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Review

Modern Techniques for Flavonoid Extraction—To Optimize or Not to Optimize?

Ana Jurinjak Tušek [1], Dunja Šamec [2,*] and Anita Šalić [3]

[1] Faculty of Food Technology and Biotechnology, University of Zagreb, 10000 Zagreb, Croatia
[2] Department of Food Technology, University North, Trg Dr. Žarka Dolinara 1, 48000 Koprivnica, Croatia
[3] Department of Thermodynamics, Mechanical Engineering and Energy, Faculty of Chemical Engineering and Technology, University of Zagreb, Marulićev Trg 19, 10000 Zagreb, Croatia
* Correspondence: dsamec@unin.hr

Abstract: Flavonoids, specialized metabolites found in plants, have a number of beneficial properties and are important for maintaining good health. Efficient extraction methods are required to extract the most bioactive compounds from plant material. Modern techniques are replacing conventional methods of flavonoids extraction in order to reduce energy and solvent consumption, increase extraction efficiency, and satisfy growing market demand as well as environmental legislation. The extraction of bioactive molecules compounds is affected by a number of variables. To determine the conditions that ensure the highest extraction yield, it is advisable to analyze the interactions between the above in parallel. In this work, an overview of the advantages and performance of modern methods (microwave-assisted extraction, ultrasound-assisted extraction, pressurized liquids-assisted extraction, and supercritical fluids extraction) for the extraction of flavonoids is presented. This work also presents the application of extraction process optimization and extraction kinetics for flavonoid extraction, using different types of experimental designs for different flavonoid sources and different extraction methods. The general conclusion of all the studies listed is that an experimental design combined with RSM modeling reduces the number of experiments that should be performed to achieve maximum extraction yield.

Keywords: flavonoids; extraction; extraction parameters optimization; modern extraction techniques

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1. Introduction

Plants produce a wide range of different specialized metabolites, traditionally referred to as 'secondary metabolites'. These are chemical compounds involved in numerous biological functions within plants, including plant responses to abiotic and biotic stresses [1]. The best-studied group of specialized plant metabolites to date are the flavonoids, which include over 6000 molecules with diverse structures [2]. Mouradov and Spangenberg [3] summarize that flavonoids in plants function, among other things, as protection against insect feeding and defense against microbes, as sunscreens to absorb UV radiation and strong light, to attract insect pollinators, as antioxidants, for pollen germination, for biological communication in the rhizosphere, and as developmental regulators involved in auxin transport and catabolism. They have been the focus of scientific attention for the past 30 years, mainly due to numerous scientific findings on their beneficial effects on human health due to their antioxidant, antimicrobial, anticancer, neuroprotective, cardioprotective, and anti-inflammatory properties [4–6]. They are used in the food industry as natural antioxidants or colorants. Flavonoids have a 15-carbon flavone backbone, C6-C3-C6 (Figure 1), with two benzene rings (A and B) connected by a trinuclear pyran ring (C). The position of the B catechol ring on the C pyran ring, as well as the

number and position of the hydroxyl groups on the catechol group of the B ring, have a major influence on the chemical properties and biological activity of flavonoids [7].

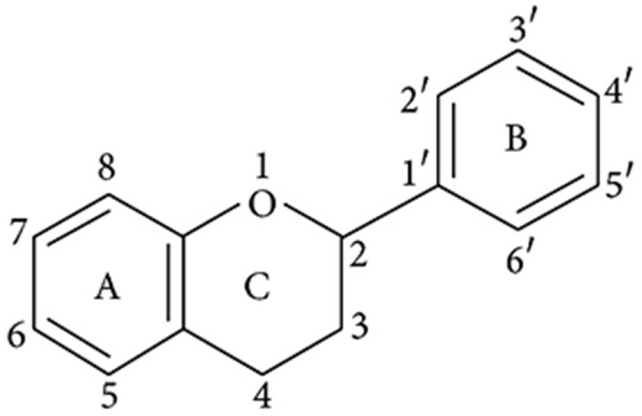


Figure 1. Flavonoids molecular structure.

Due to their important role in plants and their numerous health benefits, much attention has been paid for years to the development of the most effective methods for their extraction and characterization [8]. The most commonly used methods for characterization and quantification of known flavonoids are high performance liquid chromatography (HPLC) coupled with DAD/PDA detectors or mass spectrometry (MS). For the elucidation of unknown structures, multistep MS or NMR can be used. Gas chromatography (GC) is rarely used because it requires derivatization before analysis and derivatization is a time-consuming process involving hazardous reagents/solvents, sometimes under extreme temperature and pressure conditions [9]. Recently, the MALDI imaging method has also enabled the identification of flavonoids *in situ* in the tissue under study without extraction [10], but this method is not widely used due to its high cost. For the correct identification and further use of flavonoids, the crucial step is the extraction of flavonoids. Effective extraction techniques are necessary to extract the largest amount of bioactive chemicals from plant material [11,12]. To minimize energy and solvent consumption, increase extraction efficiency, and meet increasing market demand and environmental regulations, modern techniques (such as microwaves, ultrasound, pressurized fluids, and supercritical fluids) are replacing traditional flavonoid extraction methods [13,14]. Numerous factors such as solvent selection, temperature, contact time, liquid-to-solid ratio, particle size, and pH affect the extraction of bioactive molecular compounds [15]. In order to define the process conditions that ensure maximum extraction yield, it is recommended to simultaneously analyze the interaction between the listed factors. Therefore, mathematical and statistical tools such as response surface methodology (RSM) and artificial neural networks (ANN) are often used to study the effects of different factors and their interactions on extraction efficiency [16–18]. Although reaction surface models are commonly used to explain how process variables affect extraction efficiency, these models do not always provide data that support mass transfer and the dynamics of the extraction process, so the use of kinetic models is required to understand the extraction process [19–21]. Mathematical modeling is required to evaluate extraction kinetics and ensure the maximum product reproducibility [11,15].

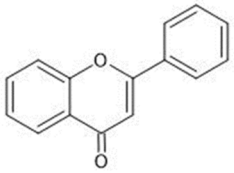
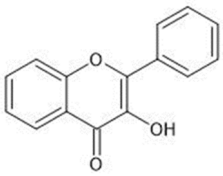
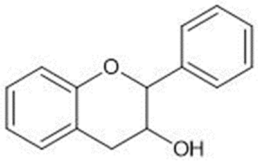
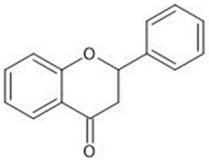
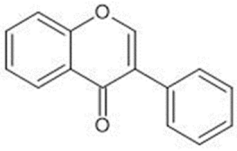
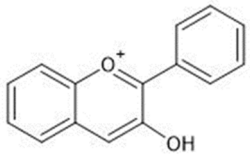
Based on the above, this paper reviews the advantages and performance of modern methods (microwave-assisted extraction, ultrasound-assisted extraction, pressurized liquid-assisted extraction, and supercritical fluid extraction) for flavonoid extraction with the emphasis on the use of new approaches such as the use of deep eutectic solvents as

environmentally friendly solvents. In addition, the application of extraction process optimization and extraction kinetics to improve the efficiency of the extraction process was also reviewed.

2. Flavonoids Classification and Sources

Flavonoids are a diverse group of specialized metabolites derived from the general structure of a 15-carbon skeleton (Figure 1). Based on their structure, which can be distinguished by the pattern of the central heterocyclic pyran ring of the flavan core structure, flavonoids can be divided into six groups: Flavones, flavonols, flavan-3-ols, flavanonols, flavanones, isoflavones, and anthocyanins (Table 1).

Table 1. The structure and examples of flavonoids from different groups.

Flavones	Flavonols	Flavan-3-ols
		
apigenin luteolin acacetin	kaempferol myricetin quercetin fisetin	cathechin epicatechin epigallocatechin
Flavanone	**Isoflavones**	**Anthocyanins**
		
hesperetine naringenin	genistein daidzein glycitein	cyanidin, delphinidin, malvidin, pelargonidin, peonidin, and petunidin

Flavonoids can occur in free form in plants, but are more commonly glycosylated, methylated, acetylated, prenylated, or polymerized [22]. Most commonly, flavonoid glycosides, *O*-glycosides, and, less commonly, *C*-glycosides are identified with a single oligosaccharide or, in some cases, a polysaccharide unit [23]. Glycosidation improves solubility, biodistribution, and metabolism by increasing transport across cell membranes [24]. Methylated flavonoids are rarer than free forms or flavonoid glycosides, and common types of methylation include *C*-methylation and *O*-methylation, which enhance flavonoid entry into cells and prevent degradation [22]. Some plants accumulate biflavonoids, flavonoid dimers consisting of two monoflavonoids through a direct link or a linear linker [25,26], or even flavonoid trimers or tetramers [27].

Flavonoids are distributed throughout the plant body, but the quality and quantity of specific flavonoids vary widely among different plants, plant organs, and even the same plants grown under different environmental conditions [28]. In general, the occurrence and amount of flavonoids in some plant samples are influenced by genetic and environmental factors, and some flavonoids may be specific to a particular plant genus, species, or even cultivar. Some examples of flavonoids detected in various plant samples are presented in Table 2.

In recent years, modern analytical techniques have become available and some flavonoids that occur at lower concentrations can now be more easily detected. In addition, new extraction methods have also been optimized to achieve the most efficient extraction.

Table 2. Examples of flavonoids molecules characterized in plant material extracts.

Source	Flavonoids Group	Characterized Molecules	Extraction Method
cocoa shell [29]	flavanols	(+)-catechin, (-)-epicatechin, procyanidine	pressurized liquid extraction
wine grape [30]	flavanols	(+)-catechin, (-)-epicatechin, (-)-epigallocatechin	ultrasound-assisted extraction
tea leaves [31]	flavanols	19 molecules including epigallocatechin gallate, epigallocatechin, epicatechin gallate, epicatechin, and their corresponding stereoisomers	conventional extraction
	flavonols	19 molecules with kaempferol, quercetin, and myricetin aglycones	
peach fruit [32]	anthocyanins	cyanidin–3–*O*–glucoside cyanidin–3–*O*–rutinoside	ultrasound-assisted extraction
	flavanols	catechin, epicatechin procyanidin B1	
	flavonols	rutin, quercetin–3–*O*–galactoside, quercetin–3–*O*–glucoside	
Astragalus membranaceus plant [33]	flavonols	isoquercitrin, astragalin	ultrasound-assisted extraction
orange peel [34]	flavanones	hesperidin, nariruti	supercritical water extraction
citrus pomace [35]	flavanones	naringin, hesperidin	enzyme-assisted extraction
dried flowers of *Trollius chinensis* Bunge [36]	flavones	orientin, vitexin and 2″-O-galactopyranosylorientin	natural deep eutectic solvents extraction
Trichosanthes kirilowii Maxim [37]	flavones	isoquercitrin, rutin, quercetin, luteoloside, luteolin, tangeretin, apigenin, apigenin-7-O-glucuronide, kaempferol, kaempferide	ultrasound-assisted extraction
Aronia melanocarpa [38]	anthocyanins	delphinidin, cyanidin, petunidin, pelargonidin, peonidin, and malvidin	ultrasonic-microwave-assisted natural deep eutectic solvent extraction
Polypodium vulgare L. [39]	flavanols	(+)-catechin-7-O-α-L-arabinoside, (+)-catechin-7-O-β-D-apioside	conventional extraction
apple samples [40]	flavanols	(+)-catechin, (-)-epicatechin, procyanidin B1, procyanidin B2, procyanidin C1	ultrasound-assisted extraction

3. Sample Preparation and Hydrolysis

Generally, flavonoids are isolated from plant tissues, from the food matrix, or from liquid samples (biological fluids or beverages). For some liquid samples, it is sufficient to centrifuge and filter them before analysis, but for some matrices the whole process is much more complex. Flavonoids can be isolated from fresh plant material, but in this case the samples should be kept at low temperature and the extraction should start soon after harvest to prevent enzymatic or chemical degradation and to modify the particles of the plant material to contribute to the release of bioactive compounds loosely bound to the cell wall polymers [41].

Many different methods can be employed in sample preparation (Figure 2) but nowadays, plant material is most commonly dried by freeze-drying, convection drying, or microwave vacuum drying (Table 3). As is evident from Table 3, most studies reported that freeze-drying is the preferred method for pretreatment of samples to obtain most of the flavonoids.

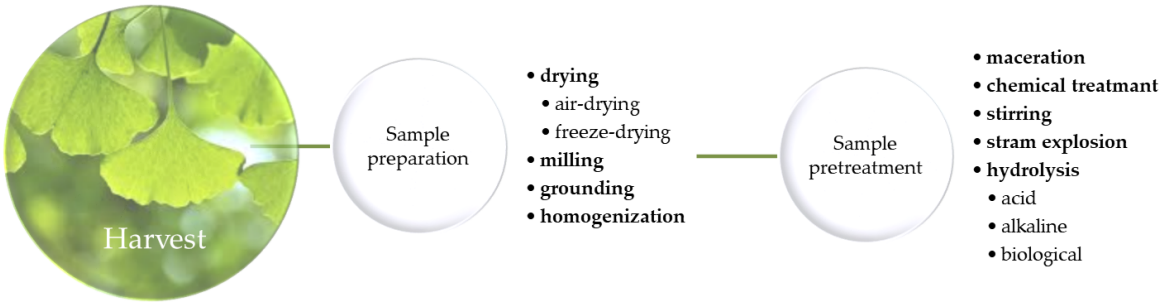


Figure 2. Main steps in sample preparation before extraction.

Table 3. Literature reports on the influence of drying methods on flavonoid content.

Sources	Drying Methods	Results
green tea (*Camellia sinensis*) leaves [42]	sun, shade, oven 60 °C, 80 °C and 100 °C, microwave and freeze-drying	the highest total flavonoid content was obtained in oven drying at 60 °C and 100 °C
lemons (*Citrus limon*)	freeze-drying and air-drying [43]	freeze-drying provides extracts with higher amounts of flavonoids
	freeze-drying and air-drying [44]	freeze-drying is more suitable for extraction of flavanones or flavones; while air-drying was the best for flavanols
Dryopteris erythrosora leaves [45]	shade one day then oven-dried at 75 °C for 48 h, dried in the sun, then oven-dried at 75 °C for 48 h, oven-dried at 75 °C for 48 h	the highest flavonoids yield was from first drying the plant material in the shade and then completing the drying process in an oven at 75 °C
birch leaves [46]	air-drying at ambient temperature, oven-drying at 40 °C and 80 °C, freeze-drying–prefreezing with liquid	freeze-drying of leaves frozen at −18 °C is preferred as a drying method

	N_2, freeze-drying–prefreezing at −18 °C, freeze-drying without prefreezing, storing frozen for 12 days without drying, and immediate extraction of fresh samples	
orange peel [47]	fresh, oven-dried and freeze-dried peel	freeze-drying preserves the concentration of the flavonoids, while oven-dried peel presented a decrease of glycosylated flavonoids and an increase of aglycone forms
Helicteres hirsuta Lour. Leaves [48]	hot-air drying, low-temperature-air drying, infrared drying and vacuum drying	the leaves dried under either hot-air drying at 80 °C, or vacuum drying at 50 °C yielded the highest amount of total flavonoid content
blueberry, cherry, cranberry and strawberry [49]	hot-air drying, freeze-drying and refractance window-drying	higher levels of flavonoids were found in all the freeze-dried samples except strawberry
Sage (*Salvia officinalis* L.) [50]	air-drying at shade and ambient 22 °C, drying in a hot air oven with natural convection at 45 °C and 65 °C, drying in a microwave oven at 600 W/30 g and 800 W/30 g of fresh plant; drying in an infrared moisture analyzer at 45 °C and 65 °C.	the highest total flavonoid content was determinate in the air-dried plants
Cosmos caudatus [51]	air-, oven- and freeze-drying	the freeze-drying and air drying were the best methods for flavonoids
Allium cepa red cv. and *A. sativum* [52]	microwave, air-drying, or freeze-drying	microwave and freeze-dried samples show similar profile
Stevia rebaudiana leaves [53]	hot air-drying, freeze-drying and shade-drying	the majority of the compounds analyzed reached their maximum values with the freeze-drying method

After drying, the samples are usually ground to a fine powder. This can be done manually with a mortar and pestle or by grinding over a long period of time. For example, Rajha et al. [54] studied the effect of particle size on the extraction of flavonoids from grape by-products and reported that the highest amount was obtained with a grinding time of 6.8 min and a solid–liquid ratio of 3 mL/g. The solid–liquid ratio is also an important parameter and depends on the plant tissue and the content of specific flavonoids we want to detect. Sometimes, the use of an excessive amount of the samples can lead to the extraction of other compounds present in the samples, which can lead to a "matrix effect" during the analysis, caused by the change in ionization efficiency of the target analyses in the presence of co-eluting compounds in the same matrix. In this case, the flavonoids of inter-

est are difficult to detect. On the other hand, the flavonoids of interest are below the detection limit if we use too small a sample amount. Therefore, this parameter also needs to be optimized. For example, for the determination of total flavonoid content in shoots of Brassicaceae, 30 mg of dehydrated samples per 1 mL of 80% methanol was used [55], while for fresh strawberries, using the same extraction solvent, 1 g per 10 mL of solvent was used [56]. Today, often deep eutectic solvents have been used for flavonoid extraction. For the extraction of flavonoids from wolfberries, 20:1 mg/mL [57] and for buckwheat sprouts, 100:1 mg/mL [58] of the ratio of extracted samples to solvent was used.

