Extraction Techniques of Procyanidins

Subjects: Biochemical Research Methods

Contributor: Cristobal Aguilar

Procyanidins are an important group of bioactive molecules known for their benefits to human health. These compounds are promising in the treatment of chronic metabolic diseases such as cancer, diabetes, and cardiovascular disease, as they prevent cell damage related to oxidative stress.

Wastes Extraction Procyanidins Ulltrasound Microwave

1. Introduction

Extraction methods have been used to recover bioactive phytochemicals from natural sources, which are of interest in human health. These methods were previously required to separate, purify and analyze bioactive compounds of plants [1] and are referred to in the literature as conventional or traditional or classical methods, among them being maceration (M), percolation (P) and successive solvent extraction (SSE). These methods have been widely used in the extraction of procyanidins. Some authors report procyanidin extraction from different food production chains, for example, raw cacao and blueberry [2][3]. However, researchers have proposed alternative methods that allow higher compound yields, process efficiency, and lower solvent use. Efficiency is an important factor in choosing the extraction method, being related to the recovery of compounds and biological stability of compounds, time, and energy-saving during the extraction process. Efficiency depends on the conditions of extraction, which could affect the structure of compounds as location and distribution of hydroxyl groups, terminal and extension units, interflavanic bonds, and interactions with other compounds [4][5].

2. Ulltrasound-Assisted Extraction

Ultrasound-assisted extraction (UAE) is a simple method with short duration and has little effect on the environment. It is considered an emerging technology and better than classical methods due to rapid mass production [6]. This type of extraction has several applications in various industries (agro-industrial wastes) to obtain polyphenols such as procyanidins [7]. For the extraction of procyanidins from by-products of wine processing, UAE has been used to study its effect on the compounds' structure and biological activity.

Extraction obtaining bioactive compounds by the ultrasound method from agro-industrial residues has been widely reported [2][8]. However, few reports of procyanidin extraction have been reported in the last five years, and most studies have focused on the evaluation of different extraction conditions on the yields of bioactive compounds [2][9][10][11][12][13][14][15]. The mechanism of extraction occurs by mechanical vibration through waves that penetrate a liquid system and form gas bubbles [16]. These bubbles are affected by the acoustic cavitation phenomenon, which

leads to their collapse. Thus, there is an increase in pressure and temperature in the medium that creates an ultrasound micro-jet in the solution [17].

Grape seeds are rich sources of oligomeric procyanidins, rather than polymeric procyanidins, which represents an advantage for different industries. The ultrasound technique was used to study the depolymerization of procyanidins, finding considerable increases in the content of polymeric procyanidins, oligomeric and catechin monomers, corresponding to 41%, 35% and 49%, respectively [18].

Researchers also used this technique by varying the frequency of the test (45 and 20 kHz), obtaining higher polymeric procyanidin concentrations at 20 kHz. The breakdown of procyanidins was expected in tests with the frequency change. However, at 45 kHz the concentration of procyanidins decreased, due to obstructions in the mass transfer that occurred during the bubble formation. The improved antioxidant activity in treatments with ultrasound was associated with the hydroxyl groups, which were identified by Fourier transform infrared spectroscopy (FTIR) analysis, and could be generated by the rupture of links between procyanidins with polysaccharides or proteins [18].

A modification to the UAE is called the high-intensity ultrasound (HIUS) technique that is characterized by working at high intensity and low-frequency conditions. HIUS is attractive because of production costs, simplicity, reduced extraction times and small environment effect. Applying ultrasound of high intensity on *Araticum* peel extracts increased antioxidant activity of procyanidins A and B. These the results were achieved with short extraction times (0.5–5.0 min) [19].

Recently, combination with cavitation methods using negative pressure has been proposed to increase the yields of procyanidins, by increasing ultrasonic power between 0.2–0.35 W/cm^2. A combination of nitrogen pressure on cavitation, collision of bubbles, cell disruption, and transfer of compounds in the extracting medium during extraction improved the yields of compounds, [2][20]. Other process conditions could affect the biological activity of procyanidins, such as vegetal material concentration, type of solvent, temperature, stirring speed, and time stirring [21][22]. Improvement of the bioavailability of procyanidins for pharmaceutical purposes has led to the development of methods for controlling the particle size of the compounds. To this goal, ultrasonic methods have been combined with the precipitation of antisolvents, with successful results under the optimal parameters of power, stirring speed, stirring of 620 W, 760 r/min, 14 min and 0.3 mg/mL, respectively, which allowed increase antioxidant activity. This may be due to the phenomenon of collision of particles by cavitation and a decrease in the agglomeration of crystals [21].

Recent advances in UAE have been explored using a macroporous resin to improve the purification and recovery of bioactive compounds, including procyanidins. The combination of these methods helps to increase extraction yield and reduce process times. The main factors that influence the quantification of the extraction process are the structure, polarity, and size of a bioactive molecule, type of resin, solution concentration, interaction resin-molecule, and ultrasound power [23]. A previous study confirmed that the employed resins (HPD-500) in ultrasonic treatments, when applied at 270–540 W for 15 and 5 min, respectively, increased adsorption capacity and mass transfer of

procyanidins from baobab fruit pulp, as compared to treatments without use of ultrasound. In this study, procyanidins B2 and C1 were identified and quantified in samples treated at high power sonication (540 W) and short exposure time (5 min), with concentrations corresponding to 751.34 ± 32.76 mg/100 g dry matter (DM) and 566.38 ± 10.78 mg/100 g DM, respectively [22]. Limwachiranon et al. [9] reported procyanidin concentrations of 20 mg in lotus seed extracts using mixed solvents (acetic acid, acetone, and water).

Another type of combination with the ultrasound technique is the use of enzymes. Research has been carried out to obtain more available bioactive compounds using enzymes in ultrasound extractions using methanol as a solvent. Martins et al. [24] studied the biotransformation of condensed tannins through the enzymatic hydrolysis of tannase alone, pectinase plus cellulase, or a mixture, in white, red and mixed of grape pomaces, which were obtained from Brazilian wine production. The content of condensed tannins decreased in the enzymatic treatments with respect to the control treatment (without enzymes) and had variations in the different grape pomaces. The best results were obtained in red grape pomace in a treatment with pectinase-cellulase (21.5 mg catechin equivalents (CE)/g DM). The main polyphenolic compounds found were catechin and procyanidin B2, catechin standing outfor all treatments, with range of values for catechin and procyanidin being from 575–2009 and 166–1071 mg CE/g DM, respectively. The highest values of these compounds were observed in the grape pomace network, although they were not affected by enzymatic treatments.

