economic and environmental success. However, as already mentioned, not many studies in this field include the application of environmental assessment tools nor economic evaluation in order to effectively demonstrate the advantages of compressed fluids technologies compared to conventional processes.

420 - improving our knowledge on chemical composition and bioactivity of extracts: in
421 general there is important advancement on the chemical knowledge of the compounds
422 responsible for the associated bioactivity of compounds/extracts obtained from natural
423 sources. This is a very active field of research and the world of compressed fluids
424 should consider the inclusion of this knowledge in multidisciplinary teams involving
425 chemists, biologists, chemical engineers, environmental chemists, etc. with the double
426 objective of improving processes towards the target compounds and of maintaining (and
427 even improving) the bioactivity associated through their transformation into different
428 entities.

429 - development of supercritical (or compressed) fluids biorefinery platforms: this area of
430 research can be seen as the integration of all the above mentioned areas; therefore, all
431 the progress we would be able to achieve could be applied. In this sense, there is a need
432 for improving the knowledge on scaling up, economic and environmental assessment of
433 supercritical technologies and its comparison to conventional processes to really
434 understand the advantages offered by the compressed fluid processes, mainly through
435 its integration into a biorefinery. Moreover, we should be able also to develop common
436 principles for processes (unit operations for extractions, separations, reactions, particle
437 formation, etc.) and how to place them into a multi-unit operations platform using
438 compressed fluids.

439 Finally, even if there has been important progress in meeting the challenges that were
440 identified few years ago, there is still a lot of work to do to translate the efforts made in
441 our laboratories to the real world. But we should keep going with the conviction that the
442 compressed fluid technologies can help improving our world, helping its sustainability
443 and pushing towards a circular bioeconomy more favorable for the human beings and
444 the planet.

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FIGURE LEGENDS.

Figure 1. Three-dimensional Hansen solubility parameter sphere of all solvent for evaluated. Blue dots inside the sphere dissolve the fucoxanthin and red squares outside do not dissolve it. 1. n-hexane (behind the sphere) 2. Dichloromethane; 3. d-limonene; 4. Ethyl acetate; 5. Ethyl lactate; 6. Ethanol, 7. Acetone, 8. Methanol, 9. Water. Reproduced and adapted with permission from [18], Copyright Elsevier, 2017.

Figure 2. Simulation flowsheet designed with SuperPro Designer 9.0 software: extracts obtained by the sequential multi-stage process. Reproduced with permission from [23], Copyright Elsevier, 2017.

Figure 3. Example schematic of a potential integrated biorefinery based on SC-CO₂ technology for the processing of grains. Reproduced with permission from [27], Copyright Elsevier, 2015.