Flavonoids are present in complex forms in matrices, and hydrolysis has often been used to remove sugar units from glycosides. Hydrolysis can be acidic, basic, or enzymatic [59]. For example, Nuutila et al. [60] obtained the best results by refluxing at 80 °C for 2 h with 1.2 M HCl in 50% aqueous methanol with the addition of 2 mg ascorbic acid as an antioxidant. Balli et al. [61] compared basic (1 g defatted flour was suspended in 25 mL MeOH:H_2O 7:3 v/v (0.1 M NaOH); the solution was sonicated at 60 °C for 1 h, then CH_3COOH was added until the pH was 6.5–7.0) and acid hydrolysis (1 g defatted flour was extracted with 25 mL MeOH:H2SO4 9:1 v/v; the solution was sonicated at 60° C for 2 h) were used for the extraction of total flavonoids from millet and reported that acid hydrolysis was able to extract the highest amount of total phenolic compounds, while basic hydrolysis underestimated the phenolic concentration. Sometimes enzymatic processes and fermentation are also used [41] before extraction to improve the extraction efficiency. Enzymatic hydrolysis prior to extraction can boost extraction efficiency by improving solvent dispersion, mass transfer, particle size reduction, and contact area [62]. Krakowska et al. [63] and Krakowska-Sieprawska, et al. [41] studied the potential of enzyme-assisted supercritical extraction of phenolic from *Medicago sativa* leaves. The degradation of the plant material was enhanced using commercially available multi enzyme preparation containing five different enzymes: xylanase, beta-glucanase, cellulase, amylase and protease. The results showed that the extraction yield was about twice as high when enzymatic hydrolysis was performed before extraction. Of course, the choice of the right hydrolysis technique depends on the experimental design and the desire to detect the flavonoids we are interested in.

After the sample has been prepared and stored appropriately, various liquid–liquid or solid–liquid extractions can be used to extract flavonoids. The most commonly used method is extraction by solvents (methanol, ethanol, acetone, water, etc.). Unfortunately, this method consumes large amounts of solvents, is time consuming, and can result in low extraction efficiency. For this reason, new technologies, new solvents, and new approaches are constantly being sought to eliminate some of the aforementioned drawbacks of the so-called traditional methods. Some of the new approaches are the application of so-called green technologies such as:

- ultrasound-assisted extraction (UAE)
- enzyme-assisted extraction (EAE)
- microwave-assisted extraction (MAE)
- pulsed electric field-assisted extraction (PEFAE)
- supercritical fluid extraction (SFE)
- liquid extraction under pressure (PLE)
- ohmic heater-assisted extraction (OHAE)

Each type of method has a specific scope depending on the target molecules to be extracted or on the plant material. The most commonly used methods for flavonoid extraction are UAE, MAE, SFE and PLE. Although these methods are described as safe, efficient, suitable for extraction of sensitive compounds, short, etc., they must be carefully selected based on the sample and target compounds, as mentioned earlier. The selection of a suitable method still does not guarantee maximum extraction efficiency, so the selected methods usually need to be optimized. In general, all extraction techniques require optimization of variables such as particle size, solvent for extraction, temperature, time

and sample-to-solvent ratio (Figure 3), and these variables should be the starting point for optimization of the extraction protocol.

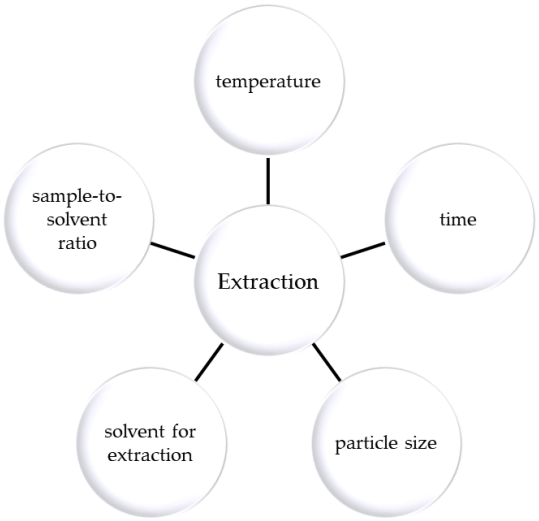


Figure 3. Common extraction variables that should be optimized for all extraction techniques.

The selection of the other variables that should be optimized depends strongly on the extraction technique. Some of them are discussed in this article depending on the chosen extraction technique.

4. Selection of Variables for the Optimization of Modern Techniques for Flavonoids Extraction

4.1. Ultrasound Assisted Extraction

As described by Yusoff et al. [64] ultrasound-assisted extraction (UAE) is considered an environmentally friendly extraction technique due to its high productivity with minimal solvent and time consumption and its suitability for molecules with high thermal sensitivity (Figure 4a). The frequency of ultrasound ranges from 20 kHz to 100 kHz, and high powers (10–1000 W/cm) can be generated, sufficient to break intermolecular bonds. When the energy is higher than 10 W/cm, a cavitation effect (growth and collapse of bubbles) occurs. When the bubble collapses near the cell wall, it generates high temperature (up to 5000 K) and high pressure (up to 100 ATM), allowing the solvent to penetrate the cell, resulting in enhanced mass transfer. In addition to mass transfer, high pressure and temperature can rupture the cell wall and cell membranes and reduce the particle size, releasing the intracellular material and promoting the extraction process [62–64]. Optimization of UAE extraction should include selection of the proper solvent, particle size, temperature, time and solvent-to-solid ratio, as in traditional methods, but also optimization of ultrasound parameters (power and frequency) [65, 64] (Figure 4b).

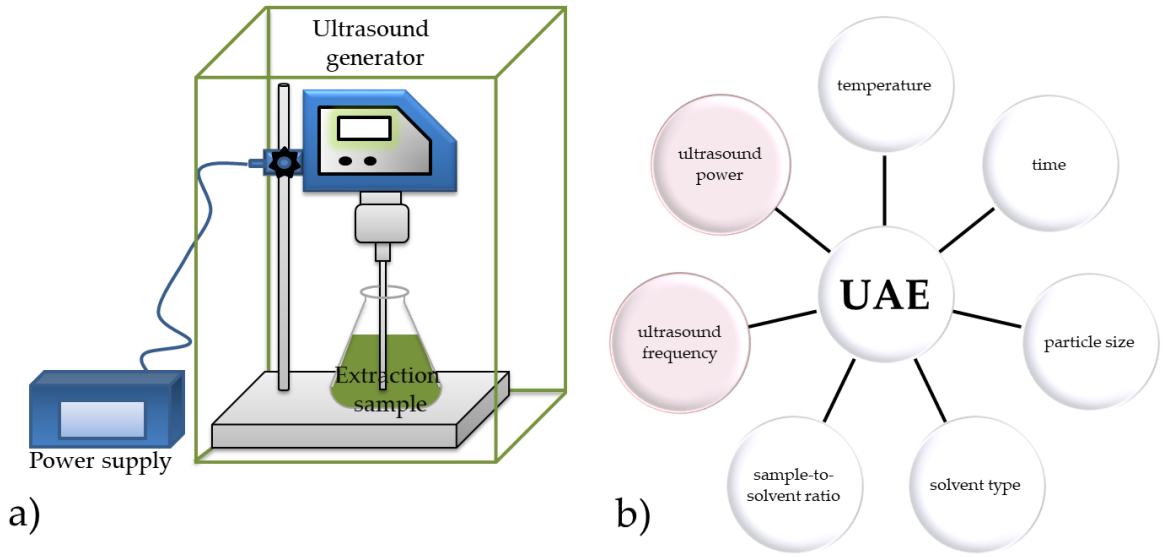


Figure 4. (**a**) Scheme of ultrasound-assisted extraction. (**b**) Specific variables that should be optimized for UAE extraction.

Liao et al. [67] analyzed the effect of the ethanol concentration, particle size, solvent-to-solid ratio, temperature, ultrasonic power and ultrasonic frequency on the extraction of flavonoids from peanut shells and showed that usage of ultrasound reduces the extraction process from 280 to 80 min in the case of Soxhlet extraction. Similarly, Zimare et al. [68] studied the effect of methanol ratio, temperature and extraction time on the total flavonoid content of *Lobelia nicatianifolia* leaves and showed that plant tissues were extensively ruptured during ultrasonication and that UAE significantly increased the antioxidant capacity of the extracts. Garcia-Castello et al. [69] compared the efficiency of conventional solid–liquid extraction and UAE for flavonoids extraction from grapefruit peels and showed that UAE was more than 50% more efficient regarding the bioactives extraction yield, while Meregalli et al. [70] compared conventional extraction and UAE for the extraction of bioactive red Araçá fruit (*Psidium cattleainum* Sabine) and presented approximately 6% higher flavonoids extraction yield when using UAE. Irakli et al. [71] explored how to increase the yield of oleuropein, hydroxytyrosol, flavonoids and phenolic acids extracted from olive leaves in order to reduce operational expenses with the potential for using reduced solvent amount, shorter extraction periods, and reduced extraction temperatures. They showed that UAE with acetone as the extraction solvent can be efficiently used to produce olive leaves extracts that are rich in bioactive compounds. Moreover, Wang et al. [72] proposed a negative pressure cavitation-based ultrasound-assisted extraction (NPC-UAE) for the efficient extraction of six flavonoids from the flower buds of *Sophora japonica* L. using ethanol as the extraction solvent and showed that the combination of the two extraction methods resulted in better extraction yields compared to the UAE method, while Saeed et al. [73] coupled enzyme-assisted extraction with the UAE method to improve the extraction efficiency of bioactive compounds from *Gymnema sylvestre*. The proposed extraction method was found to be three times more efficient than the conventional maceration performed as a control. During ultrasound-assisted solvent enzymatic extraction (UAE-EAE) ultrasonic waves promote enzymatic extraction by cracking cell walls to allow for enzyme-aided reactions and the subsequent release of desired components [74,75]. Wani et al. [76] compared the extraction efficiency of hot water extraction and the pulsed ultrasound-assisted extraction (PUSAE). Based on the extraction yield of total flavonoids, total phenols, antioxidant activity, and vitamin C from papaya pulp and peel they showed higher performance of PUSAE.

4.2. Microwave-Assisted Extraction

In microwave-assisted extraction (MAE) (Figure 5a), microwaves are used to heat the matrix [77]. Their frequency ranges from 300 MHz to 300 GHz. Magnetic and electric fields in microwaves are perpendicular to one another. The electric field causes heating by ionic conduction and dipole rotation [78]. Depending on their dielectric characteristics, the components absorb microwave radiation. The radiation promotes cell rupture, allowing liquid to penetrate through the plant matrix. On the other hand, plant material enters the solution from outside the cells [79]. According to Bagade et al. [80], the efficiency of microwave-assisted extraction is affected by: (i) solvent nature and volume, (ii) extraction time, (iii) microwave power, (iv) operating temperature and (v) properties of the matrix, and all listed factors must be taken into account during process optimization (Figure 5b).

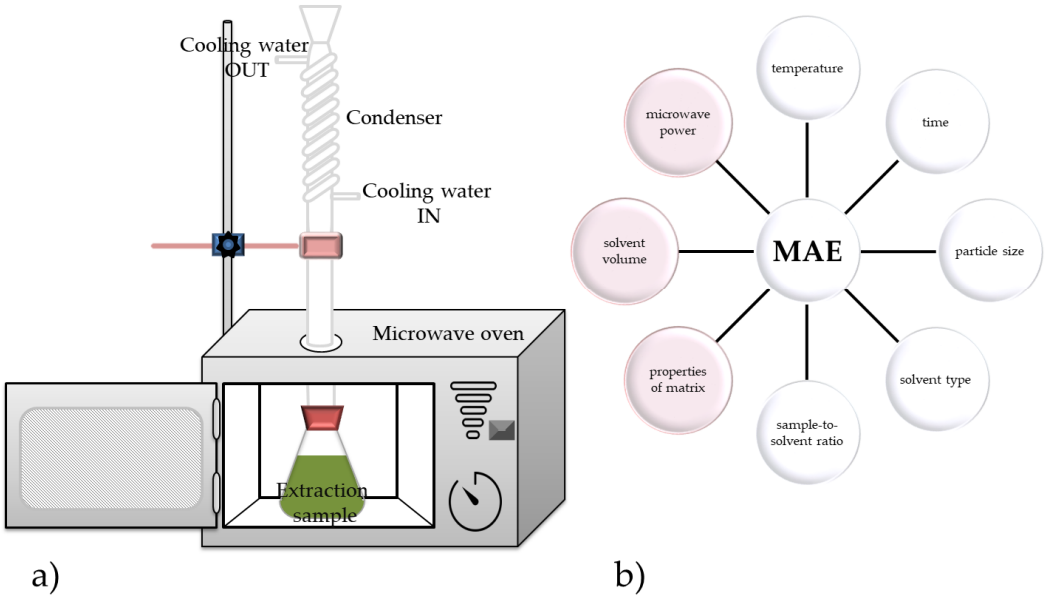


Figure 5. (**a**) Scheme of microwave assisted extraction. (**b**) Specific variables that should be optimized for UAE extraction.

Abbas et al. [81] compared the efficiency of microwave-assisted extraction, ultrasound-assisted extraction and Soxhlet extraction using ethyl acetate as solvent for the extraction of bioactive compounds from *Lagenaria siceraria* and showed that MAE was the most efficient method for the extraction of flavonoids (24.28 mg/g), while Plazzotta et al. [82] showed that MEA was more efficient than UAE for flavonoids from peach waste. Similarly, Ling et al. [64] compared maceration, ultrasonic- and microwave-assisted extraction for total phenolic content and total flavonoid content of Cassia alata. Their results showed that microwave MAE has the highest TPC and TFC yield (37.92 mg/g DW, 135.18 mg/g DW), followed by ultrasonic-assisted extraction and maceration extraction. Moreover, Elakremi et al. [83] compared the conventional maceration and MAE extraction yield of polyphenols and flavonides from *Pistacia vera* L. leaves (male and female), Alara et al. [84] compared the conventional maceration and MAE extraction yield for extraction of flavonoids from the *Vernonia amygdalina* leaf, and Dahmoune et al. [85] studied UAE and MAE for extraction of flavonoids from *Myrtus communis* L. In all the experiments described, MAE was the preferred method for obtaining the highest extraction yield of flavonoids. Similarly, Darvishzadeh and Orsat [86] presented MAE as the best method for the extraction of three flavonoids with therapeutic properties including isorhamnetin, luteolin and rutin from the leaves and flowers of the Russian olive. Akbari et al. [87] analyzed the most important factor affecting flavonoids extraction yields from fenugreek seeds and showed that ethanol concentration was the most significant and contributing

factor for the MAE process. Pinela et al. [88] analyzed the effects of processing time, extraction temperature, ethanol concentration and solid-to-liquid ratio on the flavonoids recovery from tomato using MAE and their results showed that water was preferable as a solvent.

Furthermore, Xie et al. [89] coupled MAE and aqueous two-phase systems (ATPS) for the simultaneous extraction and determination of vitexin, isovitexin, orientin and isoorientin from *Crotalaria sessiliflora* L. They described that MAE with ethanol/ammonium sulfate ATPS ensures from two to five fold higher extraction yield of specific flavonoid when compared to a mono-phase solvent such as water and ethanol. On the other hand, Gu et al. [90] evaluated the applicability of the ten ionic liquids for MAE of flavonoids hesperidin, hyperoside and rutin from the leaves of *Sorbus tianschanica* and selected 1-hexyl-3-methylimidazolium tetrafluoborate as the extracting solvent, while Liu et al. [91] enhanced flavonoids extraction from *Helichrysum arenarium* by using 1.0 M [C 8mim]Bras as the solvent.

4.3. Pressurized Liquid Extraction

Since the dissolution rate, speed of mass transport, and extraction rate of bioactive molecules, as well as specimen wettability and permeability, enhance with temperature, accelerated solvent extraction (ASE), also known as pressurized liquid extraction (PLE) (Figure 6a), is undertaken statically by utilizing heat and pressure to the solvent system and specimens [92]. According to Soria et al. [93] PLE is based on conventional heating at high temperatures and up to 200 bar of pressure, where high pressure is applied to ensure the solvent is in a liquid condition while high temperature is used to make the analytes more soluble and enhance their extraction from the material (Figure 6b).