In another study, isolation of procyanidins from lychee pericarp by ultra-high-pressure (UHP) extraction was compared to UAE and extraction with ethanol (ECE), to evaluate the polyphenolic profile and antioxidant activity of samples dried in an oven at 80 °C for 36 h. Polyphenolic compounds such as procyanidins A2, procyanidin B2, epicatechin, isoquercitrin and quercetin-3-rutinoside-7-rhamnoside were identified. The B2 procyanidins content was 1.13, 1.21 and 1.29 mg/g in ECE, UAE, UHP, respectively. However, the content of the A2 procyanidin was higher, with values of 4.46, 4.68, 4.97 mg/g in the same extraction treatments. These results were correlated with antioxidant activity tests, where the content of total polyphenols and antioxidant activity increased when UHP was used. Although studies have confirmed the presence of lychee procyanidins, few studies have focuses on the extraction of these compounds. The authors state that the yields of polyphenols could be improved with the adjustment of temperature and pressure in the extraction processes, since compounds such as anthocyanins are sensitive to heat, and in the case of procyanidins they can be polymerized at high temperature and pressure [25].

On the other hand, procyanidin oligomers have been extracted and purified mainly from by-products of the wine industry such as grape seeds. Due to their availability and cost, the extracts have been marketed in the food industry, especially the dietetic and supplementary market. Procyanidin polymers are macromolecules generated in these purification processes, for which extraction methods have been developed that allow their depolymerization and reduction in molecular size as catechins or oligomers. Structural characteristics and antioxidant activity of procyanidins and their derivatives in methodologies with an ultrasound bath and by a probe were evaluated. The conditions of both extraction methods were varied; the first with continuous and degas mode, and the second with 30% and 70% of amplitude in pulsed mode. The analyzes show the presence of 85% of polymeric procyanidins and 2.5% of monomeric and oligomeric flavan-3-ols. Increases in the molecular masses of these compounds were also observed when using an ultrasonic bath in continuous mode. In the MALDI-TOF analyses, type B procyanidins

were observed, and the best results of antioxidant activity were obtained in the probe assays at an amplitude of 70% and a procyanidin concentration of 0.01%, while for the assays carried out in the ultrasonic bath antioxidant activity was better at higher concentration of procyanidins. The data obtained on antioxidant activity were positively affected compared to controls. The authors suggest that the ultrasound method may constitute an effective strategy to modify the structure of polyphenolic compounds in grape seeds, allowing the formation of procyanidin oligomers and polymers with antioxidant activity, that apparently could happen by the breaking of linkages with proteins and/or polysaccharides [18].

Tannin contents were reported by Kim et al. [26] in grape skin and seed ultrasound-assisted extractions using methanol, ethanol and acetone at different concentrations (10, 70 and 70%, the latter with HCl addition). The highest content of these compounds was observed in seeds extracted with 70% acetone (acidified) at 14.72 mg/g. The identified compounds were monomers and dimers of tannins such as catechin, epicatechin, epigallocatechin, procyanidin B1 and B2, procyanidin B1 being the main compound extracted for all trials. The highest content was found in skin (1076 mg/kg) and seed (1741 mg/kg) using extractions by acetone and methanol at 70%, respectively. The authors indicate that the content of the type of tannin (monomer or dimer) extracted depends on the type of solvent used. In this study, methanol was more efficient for the extraction of condensed tannins as procyanidins (dimers), while molecules of lower molecular weight, such as catechins (monomers), were extracted mainly with acetone and methanol, both at 70%.

There is extensive information on the extraction of polyphenolic compounds from winemaking pomace and marc. However, few works have focused on the use of other sources such as seedless table grape residues for the optimization of extraction parameters such contact time and solid-to-solvent ratio in UAE and MAE using mixtures of water and acidified ethanol. Crupi et al. [27] used water/ethanol/phosphoric acid (70:30:1) as solvents in UAE and MAE to recover phenolic compounds of seedless table grape residues. The main polyphenolic compounds found were procyanidin B1, procyanidin B2, (+)-catechin, peonidin-3-O-glucoside, quercetin-3-O-rutinoside, quercetin-3-O-glucoside, among others.

In processing of cranberry juice (*Vaccinium macrocarpon*), three by-products are obtained skin, seed and flesh, which are called “cranberry pomace”. The use of wastes for procyanidin extraction is an alternative to reduce the costs of blueberry juice production. Researchers have evaluated the adsorption and desorption capacity of procyanidins by using different amberlite resins (XAD-7HP, XAD-761, XAD-16N, XAD-1180, FPX-66) coupled to UAE, to study if this new method is suitable for the separation and concentration of these compounds. The results showed that the adsorption and desorption capacity of procyanidins on the resin were higher with the resin XAD-7HP. The adsorption of procyanidins on the resin was most marked between the times 600 and 800, with a maximum adsorption value of 52.2 mg/g resin. XAD-7HP resin was also used to evaluate the desorption capacity of procyanidins using different solvents (30%, 50%, 70%, 95% ethanol and 70% acetone), where the highest procyanidin desorption value was found with 95% ethanol (>250 mg/g resin), the lowest desorption capacity was found with 30% ethanol and 70% acetone [28].

Procyanidins have also been extracted from cranberry leaves by negative pressure cavitation (NPCE) and its combination with UAE. This technique was called U-NPCE by the authors. The effects of ethanol concentration, ultrasonic power, temperature, extraction time, negative pressure and solid/liquid ratio were evaluated. The authors reveal that there are still no reports indicating a solvent capable of simultaneously extracting all phenolic compounds; however, methanol followed by ethanol is more efficient for this purpose [29]. In this study, ethanol was chosen because it is food grade and was evaluated at concentrations between 40 and 90%, and for ultrasonic power and negative pressure it was evaluated at 0.3–0.4 W/cm^2 and −0.06 to −0.08 Pa, respectively. Extraction yields of procyanidins, flavonoids and the total content of polyphenols were influenced by ethanol concentration. At 40% and 70% of solvent, the total content of polyphenols and procyanidins had higher values of 300 mg gallic acid equivalents (GAE)/g DM and 200 mg CE/g DM, respectively, which were obtained at a 70% concentration, while for concentrations between 80 and 90%, extraction yields were decreased. For the ultrasonic power parameter, an increase in extraction yields between 0.2 and 0.35 W was observed, and at the latter value the maximum yield of total polyphenols, procyanidins and flavonoids, was obtained. The temperature and extraction time positively affected the yields of the compounds studied in a range of values from 5 to 15 min, and from 30 to 50 °C. At these ranges, a gradual decrease was observed for the extraction time, while the temperature remained stable. Negative pressure significantly increased the yield of total polyphenols and procyanidins between −0.04 and −0.07 Pa. The same behavior was observed for a solid/liquid ratio between 1:10 and 1:30 g/mL. The variables ethanol concentration, ultrasonic power, and negative pressure were optimized by response surface methodology and evaluation of the bioactivity of the substances evaluated. From these results it was determined that the U-NPCE method was the most suitable for extraction of phenolic compounds such as procyanidins and flavonoids, especially those sensitive to heat, due to its high yield, bioactivity and shorter treatment time [2].

3. Microwave-Assisted Extraction

Microwave extraction (MAE) is a technique used for extraction of polyphenols such as condensed tannins and flavonoids. However, studies of procyanidins, catechins, and their structural differences still need to be updated [14][30][31][32][33][34][35][36]. MAE use solvents with a high dissipation factor (tan δ) or high polarity, such as methanol or water [37]. The mechanism consists of the transfer of heat to solvent by frequencies in the range of 300 MHz to 300 GHz, facilitating the disruption of cell wall and cellular structures. The interaction between solvent molecules and compounds released increases by the formation of pores that allow rapid mass transfer resulting in an efficient extraction process [38]. The results depend on factors such as concentration, volume, and chemical characteristics of the solvent and the cell wall [39]. The advantages of this technique are high-quality substance recovery, low use solvent, fewer plant materials, moderate time-extraction and paid energy transfer [40][13][41]. There are reports of other factors, such as extraction temperature, pressure, pH, solvent concentration and particle size, which influence choice of extraction method and solvent. However, the target compounds determine this selection, since the extraction process is specific for each plant material [42][39][43]. The variability of the food matrix and the process variables promote the selection of optimal conditions [44]. Various factors influence on the yield of the substances using this technique include temperature, time, type of solvent, ratio (solvent/solid) and power. Authors suggest response surface methodology (RSM) could reduce experiment size [45][46].

To increase extraction yields, process conditions could be modified. An example is the technique of microwave superheated water extraction (MWE) [41]. Previous findings revealed interactions between nonextractable procyanidin (native and oxidized) and polysaccharides in apple pomace using acetone (60%) and water as solvents with extraction temperatures above 100 °C for 2 and 5 min in each treatment [40]. Previous work was reported in extractions of microwave-assisted seed grape proanthocyanidin yield with recovery rates of 30.7 mg g^{-1} and 99.3%, respectively, compared with traditional extractions. This technique was carried out in two aqueous phases: acetone and ammonium citrate [43]. Proanthocyanidins extraction from apple pulp by MAE was evaluated and could improve yield and reduce extraction times.

The surface response methodology obtains the best extraction yields with the least use of solvent, energy, and time [47][48]. Authors have determined the optimal conditions in extraction processes from residues (bark) of the tree species from *Acacia mollissima*, where condensed tannin concentrations correspondimg to 74 mg cyanidin/g bark were achieved using 20% of methanol in water, 182 W and 3.66 min of time exposure [31].

4. Supercritical Fluid Extraction

The method of supercritical fluid extraction (SFE), is called supercritical CO_2 extraction (SC-CO_2) when CO_2 is used as a unique solvent [49]. It has potential food applications, roles in pharmaceuticals manufacturing and polymers, and is a potential tool in separation and purification of chemical compounds and natural substances with antioxidant potential [43][47][50]. Some studies have reported results about flavonoids [51][52][53], but few are specific for procyanidins from agro-industrial and agroforestry residues [54][55][56]. This technique cannot be used with a solvent such as n-hexane, chloroform, and dichloromethane. Carbon dioxide can be used with compounds which are easily degradable by temperature, since their critical points of temperature (31 °C), and pressure (74 bar) is low; besides it is inexpensive, possess low viscosity, polarity, and reactivity, is nontoxic, nonexplosive and safe for use in food [57]. CO_2 is useful in nonpolar and slightly polar substance extraction and, in the case of polyphenols other alternatives have been proposed to improve solvation properties and yields, such as CO_2 in mixtures with ethanol (EtOH) and water [58][59]. The process should be designed to take into account that water in supercritical conditions is dangerous [54][58].

Temperatures and pressure monitoring makes the extraction process highly selective, and adjusting these variables obtains bioactive compounds without thermal degradation. Other solvent properties, such as volatility and surface tension are key to produce specificity for each process [60]. Some variables should be taken into account to control processes, including solvent flow rate, temperature, pressure, time, and the features of material [8][61][62]. Another important factor is equipment cost, which affects manufacturing cost. It is crucial to evaluate cost-benefits and extraction yields for future applications [63].

Authors have suggested that SFE is better than traditional methods in compound extractions with biological activity from wastes [64]. In addition, high recovery of compounds from mixtures with solvent extract can involve improved solid/liquid contact through of swelling of the solid sample or semi-solid (matrix), and can involve a low proportion of solvent [7][55]. Other researchers have found that proanthocyanidins were obtained of 139.7, 123.8, 309.3 mg

catechin/100 g dried matter for monomeric, oligomeric and polymeric fractions, respectively, with mixtures of pure carbon dioxide, carbon dioxide-water (15%), and water-ethanol (15%) using grape marc at high concentrations, The authors attributed this to antioxidant activity obtained for this treatment (2649.6 mg α-tocopherol/100 g dried matter), which were greater compared to methanol extraction [60]. In a similar study, apple peel was extracted at 50 °C and 25 MPa with a mixture of CO_2-EtOH (25%). This was correlated strongly with antioxidant activity in the presence of catechin, epicatechin, and procyanidin B [64]. Methanol (40%) was used for the modified SFE process. Three steps for the recovery procyanidin monomers were proposed, consisting of a cycle with pure CO_2, followed by a cycle with methanol (40%)-CO_2 and finally with pure methanol. The best recovery rates of catechin (77%) and epicatechin (79%) were achieved in the second step with 60 min of exposure [56]. Other forms of grape pomace extraction, including the coupling of ultrasound techniques with supercritical fluids, has been proposed. The maximum concentrations proanthocyanidins were achieved by SFE, which correspondedto 282.8, 167.4, and 360.3 (mg catechin/100 g dried matter) for monomeric, oligomeric, and polymeric fractions, respectively. Regarding monomeric fractions, the extraction by ultrasound was 10-fold lower than by SFE [65].