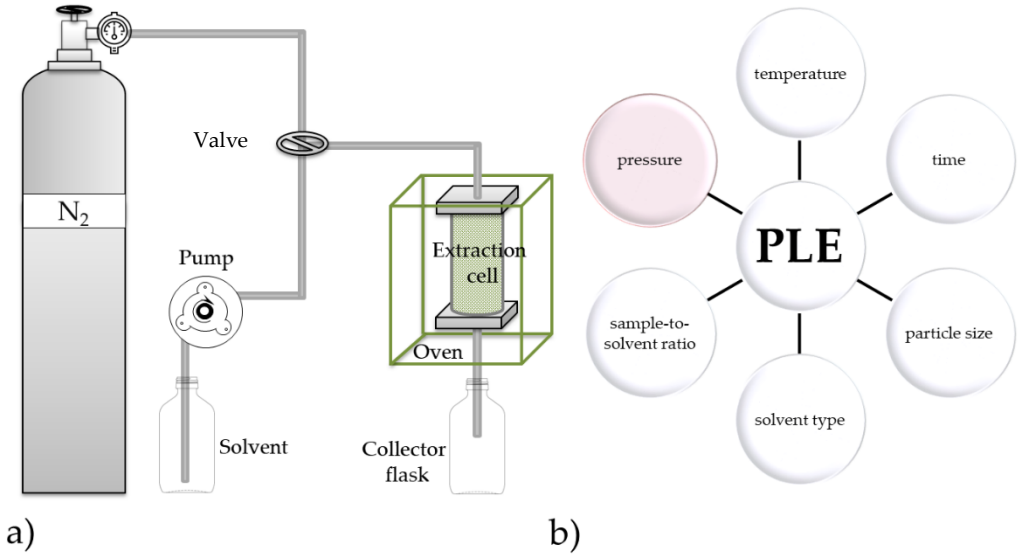


Figure 6. (**a**) Scheme of pressurized liquid extraction. (**b**) Specific variables that should be optimized for PLE extraction.

PLE technology is considered "green" extraction technology because of the decreased solvent usage (approximately 100–200 mL of solvent) and speeding up (extraction time approximately 20 min) of the extraction process [94,95] compared to traditional solid–liquid extraction techniques such as Soxhlet extraction [96]. Another practical advantage over the classic extraction method is that the extract does not need to be filtered after processing because the starting material remains in the extraction cell [97].

Quantitative extraction of various samples of environmental organic chemicals from soils and lipids, as well as the examination of food and biological samples, have all been conducted using PLE technology [98–102]. Regarding the flavonoids extraction, Kamali et al. [103] compared the extraction efficiency of percolation extraction PLE from *Dracocephalum kotschy*, Golmakami et al. [104] compared the extraction efficiency of percolation extraction PLE from the roots of *Scutellaria pinnatifida*, while Lama-Muñoz et al. [105] and Alves et al. [106] compared extraction with Soxhlet method and PLE for analysis of olive leaves bioactive molecules and extraction of bioactive compounds from *Monteverdia aquifolia* leaves, respectively. All the described studies showed extraction yield improvement when using PLE over classic extraction methods. Moreover, Corazza et al. [107] evaluated PLE extraction conditions (pressure 100–200 bar, flow rate 1–3 mL/min and time 0–60 min) using goldenberry as the extraction matrix and ethanol as the extraction solvent. They showed that the highest yield of bioactive compounds was obtained for 10 min of extraction and that the compounds were extracted at 100 bar and 200 bar regardless of the flow rate. On the other hand, Oliveira et al. [108] compared PLE and UAE for the extraction of bioactive compounds from industrial Tahiti limes (*Citrus latifólia* Tan.). While UAE was conducted with variable ultrasonic power (160–792 W), time (2–10 min), and solvent-to-feed mass ratio (20–40 kg solvent/kg dry pomace), PLE was carried out at various temperatures (60–110 °C) and time periods (5–40 min). In the case of PLE, the highest temperature (110 °C) produced the best results for the overall yield and total phenolic, with the exception of flavonoids (hesperidin and narirutin), which were not significantly affected by temperature. Both methods used ethanol and water (3:1, wt.) as the solvent. Recently, researchers have focused on combining the UAE and PLE into ultrasound-assisted pressurized liquid extraction (UAPLE) to improve the mass transfer rate and thus increase the extraction yield *[100,109,110]*

As described by da Silva et al. [97], PLE is unable to discriminate between compounds from related phenolic classes. The resulting extracts consist of a variety of compounds and therefore it is necessary to couple extraction and separation methods to obtain the target molecule. For this reason, Qian et al. [111] developed rapid pressurized liquid extraction and high-performance liquid chromatography coupled with diode array detection and mass spectrometry (HPLC-DAD–MS) for the simultaneous determination of a flavonoid (panasenoside), nine saponins (ginsenoside Rg1, Re, Rf, Rg2, Rb1, Rc, Rb2, Rb3 and Rd) and two polyacetylenes (panaxydol and panaxynol) in Folium Ginseng and Radix Ginseng. Similarly, Chaves et al. [112], Souza et al. [113] and da Silva et al. [97] combined PLE and in-line solid phase extraction to extract and concentrate phenolic molecules from lemon peel, mate (*Ilex paraguariensis*) leaves and apples, respectively. Their results showed that the new approach not only allowed fractionation of the compounds, but also gave equivalent or higher yields of all chemical classes compared to previous methods such as pressured liquid extraction alone, stirring, maceration, and ultrasound-assisted extraction.

4.4. Supercritical Fluids Extraction

Supercritical fluids extraction (SFE, Figure 7a) is categorized as a new extraction process that is a more ecologically friendly way to create native compounds that have uses in many different sectors, from sustainable sources including herbs, spices, aromatic, and medicinal plants [114,115]. This method uses supercritical fluids to isolate and remove certain bioactive molecules [116–118].

Chemical solvents known as supercritical fluids may be pressed exceeding their critical point, are often regarded as ecologically safe, and are frequently utilized in the extraction procedure because of their great performance and distinctive properties [119]. Many substances, including ammonia, ethane, ethane, fluoroform, nitrous oxide, propane, water, xenon and carbon dioxide can be used as supercritical fluids (SCF) [120]. Unquestionably, carbon dioxide is the one that is used the most frequently, because it is inexpensive,

eco-friendly, and GRAS (generally acknowledged as safe) [121]. Furthermore, CO_2 is gaseous at normal temperature and pressure, making extract recovery relatively straightforward and enabling the production of extracts without the need of solvents [122]. The ability of SFE employing CO_2 to be operated at low temperatures using a non-oxidant medium, which permits the extraction of thermally labile or readily oxidized chemicals, is also crucial for the extraction of food and natural products [123]. The limiting of the target compound and the inability to extract polar molecules is a SC-drawback, so in order to improve and aid in the polarity of SC-CO_2, ethanol must be added to the extraction system [124]. The limiting of the target compound and inability to extract polar molecules is SC-drawback. Ethanol can enhance SC-CO_2 mass-transfer and diffusivity [125].

Temperature, pressure, supercritical CO_2 flow, the presence of a modifier, and extraction time are the main variables that influence the SC-CO_2 extraction technique's effectiveness expressed as selectivity, yield, and/or extraction rate [126,127] (Figure 7b). So, the impact of the important SC-CO_2 extraction parameters must be studied in order to enhance extraction yield [128]. According to Melloul et al. [129], with the introduction of supercritical carbon dioxide extraction, a wide variety of plant sources now serve as a significant source of bioactive chemicals with intriguing uses in complex sectors including food, pharmaceutical, and cosmetics. For example, Martínez-Ávila et al. [130] applied supercritical CO_2 for the selective extraction of bioactive phytochemicals from black beans (*Phaseolus vulgaris* L.), Melloul et al. [129] for extraction of bioactive compounds from *Peganum Harmala* plant seeds, while De Aguiar et al. [131] used pure supercritical CO_2 and supercritical CO_2 with modifiers for bioactive compounds extraction from *Capsicium peppers*.

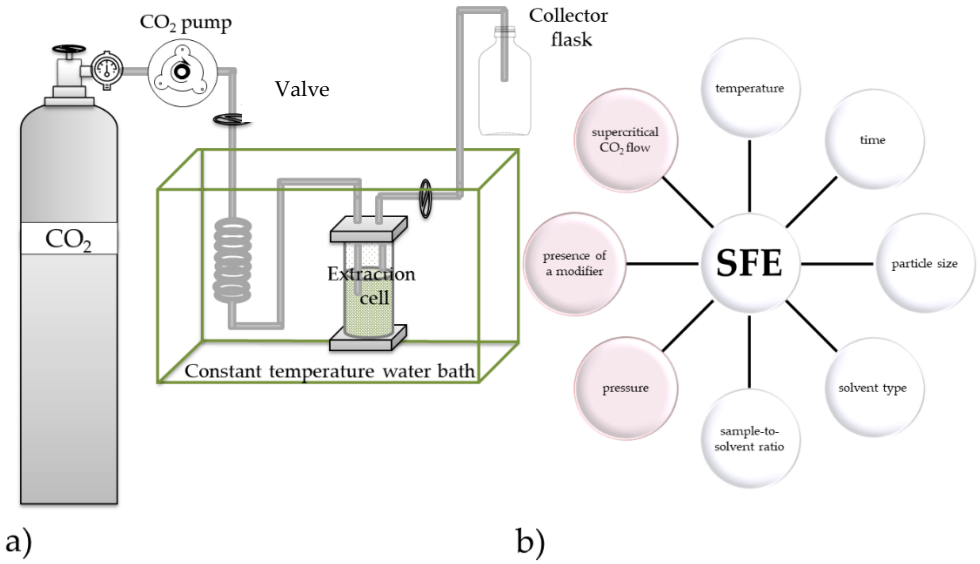


Figure 7. (**a**) Scheme of pressurized liquid extraction. (**b**) Specific variables that should be optimized for SFE extraction.

Song et al. [132] and Yang et al. [133] showed that the SFE-CO_2 extraction ensured a considerable increase in flavonoid production, antioxidant activity, and antiproliferative activity of the extracts compared with conventional Soxhlet extraction and ultrasound-assisted extraction when *Xinjiang jujube* leaves and *Puerariae lobatae* root, *Pinus massoniana* needle, *Citrus reticulata* peel and their mixture were used. Similar results were in the study by Milovanovic et al. [134] where flavonoids-rich extract (TF = 208.6–564.5 μg/g) of dandelion seeds was prepared by SFE-CO_2 extraction at temperatures of 40 and 60 °C and pressures of 100 to 450 bar and in the study by de Souza Correa et al. [135], in which a

rutin-rich extract from blackberry seeds was prepared at 70 °C and 25 MPa using ethanol as co-solvent. In the extract prepped by Song et al. [132], the authors detected eight flavonoids in the prepared extracts, namely quercetin 3-*O*-robinobioside, rutin, hyperoside (quercetin-3-O-D-galactoside), quercetin-3-O-D-glucoside, kaempferol-3-O-robinobioside, kaempferol-3-O-glucoside, quercetin-3-O-β-L-arabi-nosyl-(1→2)-*α*-L-rhamnoside and quercetin-3-O-β-D-xylosyl-(1→2)-*α*-L-rhamnoside. On the other hand, Yang et al. [136] detected six representative flavonoids (apigenin, baicalin, baicalein, luteolin, naringenin and wogonin) when performing SFE-CO_2 extraction of *Scutellaria barbata* with different percentages of ethanol as co-solvent (0–14.5%), dynamic extraction times (5–240 min), temperatures (33–62 °C) and pressures (10.5–31.5 MPa). Furthermore, Végh et al. [137] efficiently developed SFE-CO_2 method to co-extract the sesquiterpene lactones and the twelve lipophilic flavonoids simultaneously from the leaves of *Tanacetum parthenium* L. The described extraction was performed using 7% ethanol as co-solvent at a temperature of 64 °C and a pressure of 22 MPa. Uquiche et al. [138] also showed the positive effect of using co-solvent application in the SFE-CO_2 on the extraction yield of flavonoids, namely quercetin, kaempferol and resveratrol from *Leptocarpha rivularis*. In the presented study, temperature had no significant effect on the extraction yield but a positive effect of pressure on the increase of extraction yield was noticed, which was explained by the rise in CO_2's solubility due to the pressure-induced growth in its density. With growing interest in using fruit and vegetable residues at the rich source of the bioactive molecules, there is also an increasing trend in using SFE-CO_2 extraction as an effective green extraction technology for exploring the bioactive potential of food and vegetable residues. For example, Fornereto Soldan et al. [139] used SFE-CO_2 for extracting phenolics, flavonoids, fatty acids, and carotenoids from *Capsicum annuum* industrial waste, Argun et al. [140] for phenolics and flavonoids extraction from orange processing waste, Goyeneche et al. [141] for bioactives recovery from beetroot leaves, Restrepo-Serna and Cardona Alzate [142] for bioactive compounds extraction from five fruit wastes including mango peels, yellow passion fruit seeds, raspberry seeds, mandarin peels, and açaí berry exhausted pulp, and Jha and Sit [143] for the extraction of phytochemical from *Terminalia chebula* pulp.

4.5. Application of Environmentally Friendly Extraction Solvents

Although intensive work is being performed to develop new approaches to the extraction process, work continues to improve conventional methods in which extraction is based on solvent extraction. The development of new solvents for extraction has taken a step forward. To make the extraction process environmentally friendly, there is a specific focus on the selection of green solvents. Aqueous two-phase systems (ATPS, Figure 8) are recognized as an efficient alternative to the traditionally used organic solvents [144] due to their moderate process conditions, environmentally friendly qualities, capacity for continuous operation, easy scaling-up, rapid phase separation, low cost, and great throughput [58,145,146]. They can be formed by mixing of different components in water. The most common combination is two polymers and a polymer–salt (i.e., phosphate salt).

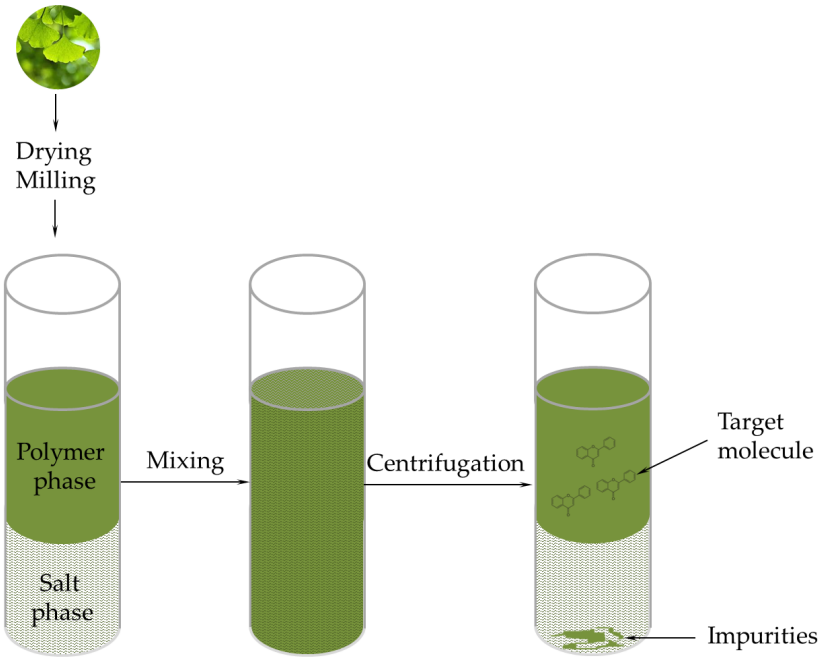


Figure 8. Schematic representation of target molecule separation using ATPS.

Zhu et al. [147] efficiently coupled UAE and ATPS for the extraction of flavonoids from jujube peels, Xu et al. [148] used ammonium sulfate-ethanol ATPS for the extraction of bioactive compounds from *Aronia melanocarpa* berries, Zhou et al. [149] selected a dipotassium hydrogen phosphate–ethanol system for extracting four flavonoids (lysioside C, nevadensin-7-sambubioside, ikarisoside B, and nevadensin) from *Lysionotus pauciflorus*, Liang et al. [150] used polyethylene glycol–ammonium sulfate ATPS as the extraction medium for extraction of flavonoids from hawthorn leaves, and Li et al. [151] applied ethanol–ammonium sulfate for flavonoids extraction from Tibetan sea-buckthorn (*Hippophae thibetana*) fruit.

Deep eutectic solvents (DESs) are becoming increasingly popular as an alternative to the traditionally used organic solvents for the extraction process [57,152–157]. DESs are often produced using safe, nontoxic, and affordable and biodegradable components [158–162]. A quaternary ammonium salt serves as both a hydrogen bond acceptor (HBA) and a hydrogen bond donor (HBD), which associate with one another through hydrogen bonding, in a DES, which is a combination of two or more compounds having a melting point lower than the individual components [160]. There are numerous examples of the use of DESs as efficient media for the extraction of bioactive molecules from various sources [163].