5. Pressurized Liquid Extraction

Pressurized liquid extraction (PLE), also called as accelerated solvent extraction (ASE), is considered a clean and green technology that generates by-products with added value from different natural sources [66][49][67][68][69]. However, few studies have been found concerning procyanidin extraction [70], though some works report total flavonoid content [61]. PLE has advantages over conventional extraction, such as the use of short exposure time and low solvent consumption. A range of pressure is employed (4 to 20 MPa) to keep solvent in a liquid state at high temperature when operating conditions are above boiling [52].

This process takes place in a closed and inert system at high temperatures, allowing rapid mass transfer and increasing dissolution of the plant material in the solvent [62]. The molecular interactions into the sample matrix are affected by high temperatures, surface tension and viscosity of the solvent. Polar substances and thermally sensitive subtannces have been extracted successfully with water and ethanol. The most common solvent used in PLE is water, being non-toxic, non-inflammable, and having a low cost [71]. According to operating conditions, the procyanidin content may vary. Studies have reported interactions between temperature, pressure, and/or time extraction. Okiyama et al. [72] performed extraction kinetics with cocoa bean shell at 60, 75 and 90 °C for 50 min and using 10.35 MPa. The highest yields of procyanidin were obtained at 90 °C, but this content decreased after 30 min. Researchers deduced possible changes in the matrix-solute. Mustafa and Turner [71] and Wijngaard et al. [73] indicated that the use of PLE did not increase the extraction of bioactive compounds with respect to solid-liquid extraction.

The use of PLE for bioactive substances extraction from Blackberry residues was evaluated using acidified water at 100 °C, which affected negatively the anthocyanin content but promoted the increase of activity antioxidant and total phenolics yield. Authors attributed these results to the possible presence of procyanidins and other compounds; however, the latter compounds were not measured. High temperatures allow the breakdown of interactions (hydrogen bonds, Van der Waals and others), which occur between the solvent and the plant material

[68]. This activity also may be a consequence of the generation of Maillard reaction products that could affect procyanidins content. Others changes in nutritional and physicochemical characteristics have been observed [61].

An interesting option is the use of enzymes with PLE to investigate compounds from crude Guarana seeds; a plant with health benefits. This work was achieved to improve concentrations of catechin (50.59 g/100 g extract) and epicatechin (31.32 g/100 g extract) pressurizing the system at 10 MPa. The results were best with treatments using water-ethanol (50% *w*/*w*) [74], and 20 times higher than a study carried out with SFE using the same plant source [75], possibly due to low affinity of CO_2 by polar molecules such as catechins [74]. Understanding of phenomena occurring in PLE has been mathematically modeled to optimize the process, determine interactions between variables, and allow scale-up [76].

Subcritical Water Extraction

A modification of PLE using only water in extraction system has been reported in the literature. Different names could be found, for example, subcritical water extraction (SWE), superheated water extraction, pressurized low polarity water extraction and pressurized hot water extraction [77], but the mechanism is the same.

This method represents an alternative use of organic solvents and could reduce negative effects to the environment and risks for human health. The use of new solvents is necessary to overcome these limitations [54]. Moreover, unlike traditional methods, it does not require removal proceedings after the process, and manipulation is automated, allowing savings of time and money. It also has good selectivity with rapid extraction. Reports have shown that treatments with SWE have a manufacturing cost higher than assays with supercritical fluids (carbon dioxide) and may be better for total flavonoid content than traditional methods, and nontraditional methods such as UAE and MAE [58][78][79][80]. SWE is used in different fields to extract bioactive compounds of different polarities, obtained using water as the solvent at high temperatures and pressures [58].

The main property of subcritical water is its dielectric constant (ε), which depends on the extraction temperature. By controlling this variable, water polarity can be changed, and thus its solvation capacity. The characteristics of water according to its dielectric constant, facilitates obtaining a wide variety of byproducts.

Other variables such as exposition-time during treatment and chemical composition of plant material represent key points in obtaining target compounds with specific characteristics. The adjustment of temperature and pressure between 100 and 374.1 °C and 1 and 221 bar, can achieve changes in viscosity, surface tension, polarity and diffusivity of water, besides improving sample solubility and mass transfer [69]. In high-temperature extractions of flavonoids, it was reported that the viscosity, density and surface tension of water can influence the structural characteristics of these compounds. Ko et al. [81] revealed the efficiency of the SWE method in extractions with residues of onion skins and sea-buckthorn leaves for nonpolar flavonoids, where temperature determined the presence of hydrogen bonding in the molecule. In this study flavonoid extractions with hydroxyl groups at low temperatures were achieved.

In previous work with winemaking residues, proanthocyanidins were extracted from grape seeds at different temperatures and cycle extractions using subcritical water. Each treatment resulted in changes in structure, linkages of catechin, and antioxidant activity of the compound. The authors indicated that this strategy allowed selectivity of processes; the type of procyanidin, number of catechin units, and ubication galloylated moieties are influenced by extraction temperature and this variable can be applied individually or sequentially. High temperatures favor polymerization of procyanidins, increased procyanidin trimers and tetramers content occurring at 150 °C, whereas subsequent treatments at 100–150 °C favored procyanidins with galloylated moieties [79].

References

1. Lohani, U.C.; Muthukumarappan, K. Application of the Pulsed Electric Field to Release Bound Phenolics in Sorghum Flour and Apple Pomace. Innov. Food Sci. Emerg. Technol. 2016, 35, 29–35.
2. Wang, T.; Guo, N.; Wang, S.X.; Kou, P.; Zhao, C.J.; Fu, Y.J. Ultrasound-Negative Pressure Cavitation Extraction of Phenolic Compounds from Blueberry Leaves and Evaluation of Its DPPH Radical Scavenging Activity. Food Bioprod. Process. 2018, 108, 69–80.
3. Li, L.; Zhang, S.; Cui, Y.; Li, Y.; Luo, L.; Zhou, P.; Sun, B. Preparative Separation of Cacao Bean Procyanidins by High-Speed Counter-Current Chromatography. J. Chromatogr. B Anal. Technol. Biomed. Life Sci. 2016, 1036–1037, 10–19.
4. Waterhouse, G.I.N.; Sun-Waterhouse, D.; Su, G.; Zhao, H.; Zhao, M. Spray-Drying of Antioxidant-Rich Blueberry Waste Extracts; Interplay Between Waste Pretreatments and Spray-Drying Process. Food Bioprocess. Technol. 2017, 10, 1074–1092.
5. Sun-Waterhouse, D.; Wang, W.; Waterhouse, G.I.N.; Wadhwa, S.S. Utilisation Potential of Feijoa Fruit Wastes as Ingredients for Functional Foods. Food Bioprocess. Technol. 2013, 6, 3441–3455.
6. Mason, T.J.; Chemat, F.; Vinatoru, M. The Extraction of Natural Products Using Ultrasound or Microwaves. Curr. Org. Chem. 2010, 15, 237–247.
7. Pudziuvelyte, L.; Jakštas, V.; Ivanauskas, L.; Laukevičienė, A.; Ibe, C.F.D.; Kursvietiene, L.; Bernatoniene, J. Different Extraction Methods for Phenolic and Volatile Compounds Recovery from Elsholtzia ciliata Fresh and Dried Herbal Materials. Ind. Crops Prod. 2018, 120, 286–294.
8. Chemat, F.; Zill-E-Huma; Khan, M.K. Applications of Ultrasound in Food Technology: Processing, Preservation and Extraction. In Ultrasonics Sonochemistry; Elsevier: Amsterdam, The Netherlands, 2011; Volume 18, pp. 813–835.
9. Limwachiranon, J.; Huang, H.; Li, L.; Duan, Z.; Luo, Z. Recovery of lotus (Nelumbo nucifera gaertn.) Seedpod flavonoids using polar macroporous resins: The updated understanding on adsorption/desorption mechanisms and the involved intermolecular attractions and bonding. Food Chem. 2019, 299, 125108.

10. Milea, A.; Aprodu, I.; Vasile, A.M.; Barbu, V.; Râpeanu, G.; Bahrim, G.E.; Stănciuc, N. Widen the Functionality of Flavonoids from Yellow Onion Skins through Extraction and Microencapsulation in Whey Proteins Hydrolysates and Different Polymers. J. Food Eng. 2019, 251, 29–35.
11. Zengin, G.; Cvetanović, A.; Gašić, U.; Stupar, A.; Bulut, G.; Senkardes, I.; Dogan, A.; Seebaluck-Sandoram, R.; Rengasamy, K.R.R.; Sinan, K.I.; et al. Chemical Composition and Bio-Functional Perspectives of Erica arborea L. Extracts Obtained by Different Extraction Techniques: Innovative Insights. Ind. Crop. Prod. 2019, 142, 111843.
12. Nakajima, V.M.; Madeira, J.V.; Macedo, G.A.; Macedo, J.A. Biotransformation Effects on Anti Lipogenic Activity of Citrus Extracts. Food Chem. 2016, 197, 1046–1053.
13. Jing, C.-L.; Dong, X.-F.; Tong, J.-M. Optimization of Ultrasonic-Assisted Extraction of Flavonoid Compounds and Antioxidants from Alfalfa Using Response Surface Method. Molecules 2015, 20, 15550–15571.
14. Cheng, X.L.; Wan, J.Y.; Li, P.; Qi, L.W. Ultrasonic/Microwave Assisted Extraction and Diagnostic Ion Filtering Strategy by Liquid Chromatography-Quadrupole Time-of-Flight Mass Spectrometry for Rapid Characterization of Flavonoids in Spatholobus suberectus. J. Chromatogr. A 2011, 1218, 5774–5786.
15. Novak, I.; Janeiro, P.; Seruga, M.; Oliveira-Brett, A.M. Ultrasound Extracted Flavonoids from Four Varieties of Portuguese Red Grape Skins Determined by Reverse-Phase High-Performance Liquid Chromatography with Electrochemical Detection. Anal. Chim. Acta 2008, 630, 107–115.
16. Salarbashi, D.; Dowom, S.A.; Bazzaz, B.S.F.; Khanzadeh, F.; Soheili, V.; Mohammadpour, A. Evaluation, Prediction and Optimization the Ultrasoundassisted Extraction Method Using Response Surface Methodology: Antioxidant and Biological Properties of Stachys parviflora L. Iran. J. Basic Med. Sci. 2016, 19, 829–841.
17. Ultrasound: Its Chemical, Physical, and Biological Effects. Available online: https://experts.illinois.edu/en/publications/ultrasound-its-chemical-physical-and-biological-effects (accessed on 9 August 2021).
18. Muñoz-Labrador, A.; Prodanov, M.; Villamiel, M. Effects of High Intensity Ultrasound on Disaggregation of a Macromolecular Procyanidin-Rich Fraction from Vitis vinifera L. Seed Extract and Evaluation of Its Antioxidant Activity. Ultrason. Sonochem. 2019, 50, 74–81.
19. Pereira, G.A.; Silva, E.K.; Peixoto Araujo, N.M.; Arruda, H.S.; Meireles, M.A.A.; Pastore, G.M. Obtaining a Novel Mucilage from Mutamba Seeds Exploring Different High-Intensity Ultrasound Process Conditions. Ultrason. Sonochem. 2019, 55, 332–340.
20. Narváez-Flores, M.; Sánchez-Madrigal, M.; Quintero-Ramos, A.; Paredes-Lizárraga, M.A.; González-Laredo, R.F.; Ruiz-Gutiérrez, M.G.; Piñón-Castillo, H.A.; Meléndez-Pizarro, C.O. Ultrasound Assisted Extraction Modeling of Fructans from Agave (Agave tequilana Weber Var.

azul) at Different Temperatures and Ultrasound Powers. Food Bioprod. Process. 2015, 96, 232–239.