Today, DESs are often used in combination with modern extraction techniques. There are also examples of the use of DESs coupled with UAE for the extraction of flavonoids. For example: (i) Shang et al. [164] examined the effectiveness of nine various choline chloride-based DES systems with various compositions (contained glucose, citric acid, glycerol, urea, citric acid, glycerol, 1,4-butanediol, lactic acid, malonic acid, malic acid, or xylosic alcohol as hydrogen bond donor) for the extraction of flavonoids from *C. paliurus* leaves and the choline chloride/1,4–butanediol system (1:5 molar ratio) was selected as the optimal system for maximizing the flavonoid extraction yield; (ii) Zhang et al. [45] analyzed the efficiency of eight DESs (hydrogen bond acceptors (HBA) were choline chloride, levulinic acid, lactic acid, malic acid, and citric acid; hydrogen bond donors (HBD) were ethylene glycol, L-proline-levulinic acid, 1,4-butanediol, and glycerol) for flavonoids extraction from *Acanthopanax senticosus* and DES composed of glycerol and levulinic acid

(1:1) was chosen as the most appropriate extraction solvent; (iii) Mansur et al. [58] evaluated 18 different choline chloride-based DESs as solvent for the flavonoids extraction from common buckwheat (*Fagopyrum esculentum*) sprouts and selected choline chloride–triethylene glycol DES with 20% water as the most efficient; (iv) Meng et al. [165] analyzed the efficiency of eight DESs (HBA: choline and L-proline; HBD: 1,4-butanediol, glucose, glycerol, lactic acid, ethylene glycol and 1,2-propanediol) for the extraction of flavonoids including quercetin, kaempferol, isorhamnetin and naringenin from the traditional Chinese herbal medicine Pollen Typhae and DES composed of choline chloride and 1,2-propanediol (ChPri) at 1:4 M ratio was selected as the most efficient; (v) Ali et al. [57] screened potential of 11 DESs (HBA: choline and L-proline; HBD: 1,2-propanediol, glycerol, ethylene glycol, malic acid, malonic acid, p-toluenesulfonic acid, levulinic acid, oxalic acod, resorcinol, xylitol and urea) for flavonoids extraction from *Lycium barbarum* L. fruit and the 1:2 M mixture of choline chloride and p-toluene sulfonic acid was more efficient to get high extraction yields of flavonoids including myricetin (57.2 mg/g), morin (12.7 mg/g), and rutin (9.1 mg/g); (vi) Rashid et al. [166] explored seven different natural deep eutectic solvents (NADESs) for the extraction of bioactive compounds from apple pomace and used choline chloride: glycerol (1:2), choline chloride: lactic acid (1:3) and choline chloride: citric acid (1:1) for further process optimization; (vii) Lei et al.[167] prepared 30 NADES and selected choline chlorice–lactatic acid as the optimal medium for the extraction of 16 flavonoids from *Selaginella moellendorffii*. DES were also used in MAE processes: (i) Liu et al. [168] selected DES, ChCl/1,4-Butanediol (1/2, mol/mol) with 20% water as the best solvent based on the highest extraction efficiency for the extraction of flavonoids from *Hibiscus manihot*; (ii) Yu et al. [169] used choline chloride–glycolic acid DES for extraction of four flavonoids (liquiritin, isoliquiritin, liquiritigenin, and isoliquiritigenin) from *Glycyrrhiza residues* and showed that maximal total extraction yield achieved with DES was 83.03% higher than that of 60% ethanol; (iii) Zhang et al. [170] studied ten different NADEs (HBA: choline chloride; HBD: lactic acid, malic acid, glacial acetic acid, glucose, fructose, sucrose, glycerol, ethylene glycol, 1,4-butanediol and urea) for the extraction of flavonoid molecules from spent sweet potato and NADES, synthesized by choline chloride and malic acid (molar ratio 1:2), exhibited the highest extraction yield.

5. Statistical and Mathematical Modeling Techniques for Optimization Flavonoid Extraction Parameters

Numerous variables, such as solvent concentration and type, extraction time, extraction temperature, solvent pH, solid-to-liquid phase ratio, etc., affect the extraction efficiency in terms of the quantity of extracted chemicals and their biological activity [171]. Therefore, all these variables and their interactions must be taken into account to obtain the highest extraction efficiency. In order to determine the best extraction settings, statistical and mathematical modeling techniques are utilized. More literature data have recently emerged that highlight the significance of using mathematical modeling tools to optimize the extraction process [12,15,172,173]. As a result, multivariate analysis approaches (such as response surface methodology) are rapidly replacing and/or being compared to one-at-a-time methodologies. In the one-factor-at-a-time method, the value of one factor is changed while the values of the other factors remain unchanged. Regardless of which optimization method is chosen, the optimization process follows the same steps as shown in Figure 9.

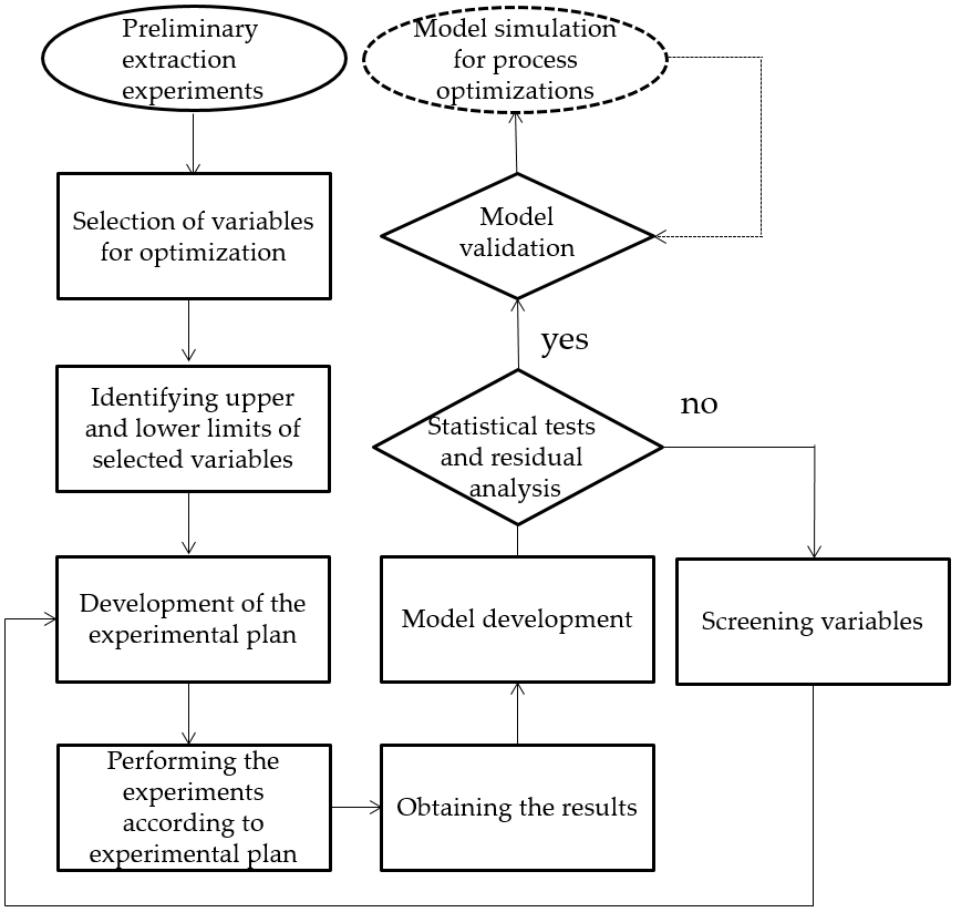
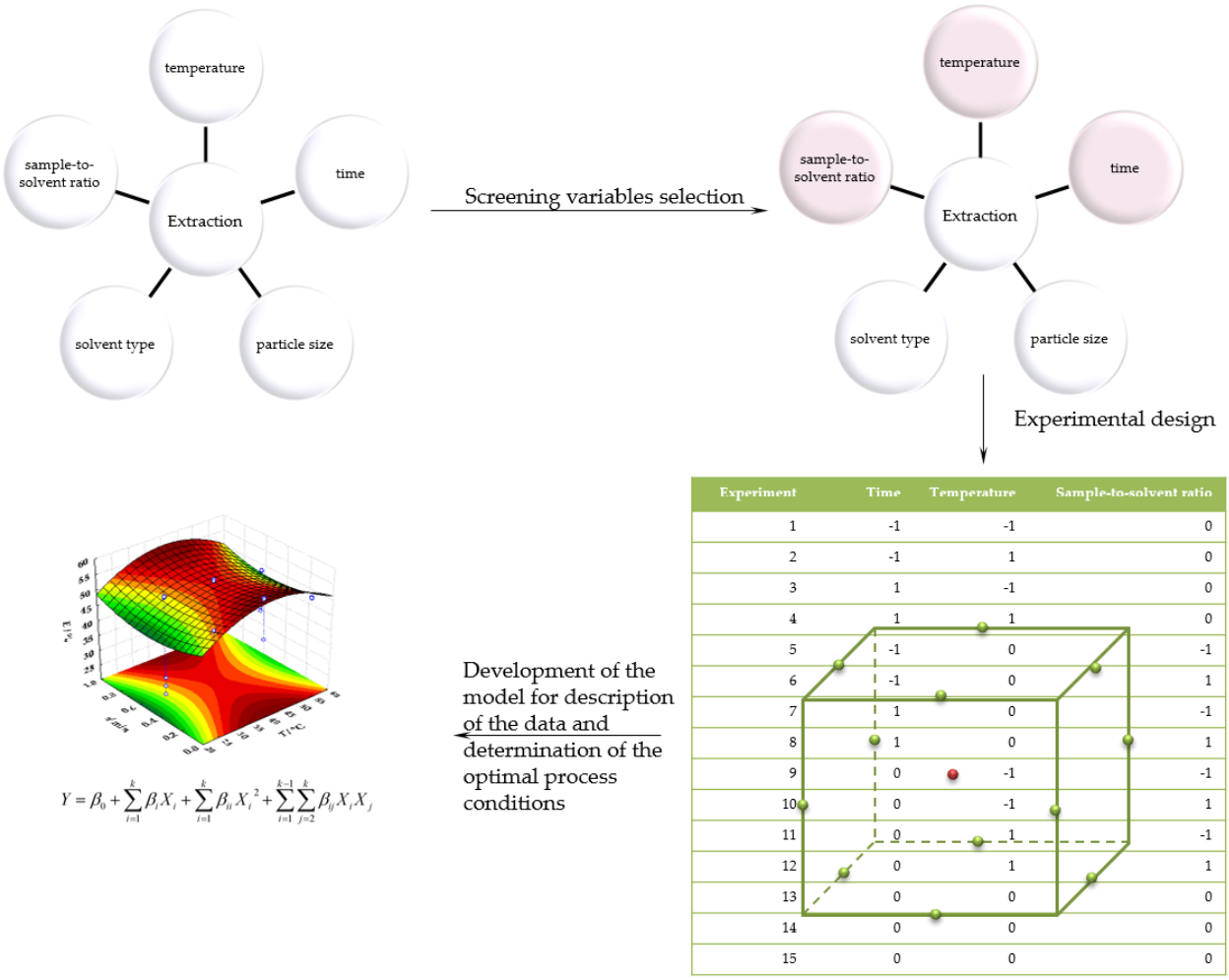


Figure 9. Flow chart for process optimization.

Experimental design-based response surface methodology (RSM) consists of mathematical and statistical methods that can be used to model and explore processes where a significant number of factors affect the final outcome [174]. To find the output–input interactions, it is essential to understand how the variables interact during the process [175]. The RSM approach ensures the selection of the appropriate process conditions by mathematically modeling the relationships between variables based on observable data [176]. According to Tirado-Kulieva et al. [17] RMS application include four stages: (i) variables selection, (ii) experimental design, (iii) development of the model for description of the data and (iv) determination of the optimal process conditions (Figure 10.).



Experiment	Time	Temperature	Sample-to-solvent ratio
1	-1	-1	0
2	-1	1	0
3	1	-1	0
4	1	1	0
5	-1	0	-1
6	-1	0	1
7	1	0	-1
8	1	0	1
9	0	-1	-1
10	0	-1	1
11	0	1	-1
12	0	1	1
13	0	0	0
14	0	0	0
15	0	0	0

Figure 10. Stages of response surface methodology application.

In order to establish the best settings for these variables that produce the greatest response, it is crucial to fit a mathematical model equation. This will allow a rough prediction of the link between the response and the independent variables [177]. The most important step presents statistical validation of the developed RSM model and if the model is not adequate, the irrelevant variables must be removed and the experimental runs must be redone [178]. After carefully choosing the variables that have a significant impact on the replies, RSM should be conducted [179]. Screening studies such as factorial designs can be used for this. The linear effects of the variables on the output are estimated using these first order designs [180]. These designs do not estimate curvature. The curvature-interaction of the variables is estimated via second-order designs such central composite and its variations (the rotatable CCD, the spherical CCD, the small composite design, and the face-centered cube), Box–Behnken, and Doelhert designs, and is then presented as a quadratic equation [181]. The application of RMS modeling for optimization of the flavonoids extraction process is given in Table 4. It is observed that different types of experiment designs and different extraction methods were used for different flavonoids sources but the general conclusion of all listed researches is that the design of the experiment coupled with RSM modeling reduces the number of experiments performed to achieve the maximum extraction yield.

Table 4. Optimization of the flavonoids extraction process.

Extraction Method	Flavonoids Source	Design of Experiment and Modeling Method	Optimal Process Conditions	Flavonoids Extraction Yield
UAE	peanut (*Arachis hypogaea* L.) [67]	Single-factor experiment and RSM	particle size of 0.285 mm, solvent to solid ratio of 40 mL/g, extraction temperature of 55 °C, ultrasonic power of 120 W and ultrasonic frequency of 45 kHz and 70% ethanol as the solvent	9.263 mg/g
UAE	leaves of *Lobelia nicotianifolia* [68]	Full factorial design and RSM	75.25% of methanol, extraction temperature 62.72 °C, and 9.44 min of extraction process.	23.78 mg/g dry weight
UAE	jujube peels [147]		K_2HPO_4 35% (w/w), ethanol 20% (w/w), solid–liquid ratio 1:30 g/mL (w/v), ultrasonic power 200 W, and extraction time 50 min	
NPC-UAE	flower buds of *Sophora japonica* L. [72]	Box–Behnken design and RSM	ethanol concentration 72%, time 16 min, liquid to solid ratio 25:1 mL/g, ultrasonic intensity 0.347 W/cm^2, negative pressure −0.07 MPa and temperature 60 °C	extraction yields of rutin, nicotiflorin, narcissin, quercetin, kaempferol and isorhamnetin were 125.17, 15.02, 25.61, 51.89, 4.32 and 6.30 mg/g
UAE	*Olea europea* L. leaves [71]	Single-factor experiment and RSM	extraction in ultrasonic bath frequency 37 kHz with 50% acetone for 10 min at 60 °C	2.94 mg/g dry weight
UAE	grapefruit peels [69]	Central composite design and RSM	extraction in ultrasonic bath frequency 40 kHz with 40% ethanol for 55 min at 25 °C	Hesperidin (0.74 mg/g dry weight) and narirutin (0.70 mg/g dry weight) were the most abundant flavonoids
UAE	*Acanthopanax senticosus* [182]	Single-factor experiments and Box–Behnken design of experiments and RSM	extraction in ultrasonic bath frequency 20 kHz. Solid-to-liquid ratio of 1:10 g/mL (ethanol as the solvent), extraction time of 35 min, and power of 200	14.83 mg/g dry weight
UAE	*Ficaria kochii* [183]	Rotatable central composite design and RSM	ratio of solvent (methanol) to raw material, 10%; extraction time, 50 min and extraction temperature, 60 °C.	11.754 mg/g dry weight
UAE	*Crinum asiaticum* [184]	Single-factor experiment and RSM	extraction in ultrasonic bath maximum power of 180 W, 60% ethanol concentration, 64 °C for extraction temperature, 1:28 (v/w) solid-to-liquid ratio with extraction time for 47 min	1.64%
UAE	guava (*Psidium guajava* L.) [185]	Face-centered design and RSM	extraction in ultrasonic bath maximum power of 250 W. Ultrasonic temperature of 62.19 °C, extraction time of 14.94 min, and loading ratio of 0.19 g/mL (water as the extraction solvent)	288.13 mg/g
UAE	*Cyclocarya paliurus* leaves [164]	Single-factor experiment and RSM	DES water content (v/v), 30%; extraction time, 30 min; temperature, 60 °C; and solid–liquid ratio, 20 mg/mL.	kaempferol (0.117 mg/g), kaempferol-7-O-α-l-rhamnoside (3.183 mg/g), quercetin (0.034 mg/g), quercetin-3-O-β-d-glucuronide (3.628 mg/g), and kaempferol-3-O-β-d-glucuronide (0.331 mg/g).
UAE	*Acanthopanax senticosus* [186]	Box–Behnken design of experiments and RSM	ultrasonic power of 500 W, water content of 28%, solid–liquid ratio of	23.928 mg/g