21. Liu, Z.; Yang, L. Antisolvent Precipitation for the Preparation of High Polymeric Procyanidin Nanoparticles under Ultrasonication and Evaluation of Their Antioxidant Activity in Vitro. Ultrason. Sonochem. 2018, 43, 208–218.
22. Ismail, B.B.; Yusuf, H.L.; Pu, Y.; Zhao, H.; Guo, M.; Liu, D. Ultrasound-Assisted Adsorption/Desorption for the Enrichment and Purification of Flavonoids from Baobab (Adansonia digitata) Fruit Pulp. Ultrason. Sonochem. 2020, 65, 104980.
23. Yu, Q.; Fan, L.; Li, J. A Novel Process for Asparagus Polyphenols Utilization by Ultrasound Assisted Adsorption and Desorption Using Resins. Ultrason. Sonochem. 2020, 63, 104920.
24. Martins, N.O.; De Brito, I.M.; Araújo, S.S.O.; Negri, G.; Carlini, E.d.A.; Mendes, F.R. Antioxidant, Anticholinesterase and Antifatigue Effects of Trichilia catigua (Catuaba). BMC Complement. Altern. Med. 2018, 18, 172.
25. Zhang, R.; Su, D.; Hou, F.; Liu, L.; Huang, F.; Dong, L.; Deng, Y.; Zhang, Y.; Wei, Z.; Zhang, M. Optimized Ultra-High-Pressure-Assisted Extraction of Procyanidins from Lychee Pericarp Improves the Antioxidant Activity of Extracts. Biosci. Biotechnol. Biochem. 2017, 81, 1576–1585.
26. Kim, H.I.; Hur, Y.Y.; Im, D.J.; Lee, D.H.; Jung, S.M.; Park, S.J.; Kim, S.J. Solvent Extraction Conditions for the Analysis of Condensed Tannins from Grape Skin and Seeds. Korean J. Food Preserv. 2019, 26, 808–813.
27. Crupi, P.; Dipalmo, T.; Clodoveo, M.L.; Toci, A.T.; Coletta, A. Seedless Table Grape Residues as a Source of Polyphenols: Comparison and Optimization of Non-Conventional Extraction Techniques. Eur. Food Res. Technol. 2018, 244, 1091–1100.
28. Gao, C.; Zhao, S.; Yagiz, Y.; Gu, L. Static, Kinetic, and Isotherm Adsorption Performances of Macroporous Adsorbent Resins for Recovery and Enrichment of Bioactive Procyanidins from Cranberry Pomace. J. Food Sci. 2018, 83, 1249–1257.
29. Mokrani, A.; Madani, K. Effect of Solvent, Time and Temperature on the Extraction of Phenolic Compounds and Antioxidant Capacity of Peach (Prunus persica L.) Fruit. Sep. Purif. Technol. 2016, 162, 68–76.
30. Casazza, A.A.; Pettinato, M.; Perego, P. Polyphenols from Apple Skins: A Study on Microwave-Assisted Extraction Optimization and Exhausted Solid Characterization. Sep. Purif. Technol. 2020, 240, 116640.
31. Rhazi, N.; Hannache, H.; Oumam, M.; Sesbou, A.; Charrier, B.; Pizzi, A.; Charrier-El Bouhtoury, F. Green Extraction Process of Tannins Obtained from Moroccan Acacia mollissima Barks by Microwave: Modeling and Optimization of the Process Using the Response Surface Methodology RSM. Arab. J. Chem. 2019, 12, 2668–2684.

32. Barrales, F.M.; Silveira, P.; Barbosa, P.D.P.M.; Ruviaro, A.R.; Paulino, B.N.; Pastore, G.M.; Macedo, G.A.; Martinez, J. Recovery of Phenolic Compounds from Citrus By-Products Using Pressurized Liquids—An Application to Orange Peel. Food Bioprod. Process. 2018, 112, 9–21.
33. Bujor, O.C.; Ginies, C.; Popa, V.I.; Dufour, C. Phenolic Compounds and Antioxidant Activity of Lingonberry (Vaccinium vitis-idaea L.) Leaf, Stem and Fruit at Different Harvest Periods. Food Chem. 2018, 252, 356–365.
34. Carniel, N.; Dallago, R.M.; Dariva, C.; Bender, J.P.; Nunes, A.L.; Zanella, O.; Bilibio, D.; Luiz Priamo, W. Microwave-Assisted Extraction of Phenolic Acids and Flavonoids from Physalis angulata. J. Food Process Eng. 2017, 40, e12433.
35. Xie, J.H.; Dong, C.J.; Nie, S.P.; Li, F.; Wang, Z.J.; Shen, M.Y.; Xie, M.Y. Extraction, Chemical Composition and Antioxidant Activity of Flavonoids from Cyclocarya paliurus (Batal.) Iljinskaja Leaves. Food Chem. 2015, 186, 97–105.
36. Sivakumar, V.; Ilanhtiraiyan, S.; Ilayaraja, K.; Ashly, A.; Hariharan, S. Influence of Ultrasound on Avaram Bark (Cassia auriculata) Tannin Extraction and Tanning. Chem. Eng. Res. Des. 2014, 92, 1827–1833.
37. Belwal, T.; Bhatt, I.D.; Rawal, R.S.; Pande, V. Microwave-Assisted Extraction (MAE) Conditions Using Polynomial Design for Improving Antioxidant Phytochemicals in Berberis asiatica Roxb. Ex DC. Leaves. Ind. Crops Prod. 2017, 95, 393–403.
38. Zhang, J.C.; Wang, C.T.; Wang, C.T.; Wang, S.X.; Sun, B.G. Changes in Components of Aqueous and Non-Aqueous Extracts from Sea Buckthorn Seed Residues through Solid State Fermentation of Monascus purpureus. BioResources 2019, 14, 2197–2215.
39. Nayak, B.; Dahmoune, F.; Moussi, K.; Remini, H.; Dairi, S.; Aoun, O.; Khodir, M. Comparison of Microwave, Ultrasound and Accelerated-Assisted Solvent Extraction for Recovery of Polyphenols from Citrus Sinensis Peels. Food Chem. 2015, 187, 507–516.
40. Fernandes, P.A.R.; Le Bourvellec, C.; Renard, C.M.G.C.; Nunes, F.M.; Bastos, R.; Coelho, E.; Wessel, D.F.; Coimbra, M.A.; Cardoso, S.M. Revisiting the Chemistry of Apple Pomace Polyphenols. Food Chem. 2019, 294, 9–18.
41. Coelho, C.; Ribeiro, M.; Cruz, A.C.S.; Domingues, M.R.M.; Coimbra, M.A.; Bunzel, M.; Nunes, F.M. Nature of Phenolic Compounds in Coffee Melanoidins. J. Agric. Food Chem. 2014, 62, 7843–7853.
42. De Freitas, M.A.; Andrade, J.C.; Alves, A.I.S.; Dos Santos, F.D.A.G.; Leite-Andrade, M.C.; Sales, D.L.; Nunes, M.; Ribeiro, P.R.V.; Melo Coutinho, H.D.; Morais-Braga, M.F.B.; et al. Use of the Natural Products from the Leaves of the Fruitfull Tree Persea Americana against Candida Sp. Biofilms Using Acrylic Resin Discs. Sci. Total Environ. 2020, 703, 134779.

43. Dang, Y.Y.; Zhang, H.; Xiu, Z.L. Microwave-Assisted Aqueous Two-Phase Extraction of Phenolics from Grape (Vitis vinifera) Seed. J. Chem. Technol. Biotechnol. 2014, 89, 1576–1581.
44. Jacotet-Navarro, M.; Rombaut, N.; Deslis, S.; Fabiano-Tixier, A.S.; Pierre, F.X.; Bily, A.; Chemat, F. Towards a “Dry” Bio-Refinery without Solvents or Added Water Using Microwaves and Ultrasound for Total Valorization of Fruit and Vegetable by-Products. Green Chem. 2016, 18, 3106–3115.
45. Garrido, T.; Gizdavic-Nikolaidis, M.; Leceta, I.; Urdanpilleta, M.; Guerrero, P.; De la Caba, K.; Kilmartin, P.A. Optimizing the Extraction Process of Natural Antioxidants from Chardonnay Grape Marc Using Microwave-Assisted Extraction. Waste Manag. 2019, 88, 110–117.
46. Vajić, U.J.; Grujić-Milanović, J.; Živković, J.; Šavikin, K.; Godevac, D.; Miloradović, Z.; Bugarski, B.; Mihailović-Stanojević, N. Optimization of Extraction of Stinging Nettle Leaf Phenolic Compounds Using Response Surface Methodology. Ind. Crops Prod. 2015, 74, 912–917.
47. Albuquerque, B.R.; Prieto, M.A.; Barreiro, M.F.; Rodrigues, A.E.; Curran, T.P.; Barros, L.; Ferreira, I.C.F.R. Catechin-Based Extract Optimization Obtained from Arbutus unedo L. Fruits Using Maceration/Microwave/Ultrasound Extraction Techniques. Ind. Crops Prod. 2017, 95, 404–415.
48. Li, Y.; Fabiano-Tixier, A.S.; Tomao, V.; Cravotto, G.; Chemat, F. Green Ultrasound-Assisted Extraction of Carotenoids Based on the Bio-Refinery Concept Using Sunflower Oil as an Alternative Solvent. Ultrason. Sonochem. 2013, 20, 12–18.
49. Wijngaard, H.H.; Ballay, M.; Brunton, N. The Optimisation of Extraction of Antioxidants from Potato Peel by Pressurised Liquids. Food Chem. 2011, 133, 1123–1130.
50. Bordalo, M.; Seabra, I.J.; Silva, A.B.; Terrasso, A.P.; Brito, C.; Serra, M.; Bronze, M.R.; Duarte, C.M.M.; Braga, M.E.M.; De Sousa, H.C.; et al. Using High-Pressure Technology to Develop Antioxidant-Rich Extracts from Bravo de Esmolfe Apple Residues. Antioxidants 2021, 10, 1469.
51. Krakowska, A.; Rafińska, K.; Walczak, J.; Buszewski, B. Enzyme-assisted optimized supercritical fluid extraction to improve Medicago sativa polyphenolics isolation. Ind. Crops Prod. 2018, 124, 931–940.
52. Garcia-Mendoza, M.P.; Paula, J.T.; Paviani, L.C.; Cabral, F.A.; Martinez-Correa, H.A. Extracts from Mango Peel By-Product Obtained by Supercritical CO2 and Pressurized Solvent Processes. LWT-Food Sci. Technol. 2015, 62, 131–137.
53. Wang, L.; Yang, B.; Du, X.; Yi, C. Optimisation of Supercritical Fluid Extraction of Flavonoids from Pueraria lobata. Food Chem. 2008, 108, 737–741.
54. Abdelmoez, W.; Nage, S.M.; Bastawess, A.; Ihab, A.; Yoshida, H. Subcritical Water Technology for Wheat Straw Hydrolysis to Produce Value Added Products. J. Clean. Prod. 2014, 70, 68–77.