			1:18 g/mL, extraction temperature of 55 °C, and extraction time of 73 min.	
UAE	common buckwheat (*Fagopyrum esculentum*) sprouts [147]	Central composite design and RSM	ultrasound power of 700 W, extraction temperature of 56 °C and extraction time of 40 min.	Recovery > 97%
UAE	*Pollen typhae* [165]	Single-factor experiment and RSM	DES composed of choline chloride and 1,2-propanediol (ChPri) at 1:4 M ratio, 30% of aqueous solution, 50:1 mg/mL for solid–liquid ratio, and 35 min for extraction time	Recovery in the range of 86.87–98.89%
UAE	*Melia azedarach* [187]	Box–Behnken design of experiments and RSM	temperature (46.4 °C), ultrasound amplitude (100%; 130 W power) and glycerol-choline chloride DES concentration (50%)	21.880 mg/g
UAE-EAE	*Gymnema sylvestre* [73]	Single-factor experiment and RSM	time, temperature, pH, and amount of enzyme cocktail were 150 min, 64.80 °C, 5.64, and 7.49 mL	54.20 mg/g
UAE	apple samples [40]	Three-level three-factor central composite design and RSM	4.61 °C, an extraction time of 26.90 min, and ultrasonic power 480 W.	6.58 mg/g
UAE	*Aronia melanocarpa* berries [148]	Box–Behnken design of experiments and RSM	ammonium sulfate concentration of 0.320 g/mL, ethanol-water ratio of 0.71, ultrasonic time of 50 min and ultrasonic power of 200 W	11.67 mg/g
UAE	*Lysionotus pauciflorus* [149]	Single-factor experiment and RSM	45 g ATPS (made of 30% ethanol/18% K_2HPO_4) in 43 °C for 30 min	four flavonoids could reach 2.56, 2.06, 3.62, and 6.28 mg/g
UAE	hawthorn leaves [150]	Box–Behnken design of experiments and RSM	ratio of solid to liquid 1:37, ultrasonic time 40 min, ultrasonic power 360 W, ultrasonic temperature 65 °C	2.86%
UAE	*Astragalus membranaceus* steams and levaes [33]	Box–Behnken design of experiments and RSM	extraction time of 35 min, ethanol concentration of 75 %, liquid–solid ratio of 40 mL/g, and extraction temperature of 58 °C	22.027 mg/g
DES-UAE	*Ixora javanica* flowers [188]	Single-factor experiment and Box–Behnken design of experiments and RSM	extraction time of 40 min, 25% water content in DES and a solid-to-liquid ratio of 1:25 g/mL	89.732 mg/g
DES-UAE	*Scutellaria baicalensis* [189]	Box–Behnken design of experiments and RSM	molar ratio of betaine/acetic acid was 1:4, the water content was 40%, the solid/liquid ratio was 1:100 g/mL, the extraction temperature was 52 °C, and the extraction time was 23 min.	scutellarin, baicalin, baicalein, wogonoside, wogonin, and oroxylin A were 0.73 ± 0.04, 11.93 ± 0.36, 2.57 ± 0.12, 1.26 ± 0.08, 0.41 ± 0.2, and 0.17 ± 0.04%, respectively
NADES-UAE	*Selaginella moellendorffii* [167]	Single-factor experiment and RSM	water content of 24%, extraction power of 260 W, liquid/solid ratio of 24:1 mL/g and extraction time of 43 min	5.72 mg/g
MAE-UAE	*Aronia melanocarpa* [38]	Box–Behnken design of experiments and RSM	microwave power was 230 W, extraction time was 367 s, extraction	4.456 mg/g

			temperature were 52 °C. Solvent NADES	
MAE	*Lagenaria siceraria* [81]	Full factorial design of experiment and RSM	optimized power and time for TFC were 480 W and 40 s	24.22 mg/L
MAE	*Trigonella-foenum graecum* [87]	One-factor at time and RSM	3 min irradiation time, microwave power 600 W, 60% solvent concentration, 1:10 g/mL of feed-to-solvent ratio and 70 °C temperature	
MAE	*Crotalaria sessiliflora L* [89]	Single-factor experiment and RSM	ethanol concentration 32% and $(NH_4)_2SO_4$ concentration 22% for formation of the ATPS, extraction temperature 80 °C, extraction time 8 min, solvent-to-material ratio 50:1.	extraction yields and recoveries ranged from 162.7 to 240.0 g/g and from 94.14% to 105.5%, respectively.
MAE	*Sorbus tianschanica* leaves [90]	Factorial design and RSM	1.0 M [C6mim][BF4], –0.08 MPa for vacuum, 19 min and 420 W for microwave irradiation time and power, and 15 mL/g for liquid–solid ratio	recovery yields more than 84.14%, 82.40% and 89.33%
MAE	tomato [88]	5-level full factorial Box–Behnken design and RSM	the global optimum processing conditions (t = 20 min; T = 180 °C; Et = 0%; and S/L = 45 g/L)	quercetin pentosylrutinoside (6.78 mg/g) and quercetin-3-O-rutinoside (11.7 mg/g)
MAE	*Pistacia vera* L. leaves [83]	Single-factor experiment and RSM	70 °C and 61 °C, and 5.6 and 12 min for male and female leaves	Male leaves: 82.16 mg/g Female leaves: 83.34 mg/g
MAE	leaves of *Vernonia amygdalina* [84]	Face-centered central composite design and RSM	7 min of irradiation time, 416 W of microwave power level, 100 ºC of temperature, and 0.10 g/mL of feed-to-solvent ratio	TFC = 87.05 mg/g
MAE	*Myrtus communis* leaves [85]	Single-factor method and RSM	extraction time 1.04 min, ethanol proportion 42%, MW powere 500 W, liquid to solid ration 32 mL/g	5.02 mg/g
MAE	Russian olive leaves and flowers [86]	Two-level fractional factorial designs and RSM	solid to solvent ratio of 7.5 (w/v), citric acid molarity of 2 M, ethanol concentration of 59.8% and 66.4%, and temperature of 97.4 °C and 97.5 °C	
MAE	*Hibiscus manihot L.* flower [168]	Taguchi orthogonal design and RSM	temperature 73 °C, time 20 min and liquid/solid ratio 26 mL/g	16.704 mg/g
MAE	*Helichrysum arenarium* [91]	Box–Behnken design and RSM	5 mL/g liquid–solid ratio, 20 min microwave irradiation time and 525 W microwave irradiation power. 1.0 M [C8mim]Br was used as the solvent for the extraction	astragalin (0.83 mg/g), quercetin (0.42 mg/g), luteolin (0.62 mg/g), kaempferol (0.99 mg/g) and apigenin (0.19 mg/g)
MAE	fruits of *Ficus racemosa* [190]	Central composite design and RSM	3.5 pH, 360.55 W microwave power and 30 s time (water as the extraction solvent)	Quercetin 36.96 mg/100 mL
MAE	Peach waste [82]	2^2-factorial design and RSM	frozen samples: microwave power of 540 W and extraction time of 50 s dried samples: microwave power of 900 W and extraction time of 50 s	TF (frozen samples) = 120.47 mg/100 g TF (dried samples) = 74.75 mg/100 g
MAE	*Apium graveolens L.* [191]	Box–Behnken design and RSM	microwave power of 500 W at 30 mL/g solid–solvent ratio with 75.6% (v/v) ethanol concentration	0.62 g/100 g

MAE	*Alpinia oxyphylla* [192]	Orthogonal design and RSM	ethanol concentration of 50%, solid–liquid ratio of 1:20, temperature of 70 C, and cycle index of 3	28.24%
MAE	*Salvia plebeian* [193]	Box–Behnken design and RSM	ethanol concentration was 56%, the ratio of material to liquid was 1:30 g/mL, the extraction time was 5 min, the extraction power was 560 W	2.38 mg/
MAE	avocado (*Persea americana* Mill.) seeds [194]	Central composite design and RSM	ethanol concentration of 58.3% (v/v), microwave power of 400 W, and extraction time of 4.8 min.	21.84 mg/g
MAE	sweet potato (*Ipomoea batatas* L.) leaves [170]	Single-factor experiments and RSM	microwave power of 470 W, extraction temperature of 54 ◦C, extraction time of 21 min, and solid–liquid ratio of 70 mg/mL.	40.21 mg/g
MAE	grape skin [195]	Box–Behnken design and RSM	solvent 60% ethanol, extraction time 5 min at 40 °C	total anthocyanins 12545.19 mg/g
PLE	aerial parts of *Dracocephalum kotschyi* [103]	Circumscribed central composite (CCC) design and RSM	temperature, pressure, static time, dynamic time, and the solvent flow rate were adjusted 74 °C, 34 bar, 11.33 min, 17.45 min, and 0.7 mL/min	6.13 mg/g
PLE	roots of *Scutellaria pinnatifida* [104]	Circumscribed central composite (CCC) design and RSM	temperature, pressure, static time, dynamic time, and the solvent flow rate were adjusted 65.8 ◦C, 39.2 bar, 12.9 min, 18.9 min, and 0.76 mL/min	127.78 mg/g
PLE	goji berry fruits [121]	Factorial experimental design and RSM	180 °C and 86% ethanol in water	TF = 3.02 mg/g
UAPLE	Passion fruit [196]	Single-factor experiments and RSM	10 g/min in 68.54 min	7.8%
SFE-CO_2	Xinjiang jujube (*Ziziphus jujuba Mill.*) leaves [132]	Box–Behnken design and RSM	temperature of 52.52 °C, a pressure of 27.12 MPa, a time of 113.42 min, and a cosolvent flow rate of 0.44 mL/mi	29.05 mg/g
SFE-CO_2	*Odontonema strictum* leave [197]	Randomized design full factorial and RSM	extraction time of 270 min and a pressure of 200 bars,	230.48 mg/g
SFE-CO_2	*Maydis stigma* [198]	Box–Behnken design and RSM	a temperature of 50.88 °C, a pressure of 41.80 MPa, a co-solvent amount of 2.488 mL/g and an extraction time of 120 min with 0.4-mm particle sizes and 20% aqueous ethanol as the co-solvent	4.24 mg/g
UAESFE	*Iberis amara* [199]	Single-factor experiments and RSM	25 MPa pressure, 46 °C temperature, 0.34 W/mL ultrasonic energy density	
SFE-CO_2	*Lippia origanoides* K. and *Lippia graveolens* K. [200]	Fractional factorial screening design and RSM	307 bar, 5% ethanol, 96 min and 43 g CO_2/min	55 mg/g
SFE-CO_2	*Leptocarpha rivularis* leaves [138]	Box–Behnken design and RSM	temperature 60 °C, pressure 20 MPa and co-solvent (ethanol) concentration 2 wt.%	176.6 mg/g
SFE-CO_2	*Terminalia chebula* pulp [143]	Central composite rotatable design using RSM coupled with desirability	RSM-DF were 3.34 mL/min, 166.94 bar, 51.97 ◦C, 67.47 min, for RSM-	RSM-DF 137 mg/mL RSM-GA 136.58 mg/mL ANN-GA 135.55 mg/mL

		function (DF) and genetic algorithm (GA) and ANN with GA	GA were 3.23 mL/min, 172.79 bar, 52.37◦C, 68.53 min, while that for ANN-GA were 3.30 mL/min, 174.07 bar, 51.18 °C, 65.23 min.	
EA-SFE	*Medicago sativa* leaves [63]	The response surface methodology (RSM) based on Box–Behnken design	the temperature of 68 °C, the pressure of 205 bar and 15.5% of the co-solvent addition	3250 mg/g

Response surface models are frequently applied to describe how process variables affect extraction effectiveness, but these models do not always provide data supporting mass transfer and the dynamics of the extraction process, requiring the application of kinetic models to gain understanding of the extraction procedure [201]. To assess the extraction kinetics and guarantee the maximum level of product repeatability, a mathematical model is necessary [67,202–204]. As stated by Piwowarska and González-Alvarez [205], in order to decrease the consumption of energy, time, and chemical reagents, mathematical modeling of solid–liquid extraction processes is a key engineering technique in the design process. Furthermore, understanding complicated mass transfer, diffusion, and thermodynamic characteristics impacting the extraction requires the use of kinetic modeling [11].

The literature shows that the solid–liquid extraction procedures for the extraction of bioactive compounds from plant materials can be described using various mathematical models. The models used include Peleg, Page, Elovich, the second-order model, diffusion model, logarithmic model and Ponomaryov's empirical equation [11] (Table 5).

Table 5. Kinetic models mostly used for the description of the solid–liquid extraction process of bioactive molecules.

Kinetic Model	Equation	Parameters
Equilibrium-dependent model [206]	$\frac{dc(t)}{dt} = k \cdot (c_e - c(t))$	c is the concentration of the dissolved substance in the liquid phase, k is the transport coefficient and c_e is the dissolved substance concentration at the equilibrium
Second-order model [207]	$\frac{dc(t)}{dt} = k \cdot (c_e - c(t))^2$	c is the concentration of the dissolved substance in the liquid phase, k is the transport coefficient and c_e is the dissolved substance concentration at the equilibrium
Peleg's model [208]	$c(t) = c_0 + \frac{t}{K_1 + K_2 \cdot t}$	c(t) presents the concentration of the dissolved substance at the time t, K_1 is Peleg's rate constant (relates to extraction rate at the very beginning of the extraction process), K_2 is Peleg's capacity constant (relates to maximum dissolved substance concentration and c_0 is the concentration of dissolved substance at time $t = 0$.
Page's model [209]	$c(t) = e^{-k \cdot t^n}$	k and n are Page's model constants and c(t) represents the concentration of dissolved substance at time t
Logarithmic model [209]	$c(t) = a \cdot \log(t) + b$	a and b are Logarithmic model constants and c(t) represents the concentration of dissolved substance at time t
Ponomaryov's model [210]	$1 - \frac{c(t)}{c_e} = b + k \cdot t$	b and k are Ponomaryov's model constants, c(t) represents the concentration at time t and c_e is the equilibrium concentration
Lewis empirical model [211]	$c(t) = e^{-a \cdot t}$	a is Lewis's model constants, and c(t) represents the concentration at time t

Henderson and Pabis empirical model [212]	$c(t) = a \cdot e^{-b \cdot t}$	a and b are Henderson and Pabis model constants and c(t) represent the concentration at time t
Power-law model [213]	$y = B \cdot t^n$	y represents extraction yield or final concentration, B extraction solvent constant, n diffusion exponent and t extraction time
Two-site kinetic model [214]	$\frac{c(t)}{c_\infty} = 1 - F \cdot e^{-k_1 \cdot t} - (1 - F) \cdot e^{-k_2 \cdot t}$	c_∞ represents the maximum extracted concentration, F denotes the number of biocompounds discharged quickly, $(1 - F)$ denoted the amount of biocompound components released gradually, k_1 and k_2 are first-order rate constants of rapid and slow phases
Mass transfer model [215]	$\frac{\partial c}{\partial t} = D \frac{\partial^2 c}{\partial x^2}$	c is concentration, t is time, D is the diffusion coefficients and x is the diffusion distance

The literature states that a kinetic model describing solid–liquid extraction can be developed using an empirical and mechanistic method [216]. The mechanistic method involves a hypothetical description of the occurrences, whereas the empirical approach is based on facts from trials. According to Sturzoiu and Stroescu [216], solid–liquid extraction includes two stages; the first stage is the washing stage, during which the solute and solvent are first mixed and the second step uses a diffusion technique for a significantly slower solute transport. As described by Sridhar et al. [217], understanding the kinetics of the extraction depends heavily on the concentration of the substances (*C*s), the extraction order (n), the activation energy (Ea), and the rate constant (*k*). An overview of the models used to describe the flavonoids extraction kinetics is given in Table 6. The viability of several mathematical models has been investigated for different flavonoids sources; however, understanding the process in the early phase of extraction presents the most challenging problem [117,218].

Table 6. Application of kinetic modeling in flavonoids extraction.

Extraction Method	Flavonoids Source	Kinetic Model	Model Performance
UAE [67]	Peanut (*Arachis hypogaea* L.)	Phenomenological model and Peleg's model	the mean absolute errors (MPE) for phenomenological model in range 0.158–0.809% and for Peleg's model in range 0.675 to 1.817%
MEA [219]	*Terminalia bellerica*	Second-order kinetic model	The average absolute relative deviation (AARD) and the relative standard deviation between the experimental data and those predicted by second-order kinetics are 0.38% and 0.62%, respectively.
MAE [91]	*Helichrysum arenarium*	First-order kinetic model	$R^2 > 0.98$
UAE [203]	Lentils (*Lens culinaris* L.)	Parabolic diffusion Power law Peleg's model Elovich's model	RMS and SEE diminished and R^2 increased in the following order: hyperbolic model → parabolic model → Elovich's equation → power-law model.
Conventional extraction [204]	Linden *(Tilia cordata* M.) flowers	Unsteady-state diffusion Film theory Ponomaryov	R^2 increased in the following order Film theory -> Empirical equation of Ponomaryov -> Unsteady diffusion through plant material
Conventional extraction (infusion) [202]	Roots of *Carlina acaulis*	change in the concentration of the target substance in the cell volume over time	

		change in the concentration of the target substance in intercellular space over time material balance equation	
PLE [29]	Cocoa shell	Peleg's model	R^2 were high in all experimental data set (0.9335–0.9930)
UAPLE [196]	Passionfruit	Spline model two-site desorption model	Spline model> two-site desorption model
UAE-SC CO_2 [136]	*Scutellaria barbata*	Second-order kinetic model	R^2 = 0.98 at all analyzed temperatures (T = 33, 39, 45, 52 °C)
SFE-CO_2 [220]	Brazilian orchid tree (*Bauhinia forficata*)	Empirical model dividing extraction process into three periods	R^2 > 0.960○for analyzed extraction conditions
SFE-CO_2 [139]	*Capsicum annuum* pepper	Logistic and spline model	R^2 > 0.99 for both models for all analyzed extraction conditions

6. Conclusions

There is a growing interest in the extraction of bioactive molecules, namely flavonoids from plant materials. It is also noted that the mentioned modern extraction methods (microwave-assisted extraction, ultrasound-assisted extraction, pressurized liquids-assisted extraction, and supercritical fluids extraction) ensure higher extraction yields with lower energy and solvent consumption compared to the classic extraction method. However, due to the different sources of bioactive molecules, it is necessary to specifically define the optimal process conditions for the selected plant material. Therefore, it is necessary to use mathematical tools to optimize the extraction process and to analyze the extraction dynamics.

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References

1. Marone, D.; Mastrangelo, A.M.; Borrelli, G.M.; Mores, A.; Laidò, G.; Russo, M.A.; Ficco, D.B.M. Specialized Metabolites: Physiological and Biochemical Role in Stress Resistance, Strategies to Improve Their Accumulation, and New Applications in Crop Breeding and Management. *Plant Physiol. Biochem.* **2022**, *172*, 48–55. https://doi.org/10.1016/j.plaphy.2021.12.037.
2. Panche, A.N.; Diwan, A.D.; Chandra, S.R. Flavonoids: An Overview. *J. Nutr. Sci.* **2016**, *5*, e47. https://doi.org/10.1017/jns.2016.41.
3. Mouradov, A.; Spangenberg, G. Flavonoids: A Metabolic Network Mediating Plants Adaptation to Their Real Estate. *Front. Plant Sci.* **2014**, *5*, 620. https://doi.org/10.3389/fpls.2014.00620.
4. Nabavi, S.F.; Khan, H.; D'onofrio, G.; Šamec, D.; Shirooie, S.; Dehpour, A.R.; Argüelles, S.; Habtemariam, S.; Sobarzo-Sanchez, E. Apigenin as Neuroprotective Agent: Of Mice and Men. *Pharmacol. Res.* **2017**, *128*, 359–365. https://doi.org/10.1016/j.phrs.2017.10.008.
5. Budzynska, B.; Faggio, C.; Kruk-Slomka, M.; Samec, D.; Nabavi, S.F.; Sureda, A.; Devi, K.P.; Nabavi, S.M. Rutin as Neuroprotective Agent: From Bench to Bedside. *Curr. Med. Chem.* **2019**, *26*, 5152–5164. https://doi.org/10.2174/0929867324666171003114154.

6. Shen, N.; Wang, T.; Gan, Q.; Liu, S.; Wang, L.; Jin, B. Plant Flavonoids: Classification, Distribution, Biosynthesis, and Antioxidant Activity. *Food Chem.* **2022**, *383*, 132531. https://doi.org/10.1016/j.foodchem.2022.132531.
7. Dias, M.C.; Pinto, D.C.G.A.; Silva, A.M.S. Plant Flavonoids: Chemical Characteristics and Biological Activity. *Molecules* **2021**, *26*, 5377. https://doi.org/10.3390/molecules26175377.
8. Silva, A.S.; Reboredo-Rodríguez, P.; Sanchez-Machado, D.I.; López-Cervantes, J.; Barreca, D.; Pittala, V.; Samec, D.; Orhan, I.E.; Gulcan, H.O.; Forbes-Hernandez, T.Y.; et al. Evaluation of the Status Quo of Polyphenols Analysis: Part II—Analysis Methods and Food Processing Effects. *Compr. Rev. Food Sci. Food Saf.* **2020**, *19*, 3219–3240. https://doi.org/10.1111/1541-4337.12626.
9. Šamec, D.; Zeljković, S.Ć. *Analytical Methods Focused on Studying Phytonutrients in Food*; Elsevier: Amsterdam, The Netherlands, 2019; ISBN 9780128153543.
10. Šamec, D.; Pierz, V.; Srividya, N.; Wüst, M.; Lange, B.M. Assessing Chemical Diversity in Psilotum Nudum (l.) Beauv., a Pantropical Whisk Fern That Has Lost Many of Its Fern-like Characters. *Front. Plant Sci.* **2019**, *10*, 868. https://doi.org/10.3389/fpls.2019.00868.
11. Jurinjak Tušek, A.; Benković, M.; Belščak Cvitanović, A.; Valinger, D.; Jurina, T.; Gajdoš Kljusurić, J. Kinetics and Thermodynamics of the Solid-Liquid Extraction Process of Total Polyphenols, Antioxidants and Extraction Yield from Asteraceae Plants. *Ind. Crops Prod.* **2016**, *91*, 205–214. https://doi.org/10.1016/j.indcrop.2016.07.015.
12. Valinger, D.; Kušen, M.; Benković, M.; Jurina, T.; Panić, M.; Radojčić Redovniković, I.; Kljusurić, J.G.; Tušek, A.J. Enhancement of the Green Extraction of Bioactive Molecules from Olea Europaea Leaves. *Separations* **2022**, *9*, 33. https://doi.org/10.3390/separations9020033.
13. Chávez-González, M.L.; Sepúlveda, L.; Verma, D.K.; Luna-García, H.A.; Rodríguez-Durán, L.V.; Ilina, A.; Aguilar, C.N. Conventional and Emerging Extraction Processes of Flavonoids. *Processes* **2020**, *8*, 434. https://doi.org/10.3390/pr8040434.
14. Rodríguez De Luna, S.L.; Ramírez-Garza, R.E.; Serna Saldívar, S.O. Environmentally Friendly Methods for Flavonoid Extraction from Plant Material: Impact of Their Operating Conditions on Yield and Antioxidant Properties. *Sci. World J.* **2020**, *2020*, 6792069. https://doi.org/10.1155/2020/6792069.
15. Matešić, N.; Jurina, T.; Benković, M.; Panić, M.; Valinger, D.; Gajdoš Kljusurić, J.; Jurinjak Tušek, A. Microwave-Assisted Extraction of Phenolic Compounds from Cannabis Sativa L.: Optimization and Kinetics Study. *Sep. Sci. Technol.* **2021**, *56*, 2047–2060. https://doi.org/10.1080/01496395.2020.1804938.
16. Maran, J.P.; Sivakumar, V.; Thirugnanasambandham, K.; Sridhar, R. Artificial Neural Network and Response Surface Methodology Modeling in Mass Transfer Parameters Predictions during Osmotic Dehydration of *Carica Papaya* L. *Alexandria Eng. J.* **2013**, *52*, 507–516. https://doi.org/10.1016/J.AEJ.2013.06.007.
17. Tirado-Kulieva, V.A.; Sánchez-Chero, M.; Villegasyarlequé, M.; Aguilar, G.F.V.; Carrión-Barco, G.; Santa Cruz, A.G.Y.; Sánchez-Chero, J. An Overview on the Use of Response Surface Methodology to Model and Optimize Extraction Processes in the Food Industry. *Curr. Res. Nutr. Food Sci.* **2021**, *9*, 745–754. https://doi.org/10.12944/CRNFSJ.9.3.03.
18. Alam, P.; Noman, O.M.; Herqash, R.N.; Almarfadi, O.M.; Akhtar, A.; Alqahtani, A.S. Response Surface Methodology (RSM)-Based Optimization of Ultrasound-Assisted Extraction of Sennoside A, Sennoside B, Aloe-Emodin, Emodin, and Chrysophanol from Senna Alexandrina (Aerial Parts): HPLC-UV and Antioxidant Analysis. *Molecules* **2022**, *27*, 298. https://doi.org/10.3390/MOLECULES27010298.
19. Agu, C.M.; Menkiti, M.C.; Ohale, P.E.; Ugonabo, V.I. Extraction Modeling, Kinetics, and Thermodynamics of Solvent Extraction of Irvingia Gabonensis Kernel Oil, for Possible Industrial Application. *Eng. Rep.* **2021**, *3*, e12306. https://doi.org/10.1002/ENG2.12306.
20. Hobbi, P.; Okoro, O.V.; Delporte, C.; Alimoradi, H.; Podstawczyk, D.; Nie, L.; Bernaerts, K.V.; Shavandi, A. Kinetic Modelling of the Solid–Liquid Extraction Process of Polyphenolic Compounds from Apple Pomace: Influence of Solvent Composition and Temperature. *Bioresour. Bioprocess.* **2021**, *8*, 114. https://doi.org/10.1186/s40643-021-00465-4.
21. Dao, P.T.; Nguyen, M. Van; Tran, Q.N.; Van Lam, T. Experimental and Kinetic Modeling Studies on Extraction of Essential Oil from Vietnamese Calamondin (Citrus Microcarpa) by Hydro-Distillation Process. *Iran. J. Chem. Chem. Eng.* **2022**., in press, https://doi.org/10.30492/IJCCE.2022.530134.4724.
22. Wen, L.; Jiang, Y.; Yang, J.; Zhao, Y.; Tian, M.; Yang, B. Structure, Bioactivity, and Synthesis of Methylated Flavonoids. *Ann. N. Y. Acad. Sci.* **2017**, *1398*, 120–129. https://doi.org/10.1111/nyas.13350.
23. Rauter, A.P.; Lopes, R.G.; Martins, A. *C* -Glycosylflavonoids: Identification, Bioactivity and Synthesis. *Nat. Prod. Commun.* **2007**, *2*, 1934578X0700201. https://doi.org/10.1177/1934578X0700201125.
24. Kytidou, K.; Artola, M.; Overkleeft, H.S.; Aerts, J.M.F.G. Plant Glycosides and Glycosidases: A Treasure-Trove for Therapeutics. *Front. Plant Sci.* **2020**, *11*, 357. https://doi.org/10.3389/fpls.2020.00357.
25. He, X.; Yang, F.; Huang, X. Proceedings of Chemistry, Pharmacology, Pharmacokinetics and Synthesis of Biflavonoids. *Molecules* **2021**, *26*, 6088. https://doi.org/10.3390/molecules26196088.
26. Šamec, D.; Karalija, E.; Dahija, S.; Hassan, S.T.S. Biflavonoids: Important Contributions to the Health Benefits of Ginkgo (*Ginkgo Biloba* L.). *Plants* **2022**, *11*, 1381. https://doi.org/10.3390/plants11101381.
27. Luo, Y.; Jian, Y.; Liu, Y.; Jiang, S.; Muhammad, D.; Wang, W. Flavanols from Nature: A Phytochemistry and Biological Activity Review. *Molecules* **2022**, *27*, 719. https://doi.org/10.3390/molecules27030719.
28. Nabavi, S.M.; Šamec, D.; Tomczyk, M.; Milella, L.; Russo, D.; Habtemariam, S.; Suntar, I.; Rastrelli, L.; Daglia, M.; Xiao, J.; et al. Flavonoid Biosynthetic Pathways in Plants: Versatile Targets for Metabolic Engineering. *Biotechnol. Adv.* **2018**, *38*, 107316. https://doi.org/10.1016/j.biotechadv.2018.11.005.

29. 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. https://doi.org/10.1016/j.foodres.2018.07.055.
30. Hernández, M.M.; Pesquera-Alegría, C.; Manso-Martínez, C.; Menéndez, C.M. Antioxidant Capacity and Flavanol Composition of Seed Extracts from a Grenache × Tempranillo Population: Effect of Sex and Color. *Ind. Crops Prod.* **2020**, *161*, 113177. https://doi.org/10.1016/j.indcrop.2020.113177.
31. Liu, Z.; Bruins, M.E.; de Bruijn, W.J.C.; Vincken, J.P. A Comparison of the Phenolic Composition of Old and Young Tea Leaves Reveals a Decrease in Flavanols and Phenolic Acids and an Increase in Flavonols upon Tea Leaf Maturation. *J. Food Compos. Anal.* **2020**, *86*, 103385. https://doi.org/10.1016/j.jfca.2019.103385.
32. Ding, T.; Cao, K.; Fang, W.; Zhu, G.; Chen, C.; Wang, X.; Wang, L. Evaluation of Phenolic Components (Anthocyanins, Flavanols, Phenolic Acids, and Flavonols) and Their Antioxidant Properties of Peach Fruits. *Sci. Hortic.* **2020**, *268*, 109365. https://doi.org/10.1016/j.scienta.2020.109365.
33. Cui, L.; Ma, Z.; Wang, D.; Niu, Y. Ultrasound-Assisted Extraction, Optimization, Isolation, and Antioxidant Activity Analysis of Flavonoids from Astragalus Membranaceus Stems and Leaves. *Ultrason. Sonochem.* **2022**, *90*, 106190. https://doi.org/10.1016/j.ultsonch.2022.106190.
34. Lachos-Perez, D.; Baseggio, A.M.; Mayanga-Torres, P.C.; Maróstica, M.R.; Rostagno, M.A.; Martínez, J.; Forster-Carneiro, T. Subcritical Water Extraction of Flavanones from Defatted Orange Peel. *J. Supercrit. Fluids* **2018**, *138*, 7–16. https://doi.org/10.1016/j.supflu.2018.03.015.
35. Barbosa, P. de P.M.; Ruviaro, A.R.; Martins, I.M.; Macedo, J.A.; LaPointe, G.; Macedo, G.A. Enzyme-Assisted Extraction of Flavanones from Citrus Pomace: Obtention of Natural Compounds with Anti-Virulence and Anti-Adhesive Effect against Salmonella Enterica Subsp. Enterica Serovar Typhimurium. *Food Control* **2021**, *120*, 107525. https://doi.org/10.1016/j.foodcont.2020.107525.
36. Duan, L.; Zhang, W.H.; Zhang, Z.H.; Liu, E.H.; Guo, L. Evaluation of Natural Deep Eutectic Solvents for the Extraction of Bioactive Flavone C-Glycosides from Flos Trollii. *Microchem. J.* **2019**, *145*, 180–186. https://doi.org/10.1016/j.microc.2018.10.031.
37. Zhang, H.-Q.; Liu, P.; Duan, J.-A.; Dong, L.; Shang, E.-X.; Qian, D.-W.; Xiao, P.; Zhao, M.; Li, W.-W. wen Hierarchical Extraction and Simultaneous Determination of Flavones and Triterpenes in Different Parts of Trichosanthes Kirilowii Maxim. by Ultra-High-Performance Liquid Chromatography Coupled with Tandem Mass Spectrometry. *J. Pharm. Biomed. Anal.* **2019**, *167*, 114–122. https://doi.org/10.1016/j.jpba.2019.02.003.
38. Lin, S.; Meng, X.; Tan, C.; Tong, Y.; Wan, M.; Wang, M.; Zhao, Y.; Deng, H.; Kong, Y.; Ma, Y. Composition and Antioxidant Activity of Anthocyanins from Aronia Melanocarpa Extracted Using an Ultrasonic-Microwave-Assisted Natural Deep Eutectic Solvent Extraction Method. *Ultrason. Sonochem.* **2022**, *89*, 106102. https://doi.org/10.1016/j.ultsonch.2022.106102.
39. Gleńsk, M.; Dudek, M.K.; Ciach, M.; Włodarczyk, M. Isolation and Structural Determination of Flavan-3-Ol Derivatives from the *Polypodium Vulgare* L. Rhizomes Water Extract. *Nat. Prod. Res.* **2021**, *35*, 1474–1483. https://doi.org/10.1080/14786419.2019.1655302.
40. Liaudanskas, M.; Zymone, K.; Viškelis, J.; Janulis, V. Optimisation of the Extraction of Flavonoids from Apples Using Response Surface Methodology. *Ital. J. Food Sci.* **2018**, *30*, 89–101.
41. Krakowska-Sieprawska, A.; Kiełbasa, A.; Rafińska, K.; Ligor, M.; Buszewski, B. Modern Methods of Pre-Treatment of Plant Material for the Extraction of Bioactive Compounds. *Molecules* **2022**, *27*, 730. https://doi.org/10.3390/molecules27030730.
42. Roshanak, S.; Rahimmalek, M.; Goli, S.A.H. Evaluation of Seven Different Drying Treatments in Respect to Total Flavonoid, Phenolic, Vitamin C Content, Chlorophyll, Antioxidant Activity and Color of Green Tea (Camellia Sinensis or C. Assamica) Leaves. *J. Food Sci. Technol.* **2016**, *53*, 721–729. https://doi.org/10.1007/s13197-015-2030-x.
43. Ledesma-Escobar, C.A.; Priego-Capote, F.; Luque de Castro, M.D. Comparative Study of the Effect of Sample Pretreatment and Extraction on the Determination of Flavonoids from Lemon (Citrus Limon). *PLoS ONE* **2016**, *11*, e0148056. https://doi.org/10.1371/journal.pone.0148056.
44. Ledesma-Escobar, C.A.; Priego-Capote, F.; Luque de Castro, M.D. Effect of Sample Pretreatment on the Extraction of Lemon (Citrus Limon) Components. *Talanta* **2016**, *153*, 386–391. https://doi.org/10.1016/j.talanta.2016.03.024.
45. Zhang, X.; Wang, X.; Wang, M.; Cao, J.; Xiao, J.; Wang, Q. Effects of Different Pretreatments on Flavonoids and Antioxidant Activity of Dryopteris Erythrosora Leave. *PLoS ONE* **2019**, *14*, e0200174. https://doi.org/10.1371/journal.pone.0200174.
46. Keinänen, M.; Julkunen-Tiitto, R. Effect of Sample Preparation Method on Birch (Betula Pendula Roth) Leaf Phenolics. *J. Agric. Food Chem.* **1996**, *44*, 2724–2727. https://doi.org/10.1021/jf960168x.
47. Molina-Calle, M.; Priego-Capote, F.; de Castro, M.D.L. Development and Application of a Quantitative Method for Determination of Flavonoids in Orange Peel: Influence of Sample Pretreatment on Composition. *Talanta* **2015**, *144*, 349–355. https://doi.org/10.1016/j.talanta.2015.05.054.
48. Pham, H.; Nguyen, V.; Vuong, Q.; Bowyer, M.; Scarlett, C. Effect of Extraction Solvents and Drying Methods on the Physicochemical and Antioxidant Properties of Helicteres Hirsuta Lour. Leaves. *Technologies* **2015**, *3*, 285–301. https://doi.org/10.3390/technologies3040285.
49. Nemzer, B.; Vargas, L.; Xia, X.; Sintara, M.; Feng, H. Phytochemical and Physical Properties of Blueberries, Tart Cherries, Strawberries, and Cranberries as Affected by Different Drying Methods. *Food Chem.* **2018**, *262*, 242–250. https://doi.org/10.1016/j.foodchem.2018.04.047.