55. Pereira, C.; Meireles, M. Supercritical Fluid Extraction of Bioactive Compounds: Fundamentals, Applications and Economic Perspectives. Food Bioprocess. Technol. 2010, 3, 340–372.
56. Ashraf-Khorassani, M.; Taylor, L.T. Sequential Fractionation of Grape Seeds into Oils, Polyphenols, and Procyanidins via a Single System Employing CO2-Based Fluids. J. Agric. Food Chem. 2004, 52, 2440–2444.
57. Sánchez-Vicente, Y.; Cabañas, A.; Renuncio, J.A.R.; Pando, C. Supercritical Fluid Extraction of Peach (Prunus persica) Seed Oil Using Carbon Dioxide and Ethanol. J. Supercrit. Fluids 2009, 49, 167–173.
58. Todd, R.; Baroutian, S. A Techno-Economic Comparison of Subcritical Water, Supercritical CO2 and Organic Solvent Extraction of Bioactives from Grape Marc. J. Clean. Prod. 2017, 158, 349–358.
59. Cardenas-Toro, F.P.; Forster-Carneiro, T.; Rostagno, M.A.; Petenate, A.J.; Maugeri Filho, F.; Meireles, M.A.A. Integrated Supercritical Fluid Extraction and Subcritical Water Hydrolysis for the Recovery of Bioactive Compounds from Pressed Palm Fiber. J. Supercrit. Fluids 2014, 93, 42–48.
60. Da Porto, C.; Decorti, D.; Natolino, A. Water and Ethanol as Co-Solvent in Supercritical Fluid Extraction of Proanthocyanidins from Grape Marc: A Comparison and a Proposal. J. Supercrit. Fluids 2014, 87, 1–8.
61. Shang, Y.F.; Kim, S.M.; Um, B.H. Optimisation of Pressurised Liquid Extraction of Antioxidants from Black Bamboo Leaves. Food Chem. 2014, 154, 164–170.
62. Pereira, R.G.; Garcia, V.L.; Nova Rodrigues, M.V.; Martínez, J. Extraction of Lignans from Phyllanthus amarus Schum. & Thonn Using Pressurized Liquids and Low Pressure Methods. Sep. Purif. Technol. 2016, 158, 204–211.
63. Veggi, P.C.; Prado, J.M.; Bataglion, G.A.; Eberlin, M.N.; Angela, M.; Meireles, A. The Journal of Supercritical Fluids Obtaining Phenolic Compounds from Jatoba (Hymenaea courbaril L.) Bark by Supercritical Fluid Extraction. J. Supercrit. Fluids 2014, 89, 68–77.
64. Massias, A.; Boisard, S.; Baccaunaud, M.; Leal Calderon, F.; Subra-Paternault, P. Recovery of Phenolics from Apple Peels Using CO2 + Ethanol Extraction: Kinetics and Antioxidant Activity of Extracts. J. Supercrit. Fluids 2015, 98, 172–182.
65. Da Porto, C.; Natolino, A.; Decorti, D. The Combined Extraction of Polyphenols from Grape Marc: Ultrasound Assisted Extraction Followed by Supercritical CO2 Extraction of Ultrasound-Raffinate. LWT 2015, 61, 98–104.
66. Corazza, G.O.; Bilibio, D.; Zanella, O.; Nunes, A.L.; Bender, J.P.; Carniel, N.; Dos Santos, P.P.; Priamo, W.L. Pressurized Liquid Extraction of Polyphenols from Goldenberry: Influence on Antioxidant Activity and Chemical Composition. Food Bioprod. Process. 2018, 112, 63–68.

67. Viganó, J.; Brumer, I.Z.; Braga, P.A.D.C.; Da Silva, J.K.; Maróstica Júnior, M.R.; Reyes Reyes, F.G.; Martínez, J. Pressurized Liquids Extraction as an Alternative Process to Readily Obtain Bioactive Compounds from Passion Fruit Rinds. Food Bioprod. Process. 2016, 100, 382–390.
68. Machado, A.P.D.F.; Pasquel-Reátegui, J.L.; Barbero, G.F.; Martínez, J. Pressurized Liquid Extraction of Bioactive Compounds from Blackberry (Rubus fruticosus L.) Residues: A Comparison with Conventional Methods. Food Res. Int. 2015, 77, 675–683.
69. Golmakani, E.; Mohammadi, A.; Ahmadzadeh Sani, T.; Kamali, H. Phenolic and flavonoid content and antioxidants capacity of pressurized liquid extraction and perculation method from roots of Scutellaria pinnatifida A. Hamilt. subsp alpina (Bornm) Rech. F. J. Supercrit. Fluids 2014, 95, 318–324.
70. Monrad, J.K.; Howard, L.R.; King, J.W.; Srinivas, K.; Mauromoustakos, A. Subcritical Solvent Extraction of Procyanidins from Dried Red Grape Pomace. J. Agric. Food Chem. 2010, 58, 4014–4021.
71. Mustafa, A.; Turner, C. Pressurized Liquid Extraction as a Green Approach in Food and Herbal Plants Extraction: A Review. Anal. Chim. Acta 2011, 703, 8–18.
72. Okiyama, D.C.G.; Soares, I.D.; Cuevas, M.S.; Crevelin, E.J.; Moraes, L.A.B.; Melo, M.P.; Oliveira, A.L.; Rodrigues, C.E.C. Pressurized Liquid Extraction of Flavanols and Alkaloids from Cocoa Bean Shell Using Ethanol as Solvent. Food Res. Int. 2018, 114, 20–29.
73. Wijngaard, H.; Hossain, M.B.; Rai, D.K.; Brunton, N. Techniques to Extract Bioactive Compounds from Food By-Products of Plant Origin. Food Res. Int. 2012, 46, 505–513.
74. Santana, Á.L.; Queirós, L.D.; Martínez, J.; Macedo, G.A. Pressurized Liquid- and Supercritical Fluid Extraction of Crude and Waste Seeds of Guarana (Paullinia cupana): Obtaining of Bioactive Compounds and Mathematical Modeling. Food Bioprod. Process. 2019, 117, 194–202.
75. Marques, L.L.M.; Panizzon, G.P.; Aguiar, B.A.A.; Simionato, A.S.; Cardozo-Filho, L.; Andrade, G.; De Oliveira, A.G.; Guedes, T.A.; De Mello, J.C.P. Guaraná (Paullinia cupana) Seeds: Selective Supercritical Extraction of Phenolic Compounds. Food Chem. 2016, 212, 703–711.
76. Pereira, D.T.V.; Tarone, A.G.; Cazarin, C.B.B.; Barbero, G.F.; Martínez, J. Pressurized Liquid Extraction of Bioactive Compounds from Grape Marc. J. Food Eng. 2019, 240, 105–113.
77. Pronyk, C.; Mazza, G. Design and Scale-up of Pressurized Fluid Extractors for Food and Bioproducts. J. Food Eng. 2009, 95, 215–226.
78. Cvetanović, A.; Švarc-Gajić, J.; Zeković, Z.; Mašković, P.; Đurović, S.; Zengin, G.; Delerue-Matos, C.; Lozano-Sánchez, J.; Jakišić, A. Chemical and Biological Insights on Aronia Stems Extracts Obtained by Different Extraction Techniques: From Wastes to Functional Products. J. Supercrit. Fluids 2017, 128, 173–181.

79. García-Marino, M.; Rivas-Gonzalo, J.C.; Ibáñez, E.; García-Moreno, C. Recovery of Catechins and Proanthocyanidins from Winery By-Products Using Subcritical Water Extraction. Anal. Chim. Acta 2006, 563, 44–50.
80. Turner, C. Overview of Modern Extraction Techniques for Food and Agricultural Samples. In Modern Extraction Techniques; ACS Symposium Series; ACS Publications: Washington, DC, USA, 2006; Volume 926, pp. 3–19.
81. Ko, M.J.; Cheigh, C.I.; Chung, M.S. Relationship Analysis between Flavonoids Structure and Subcritical Water Extraction (SWE). Food Chem. 2014, 143, 147–155.