50. Hamrouni-Sellami, I.; Rahali, F.Z.; Rebey, I.B.; Bourgou, S.; Limam, F.; Marzouk, B. Total Phenolics, Flavonoids, and Antioxidant Activity of Sage (*Salvia Officinalis* L.) Plants as Affected by Different Drying Methods. *Food Bioprocess Technol.* **2013**, *6*, 806–817. https://doi.org/10.1007/s11947-012-0877-7.
51. Mediani, A.; Abas, F.; Khatib, A.; Maulidiani, H.; Shaari, K.; Choi, Y.H.; Lajis, N.H. 1H-NMR-Based Metabolomics Approach to Understanding the Drying Effects on the Phytochemicals in Cosmos Caudatus. *Food Res. Int.* **2012**, *49*, 763–770. https://doi.org/10.1016/j.foodres.2012.09.022.
52. Farag, M.; Ali, S.; Hodaya, R.; El-Seedi, H.; Sultani, H.; Laub, A.; Eissa, T.; Abou-Zaid, F.; Wessjohann, L. Phytochemical Profiles and Antimicrobial Activities of Allium Cepa Red Cv. and A. Sativum Subjected to Different Drying Methods: A Comparative MS-Based Metabolomics. *Molecules* **2017**, *22*, 761. https://doi.org/10.3390/molecules22050761.
53. Periche, A.; Castelló, M.L.; Heredia, A.; Escriche, I. Effect of Different Drying Methods on the Phenolic, Flavonoid and Volatile Compounds of Stevia Rebaudiana Leaves. *Flavour Fragr. J.* **2016**, *31*, 173–177. https://doi.org/10.1002/ffj.3298.
54. Rajha, H.N.; Darra, N.E.; Vorobiev, E.; Louka, N.; Maroun, R.G. An Environment Friendly, Low-Cost Extraction Process of Phenolic Compounds from Grape Byproducts. Optimization by Multi-Response Surface Methodology. *Food Nutr. Sci.* **2013**, *04*, 650–659. https://doi.org/10.4236/fns.2013.46084.
55. Šamec, D.; Pavlović, I.; Radojčić Redovniković, I.; Salopek-Sondi, B. Comparative Analysis of Phytochemicals and Activity of Endogenous Enzymes Associated with Their Stability, Bioavailability and Food Quality in Five Brassicaceae Sprouts. *Food Chem.* **2018**, *269*, 96–102. https://doi.org/10.1016/j.foodchem.2018.06.133.
56. Šamec, D.; Maretić, M.; Lugarić, I.; Mešić, A.; Salopek-Sondi, B.; Duralija, B. Assessment of the Differences in the Physical, Chemical and Phytochemical Properties of Four Strawberry Cultivars Using Principal Component Analysis. *Food Chem.* **2016**, *194*, 828–834. https://doi.org/10.1016/j.foodchem.2015.08.095.
57. Ali, M.C.; Chen, J.; Zhang, H.; Li, Z.; Zhao, L.; Qiu, H. Effective Extraction of Flavonoids from *Lycium Barbarum* L. Fruits by Deep Eutectic Solvents-Based Ultrasound-Assisted Extraction. *Talanta* **2019**, *203*, 16–22. https://doi.org/10.1016/j.talanta.2019.05.012.
58. Mansur, A.R.; Song, N.-E.; Jang, H.W.; Lim, T.-G.; Yoo, M.; Nam, T.G. Optimizing the Ultrasound-Assisted Deep Eutectic Solvent Extraction of Flavonoids in Common Buckwheat Sprouts. *Food Chem.* **2019**, *293*, 438–445. https://doi.org/10.1016/j.foodchem.2019.05.003.
59. Stalikas, C.D. Extraction, Separation, and Detection Methods for Phenolic Acids and Flavonoids. *J. Sep. Sci.* **2007**, *30*, 3268–3295. https://doi.org/10.1002/jssc.200700261.
60. Nuutila, A.; Kammiovirta, K.; Oksman-Caldentey, K.-M. Comparison of Methods for the Hydrolysis of Flavonoids and Phenolic Acids from Onion and Spinach for HPLC Analysis. *Food Chem.* **2002**, *76*, 519–525. https://doi.org/10.1016/S0308-8146(01)00305-3.
61. Balli, D.; Bellumori, M.; Orlandini, S.; Cecchi, L.; Mani, E.; Pieraccini, G.; Mulinacci, N.; Innocenti, M. Optimized Hydrolytic Methods by Response Surface Methodology to Accurately Estimate the Phenols in Cereal by HPLC-DAD: The Case of Millet. *Food Chem.* **2020**, *303*, 125393. https://doi.org/10.1016/j.foodchem.2019.125393.
62. Ricochon, G.; Muniglia, L. Influence of enzymes on the oil extraction processes in aqueous media. *Ol. Corps Gras Lipides* **2010**, *17*, 356–359. https://doi.org/10.1051/OCL.2010.0337.
63. 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. https://doi.org/10.1016/J.INDCROP.2018.08.004.
64. Ling, Y.Y.; Fun, P.S.; Yeop, A.; Yusoff, M.M.; Gimbun, J. Assessment of Maceration, Ultrasonic and Microwave Assisted Extraction for Total Phenolic Content, Total Flavonoid Content and Kaempferol Yield from Cassia Alata via Microstructures Analysis. *Mater. Today: Proc.* **2019**, *19*, 1273–1279.
65. Charpe, T.W.; Rathod, V.K. Effect of Ethanol Concentration in Ultrasound Assisted Extraction of Glycyrrhizic Acid from Licorice Root. *Iran. J. Chem. Eng.* **2014**, *11,* 21-23, .
66. Bakin, I.A.; Mustafina, A.S.; Aleksenko, L.A.; Shkolnikova, M.N. Intensification of Extraction of Phytocomponents from Berry Raw Materials. *IOP Conf. Ser. Earth Environ. Sci.* **2021**, *640*, 022066.
67. Liao, J.; Guo, Z.; Yu, G. Process Intensification and Kinetic Studies of Ultrasound-Assisted Extraction of Flavonoids from Peanut Shells. *Ultrason. Sonochem.* **2021**, *76*, 105661. https://doi.org/10.1016/J.ULTSONCH.2021.105661.
68. Zimare, S.B.; Mankar, G.D.; Barmukh, R.B. Optimization of Ultrasound-Assisted Extraction of Total Phenolics and Flavonoids from the Leaves of Lobelia Nicotianifolia and Their Radical Scavenging Potential. *Curr. Res. Green Sustain. Chem.* **2021**, *4*, 100109. https://doi.org/10.1016/J.CRGSC.2021.100109.
69. Garcia-Castello, E.M.; Rodriguez-Lopez, A.D.; Mayor, L.; Ballesteros, R.; Conidi, C.; Cassano, A. Optimization of Conventional and Ultrasound Assisted Extraction of Flavonoids from Grapefruit (*Citrus Paradisi* L.) Solid Wastes. *LWT* **2015**, *64*, 1114–1122. https://doi.org/10.1016/j.lwt.2015.07.024.
70. Meregalli, M.M.; Puton, B.M.S.; Camera, F.D.M.; Amaral, A.U.; Zeni, J.; Cansian, R.L.; Mignoni, M.L.; Backes, G.T. Conventional and Ultrasound-Assisted Methods for Extraction of Bioactive Compounds from Red Araçá Peel (Psidium Cattleianum Sabine). *Arab. J. Chem.* **2020**, *13*, 5800–5809. https://doi.org/10.1016/j.arabjc.2020.04.017.
71. Irakli, M.; Chatzopoulou, P.; Ekateriniadou, L. Optimization of Ultrasound-Assisted Extraction of Phenolic Compounds: Oleuropein, Phenolic Acids, Phenolic Alcohols and Flavonoids from Olive Leaves and Evaluation of Its Antioxidant Activities. *Ind. Crops Prod.* **2018**, *124*, 382–388. https://doi.org/10.1016/j.indcrop.2018.07.070.

72. Wang, G.; Cui, Q.; Yin, L.J.; Li, Y.; Gao, M.Z.; Meng, Y.; Li, J.; Zhang, S.D.; Wang, W. Negative Pressure Cavitation Based Ultrasound-Assisted Extraction of Main Flavonoids from Flos Sophorae Immaturus and Evaluation of Its Extraction Kinetics. *Sep. Purif. Technol.* **2020**, *244*, 115805. https://doi.org/10.1016/j.seppur.2019.115805.
73. Saeed, R.; Ahmed, D.; Mushtaq, M. Ultrasound-Aided Enzyme-Assisted Efficient Extraction of Bioactive Compounds from Gymnema Sylvestre and Optimization as per Response Surface Methodology. *Sustain. Chem. Pharm.* **2022**, *29*, 100818. https://doi.org/10.1016/j.scp.2022.100818.
74. Singla, M.; Sit, N. Application of Ultrasound in Combination with Other Technologies in Food Processing: A Review. *Ultrason. Sonochem.* **2021**, *73*, 1350–4177.
75. Lu, X.; Du, H.; Liu, Y.; Wang, Y.; Li, D.; Wang, L. Effect of Ultrasound-Assisted Solvent Enzymatic Extraction on Fatty Acid Profiles, Physicochemical Properties, Bioactive Compounds, and Antioxidant Activity of Elaeagnus Mollis Oil. *Foods* **2022**, *11*, 359. https://doi.org/10.3390/foods11030359.
76. Wani, K.M.; Uppaluri, R.V.S. Pulsed Ultrasound-Assisted Extraction of Bioactive Compounds from Papaya Pulp and Papaya Peel Using Response Surface Methodology: Optimization and Comparison with Hot Water Extraction. *Appl. Food Res.* **2022**, *2*, 100178. https://doi.org/10.1016/j.afres.2022.100178.
77. Yadav, N.; Sharma, S.; Joys, J.S.; Kumar, S. Microwave Assisted Extraction of Bioactive Compounds: A Brief Review. *J. Indian Chem. Soc.* **2020**, *97*, 1–7.
78. Routray, W.; Orsat, V. Microwave Assisted Extraction of Flavonoids: A Comprehensive Overview. In *Reference Module in Food Science*; Elsevier: Amsterdam, The Netherlands, 2019.
79. Cerdá-Bernad, D.; Baixinho, J.P.; Fernández, N.; Frutos, M.J. Evaluation of Microwave-Assisted Extraction as a Potential Green Technology for the Isolation of Bioactive Compounds from Saffron (*Crocus Sativus* L.) Floral By-Products. *Foods* **2022**, *11*, 2335. https://doi.org/10.3390/foods11152335.
80. Bagade, S.B.; Patil, M. Recent Advances in Microwave Assisted Extraction of Bioactive Compounds from Complex Herbal Samples: A Review. *Crit. Rev. Anal. Chem.* **2021**, *51*, 138–149.
81. Abbas, M.; Ahmed, D.; Qamar, M.T.; Ihsan, S.; Noor, Z.I. Optimization of Ultrasound-Assisted, Microwave-Assisted and Soxhlet Extraction of Bioactive Compounds from Lagenaria Siceraria: A Comparative Analysis. *Bioresour. Technol. Reports* **2021**, *15*, 100746. https://doi.org/10.1016/j.biteb.2021.100746.
82. Plazzotta, S.; Ibarz, R.; Manzocco, L.; Martín-Belloso, O. Optimizing the Antioxidant Biocompound Recovery from Peach Waste Extraction Assisted by Ultrasounds or Microwaves. *Ultrason. Sonochem.* **2019**, *63*, 104954. https://doi.org/10.1016/j.ultsonch.2019.104954.
83. Elakremi, M.; Sillero, L.; Ayed, L.; ben Mosbah, M.; Labidi, J.; ben Salem, R.; Moussaoui, Y. Vera L.P. Leaves as a Renewable Source of Bioactive Compounds via Microwave Assisted Extraction. *Sustain. Chem. Pharm.* **2022**, *29*, 100815. https://doi.org/10.1016/j.scp.2022.100815.
84. Alara, O.R.; Abdurahman, N.H.; Olalere, O.A. Optimization of Microwave-Assisted Extraction of Flavonoids and Antioxidants from Vernonia Amygdalina Leaf Using Response Surface Methodology. *Food Bioprod. Process.* **2018**, *107*, 36–48. https://doi.org/10.1016/j.fbp.2017.10.007.
85. Dahmoune, F.; Nayak, B.; Moussi, K.; Remini, H.; Madani, K. Optimization of Microwave-Assisted Extraction of Polyphenols from *Myrtus Communis* L. Leaves. *Food Chem.* **2015**, *166*, 585–595. https://doi.org/10.1016/j.foodchem.2014.06.066.
86. Darvishzadeh, P.; Orsat, V. Microwave-Assisted Extraction of Antioxidant Compounds from Russian Olive Leaves and Flowers: Optimization, HPLC Characterization and Comparison with Other Methods. *J. Appl. Res. Med. Aromat. Plants* **2022**, *27*, 100368. https://doi.org/10.1016/j.jarmap.2021.100368.
87. Akbari, S.; Abdurahman, N.H.; Yunus, R.M.; Fayaz, F. Microwave-Assisted Extraction of Saponin, Phenolic and Flavonoid Compounds from Trigonella Foenum-Graecum Seed Based on Two Level Factorial Design. *J. Appl. Res. Med. Aromat. Plants* **2019**, *14*, 100212. https://doi.org/10.1016/j.jarmap.2019.100212.
88. Pinela, J.; Prieto, M.A.; Carvalho, A.M.; Barreiro, M.F.; Oliveira, M.B.P.P.; Barros, L.; Ferreira, I.C.F.R. Microwave-Assisted Extraction of Phenolic Acids and Flavonoids and Production of Antioxidant Ingredients from Tomato: A Nutraceutical-Oriented Optimization Study. *Sep. Purif. Technol.* **2016**, *164*, 114–124. https://doi.org/10.1016/j.seppur.2016.03.030.
89. Xie, X.; Zhu, D.; Zhang, W.; Huai, W.; Wang, K.; Huang, X.; Zhou, L.; Fan, H. Microwave-Assisted Aqueous Two-Phase Extraction Coupled with High Performance Liquid Chromatography for Simultaneous Extraction and Determination of Four Flavonoids in *Crotalaria Sessiliflora* L. *Ind. Crops Prod.* **2017**, *95*, 632–642. https://doi.org/10.1016/j.indcrop.2016.11.032.
90. Gu, H.; Chen, F.; Zhang, Q.; Zang, J. Application of Ionic Liquids in Vacuum Microwave-Assisted Extraction Followed by Macroporous Resin Isolation of Three Flavonoids Rutin, Hyperoside and Hesperidin from Sorbus Tianschanica Leaves. *J. Chromatogr. B Anal. Technol. Biomed. Life Sci.* **2016**, *1014*, 45–55. https://doi.org/10.1016/j.jchromb.2016.01.045.
91. Liu, X.; Jing, X.; Li, G. A Process to Acquire Essential Oil by Distillation Concatenated Liquid-Liquid Extraction and Flavonoids by Solid-Liquid Extraction Simultaneously from Helichrysum Arenarium (L.) Moench Inflorescences under Ionic Liquid-Microwave Mediated. *Sep. Purif. Technol.* **2019**, *209*, 164–174. https://doi.org/10.1016/j.seppur.2018.07.028.
92. Zhang, K.; Wong, J.W. Solvent-Based Extraction Techniques for the Determination of Pesticides in Food. In *Comprehensive Sampling and Sample Preparation*; Elsevier Inc.: Amsterdam, The Netherlands, 2011; Volume 4, pp. 245–261, ISBN 9780123813749.
93. Soria, A.C.; Brokł, M.; Sanz, M.L.; Martínez-Castro, I. Sample Preparation for the Determination of Carbohydrates in Food and Beverages. In *Comprehensive Sampling and Sample Preparation*; Elsevier Inc.: Amsterdam, The Netherlands, 2012; Volume 4, pp. 213–243, ISBN 9780123813749.

94. 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. https://doi.org/10.1016/j.foodres.2014.12.042.
95. Otero, P.; Quintana, S.E.; Reglero, G.; Fornari, T.; García-Risco, M.R. 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* **2018**, *16*, 156. https://doi.org/10.3390/md16050156.
96. Primbs, T.; Genualdi, S.; Simonich, S. Solvent Selection for Pressurized Liquid Extraction of Polymeric Sorbents Used in Air Sampling. *Environ. Toxicol. Chem.* **2007**, *27*, 1267–1272. https://doi.org/10.1897/07-566.
97. da Silva, L.C.; Souza, M.C.; Sumere, B.R.; Silva, L.G.S.; da Cunha, D.T.; Barbero, G.F.; Bezerra, R.M.N.; Rostagno, M.A. Simultaneous Extraction and Separation of Bioactive Compounds from Apple Pomace Using Pressurized Liquids Coupled On-Line with Solid-Phase Extraction. *Food Chem.* **2020**, *318*, 126450. https://doi.org/10.1016/j.foodchem.2020.126450.
98. Leyva-Jiménez, F.J.; Lozano-Sánchez, J.; Borrás-Linares, I.; Arráez-Román, D.; Segura-Carretero, A. Comparative Study of Conventional and Pressurized Liquid Extraction for Recovering Bioactive Compounds from Lippia Citriodora Leaves. *Food Res. Int.* **2018**, *109*, 213–222. https://doi.org/10.1016/j.foodres.2018.04.035.
99. Fuentes, J.A.M.; López-Salas, L.; Borrás-Linares, I.; Navarro-Alarcón, M.; Segura-Carretero, A.; Lozano-Sánchez, J. Development of an Innovative Pressurized Liquid Extraction Procedure by Response Surface Methodology to Recover Bioactive Compounds from Carao Tree Seeds. *Foods* **2021**, *10*, 398. https://doi.org/10.3390/foods10020398.
100. Carreira-Casais, A.; Otero, P.; Garcia-Perez, P.; Garcia-Oliveira, P.; Pereira, A.G.; Carpena, M.; Soria-Lopez, A.; Simal-Gandara, J.; Prieto, M.A. Benefits and Drawbacks of Ultrasound-Assisted Extraction for the Recovery of Bioactive Compounds from Marine Algae. *Int. J. Environ. Res. Public Health* **2021**, *18*, 9153. https://doi.org/10.3390/IJERPH18179153.
101. Li, J.; Pettinato, M.; Campardelli, R.; De Marco, I.; Perego, P. High-Pressure Technologies for the Recovery of Bioactive Molecules from Agro-Industrial Waste. *Appl. Sci.* **2022**, *12*, 3642.
102. Tejedor-Calvo, E.; García-Barreda, S.; Sánchez, S.; Morte, A.; Siles-Sánchez, M.D.L.N.; Soler-Rivas, C.; Santoyo, S.; Marco, P. Application of Pressurized Liquid Extractions to Obtain Bioactive Compounds from Tuber Aestivum and Terfezia Claveryi. *Foods* **2022**, *11*, 298. https://doi.org/10.3390/foods11030298.
103. Kamali, H.; Khodaverdi, E.; Hadizadeh, F.; Ghaziaskar, S.H. Optimization of Phenolic and Flavonoid Content and Antioxidants Capacity of Pressurized Liquid Extraction from Dracocephalum Kotschyi via Circumscribed Central Composite. *J. Supercrit. Fluids* **2016**, *107*, 307–314. https://doi.org/10.1016/j.supflu.2015.09.028.
104. 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. https://doi.org/10.1016/j.supflu.2014.09.020.
105. Lama-Muñoz, A.; Contreras, M. del M.; Espínola, F.; Moya, M.; Romero, I.; Castro, E. Content of Phenolic Compounds and Mannitol in Olive Leaves Extracts from Six Spanish Cultivars: Extraction with the Soxhlet Method and Pressurized Liquids. *Food Chem.* **2020**, *320*, 126626. https://doi.org/10.1016/j.foodchem.2020.126626.
106. Alves, T.P.; Triques, C.C.; Palsikowski, P.A.; da Silva, C.; Fiorese, M.L.; da Silva, E.A.; Fagundes-Klen, M.R. Improved Extraction of Bioactive Compounds from Monteverdia Aquifolia Leaves by Pressurized-Liquid and Ultrasound-Assisted Extraction: Yield and Chemical Composition. *J. Supercrit. Fluids* **2022**, *181*, 105468. https://doi.org/10.1016/j.supflu.2021.105468.
107. 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. https://doi.org/10.1016/j.fbp.2018.09.001.
108. Oliveira, A.M.B.; Viganó, J.; Sanches, V.L.; Rostagno, M.A.; Martínez, J. Extraction of Potential Bioactive Compounds from Industrial Tahiti Lime (Citrus Latifólia Tan.) by-Product Using Pressurized Liquids and Ultrasound-Assisted Extraction. *Food Res. Int.* **2022**, *157*, 111381. https://doi.org/10.1016/j.foodres.2022.111381.
109. Santos, K.A.; Gonçalves, J.E.; Cardozo-Filho, L.; da Silva, E.A. Pressurized Liquid and Ultrasound-Assisted Extraction of α-Bisabolol from Candeia (Eremanthus Erythropappus) Wood. *Ind. Crops Prod.* **2019**, *130*, 428–435. https://doi.org/10.1016/j.indcrop.2019.01.013.
110. Andrade, T.A.; Hamerski, F.; López Fetzer, D.E.; Roda-Serrat, M.C.; Corazza, M.L.; Norddahl, B.; Errico, M. Ultrasound-Assisted Pressurized Liquid Extraction of Anthocyanins from Aronia Melanocarpa Pomace. *Sep. Purif. Technol.* **2021**, *276*, 119290. https://doi.org/10.1016/j.seppur.2021.119290.
111. Qian, Z.M.; Lu, J.; Gao, Q.P.; Li, S.P. Rapid Method for Simultaneous Determination of Flavonoid, Saponins and Polyacetylenes in Folium Ginseng and Radix Ginseng by Pressurized Liquid Extraction and High-Performance Liquid Chromatography Coupled with Diode Array Detection and Mass Spectrometry. *J. Chromatogr. A* **2009**, *1216*, 3825–3830. https://doi.org/10.1016/j.chroma.2009.02.065.
112. Chaves, J.O.; Sanches, V.L.; Viganó, J.; de Souza Mesquita, L.M.; de Souza, M.C.; da Silva, L.C.; Acunha, T.; Faccioli, L.H.; Rostagno, M.A. Integration of Pressurized Liquid Extraction and In-Line Solid-Phase Extraction to Simultaneously Extract and Concentrate Phenolic Compounds from Lemon Peel (*Citrus Limon* L.). *Food Res. Int.* **2022**, *157*, 111252. https://doi.org/10.1016/j.foodres.2022.111252.
113. Souza, M.C.; Silva, L.C.; Chaves, J.O.; Salvador, M.P.; Sanches, V.L.; da Cunha, D.T.; Foster Carneiro, T.; Rostagno, M.A. Simultaneous Extraction and Separation of Compounds from Mate (Ilex Paraguariensis) Leaves by Pressurized Liquid

Extraction Coupled with Solid-Phase Extraction and in-Line UV Detection. *Food Chem. Mol. Sci.* **2021**, *2*, 100008. https://doi.org/10.1016/j.fochms.2020.100008.
114. Gilbert-López, B.; Barranco, A.; Herrero, M.; Cifuentes, A.; Ibáñez, E. Development of New Green Processes for the Recovery of Bioactives from Phaeodactylum Tricornutum. *Food Res. Int.* **2017**, *99*, 1056–1065. https://doi.org/10.1016/j.foodres.2016.04.022.
115. Uwineza, P.A.; Waśkiewicz, A. Recent Advances in Supercritical Fluid Extraction of Natural Bioactive Compounds from Natural Plant Materials. *Molecules* **2020**, *25*, 3847.
116. Wrona, O.; Rafińska, K.; Możeński, C.; Buszewski, B. Supercritical Fluid Extraction of Bioactive Compounds from Plant Materials. *J. AOAC Int.* **2017**, *100*, 1624–1635.
117. Zhang, Q.W.; Lin, L.G.; Ye, W.C. Techniques for Extraction and Isolation of Natural Products: A Comprehensive Review. *Chin. Med.* **2018**, *13*, 20.
118. Molino, A.; Mehariya, S.; Di Sanzo, G.; Larocca, V.; Martino, M.; Leone, G.P.; Marino, T.; Chianese, S.; Balducchi, R.; Musmarra, D. Recent Developments in Supercritical Fluid Extraction of Bioactive Compounds from Microalgae: Role of Key Parameters, Technological Achievements and Challenges. *J. CO2 Util.* **2020**, *36*, 196–209. https://doi.org/10.1016/j.jcou.2019.11.014.
119. Chaudhary, A.; Dwivedi, A.; Upadhyayula, S. Supercritical Fluids as Green Solvents. In *Handbook of Greener Synthesis of Nanomaterials and Compounds: Volume 1: Fundamental Principles and Methods*; Elsevier: Amsterdam, The Netherlands, 2021; pp. 891–916, ISBN 9780128219386.
120. Williams, J.R.; Clifford, A.A.; Al-Saidi, S.H.R. Supercritical Fluids and Their Applications in Biotechnology and Related Areas. *Appl. Biochem. Biotechnol.* **2002**, *22*, 263–286. https://doi.org/10.1385/MB:22:3:263.
121. Tripodo, G.; Ibáñez, E.; Cifuentes, A.; Gilbert-López, B.; Fanali, C. Optimization of Pressurized Liquid Extraction by Response Surface Methodology of Goji Berry (*Lycium Barbarum* L.) Phenolic Bioactive Compounds. *Electrophoresis* **2018**, *39*, 1673–1682. https://doi.org/10.1002/elps.201700448.
122. Jozwiak, A.; Brzozowski, R.; Bujnowski, Z.; Chojnacki, T.; Swiezewska, E. Application of Supercritical CO2for Extraction of Polyisoprenoid Alcohols and Their Esters from Plant Tissues. *J. Lipid Res.* **2013**, *54*, 2023–2028. https://doi.org/10.1194/jlr.D038794.
123. Herrero, M.; Mendiola, J.A.; Cifuentes, A.; Ibáñez, E. Supercritical Fluid Extraction: Recent Advances and Applications. *J. Chromatogr. A* **2010**, *1217*, 2495–2511.
124. Putra, N.R.; Wibobo, A.G.; Machmudah, S.; Winardi, S. Recovery of Valuable Compounds from Palm-Pressed Fiber by Using Supercritical CO2 Assisted by Ethanol: Modeling and Optimization. *Sep. Sci. Technol.* **2019**, *55*, 3126–3139. https://doi.org/10.1080/01496395.2019.1672740.
125. Woźniak, L.; Marszalek, K.; Skapska, S.; Jedrzejczak, R. The Application of Supercritical Carbon Dioxide and Ethanol for the Extraction of Phenolic Compounds from Chokeberry Pomace. *Appl. Sci.* **2017**, *7*, 322. https://doi.org/10.3390/APP7040322.
126. He, J.Z.; Shao, P.; Liu, J.H.; Ru, Q.M. Supercritical Carbon Dioxide Extraction of Flavonoids from Pomelo (Citrus Grandis (L.) Osbeck) Peel and Their Antioxidant Activity. *Int. J. Mol. Sci.* **2012**, *13*, 13065–13078. https://doi.org/10.3390/ijms131013065.
127. Vinitha, U.G.; Sathasivam, R.; Muthuraman, M.S.; Park, S.U. Intensification of Supercritical Fluid in the Extraction of Flavonoids: A Comprehensive Review. *Physiol. Mol. Plant Pathol.* **2022**, *118*, 101815. https://doi.org/10.1016/j.pmpp.2022.101815.
128. Liu, X.; Gao, X. IOP Conference Series: Earth and Environmental Science Optimization of Supercritical CO 2 Fluid Extraction Conditions of Flavonoids from Spina Gleditsiae You May Also like Optimization of Supercritical CO 2 Fluid Extraction of Flavonoids from Spina Gledit. *IOP Conf. Ser. Earth Environ. Sci* **2018**, *186*, 12077. https://doi.org/10.1088/1755-1315/186/3/012077.
129. Melloul, S.; Zehioua, R.; Meniai, A.H. Supercritical CO2 Extraction of Bioactive Compounds from Local Peganum Harmala Plant Seeds and Optimization of the Extraction Yield and the Antioxidant Activities. *Sustain. Chem. Pharm.* **2022**, *28*, 100729. https://doi.org/10.1016/j.scp.2022.100729.
130. Martínez-Ávila, M.; Rodríguez-Rodríguez, J.; Gutiérrez Uribe, J.A.; Guajardo-Flores, D. Selective Supercritical Fluid Extraction of Non-Polar Phytochemicals from Black Beans (*Phaseolus Vulgaris* L.) by-Products. *J. Supercrit. Fluids* **2022**, *189*, 105730. https://doi.org/10.1016/j.supflu.2022.105730.
131. De Aguiar, A.C.; Viganó, J.; da Silva Anthero, A.G.; Dias, A.L.B.; Hubinger, M.D.; Martínez, J. Supercritical Fluids and Fluid Mixtures to Obtain High-Value Compounds from Capsicum Peppers. *Food Chem. X* **2022**, *13*, 100228. https://doi.org/10.1016/j.fochx.2022.100228.
132. Song, L.; Liu, P.; Yan, Y.; Huang, Y.; Bai, B.; Hou, X.; Zhang, L. Supercritical CO2 Fluid Extraction of Flavonoid Compounds from Xinjiang Jujube (Ziziphus Jujuba Mill.) Leaves and Associated Biological Activities and Flavonoid Compositions. *Ind. Crops Prod.* **2019**, *139*, 111508. https://doi.org/10.1016/j.indcrop.2019.111508.
133. Yang, L.; Zhao, Z.; Wang, G.; Ruan, X.; Wu, Q.; Luo, C.; Wu, Z.; Wei, F.; Zhao, Y.; Wang, Q. Supercritical Extraction and Antioxidant Activity of Major Ingredients in Puerariae Lobatae Root, Pinus Massoniana Needle, Citrus Reticulata Peel and Their Mixture. *J. CO2 Util.* **2021**, *48*, 101518. https://doi.org/10.1016/j.jcou.2021.101518.
134. Milovanovic, S.; Grzegorczyk, A.; Świątek, Ł.; Dębczak, A.; Tyskiewicz, K.; Konkol, M. Dandelion Seeds as a New and Valuable Source of Bioactive Extracts Obtained Using the Supercritical Fluid Extraction Technique. *Sustain. Chem. Pharm.* **2022**, *29*, 100796. https://doi.org/10.1016/j.scp.2022.100796.
135. de Souza Correa, M.; Boschen, N.L.; Rodrigues, P.R.P.; Corazza, M.L.; de Paula Scheer, A.; Ribani, R.H. Supercritical CO2 with Co-Solvent Extraction of Blackberry (Rubus Spp. Xavante Cultivar) Seeds. *J. Supercrit. Fluids* **2022**, *189*, 105702. https://doi.org/10.1016/j.supflu.2022.105702.

136. Yang, Y.C.; Wang, C.S.; Wei, M.C. Kinetics and Mass Transfer Considerations for an Ultrasound-Assisted Supercritical CO2 Procedure to Produce Extracts Enriched in Flavonoids from Scutellaria Barbata. *J. CO2 Util.* **2019**, *32*, 219–231. https://doi.org/10.1016/j.jcou.2019.04.008.
137. Végh, K.; Riethmüller, E.; Hosszú, L.; Darcsi, A.; Müller, J.; Alberti, .; Tóth, A.; Béni, S.; Könczöl, .; Balogh, G.T.; et al. Three Newly Identified Lipophilic Flavonoids in Tanacetum Parthenium Supercritical Fluid Extract Penetrating the Blood-Brain Barrier. *J. Pharm. Biomed. Anal.* **2018**, *149*, 488–493. https://doi.org/10.1016/j.jpba.2017.11.029.
138. Uquiche, E.L.; Toro, M.T.; Quevedo, R.A. Supercritical Extraction with Carbon Dioxide and Co-Solvent from Leptocarpha Rivularis. *J. Appl. Res. Med. Aromat. Plants* **2019**, *14*, 100210. https://doi.org/10.1016/j.jarmap.2019.100210.
139. Fornereto Soldan, A.C.; Arvelos, S.; Watanabe, É.O.; Hori, C.E. Supercritical Fluid Extraction of Oleoresin from Capsicum Annuum Industrial Waste. *J. Clean. Prod.* **2021**, *297*, 126593. https://doi.org/10.1016/j.jclepro.2021.126593.
140. Argun, M.E.; Argun, M.Ş.; Arslan, F.N.; Nas, B.; Ates, H.; Tongur, S.; Cakmakcı, O. Recovery of Valuable Compounds from Orange Processing Wastes Using Supercritical Carbon Dioxide Extraction. *J. Clean. Prod.* **2022**, *375*, 134169. https://doi.org/10.1016/j.jclepro.2022.134169.
141. Goyeneche, R.; Di Scala, K.; Ramirez, C.L.; Fanovich, M.A. Recovery of Bioactive Compounds from Beetroot Leaves by Supercritical CO2 Extraction as a Promising Bioresource. *J. Supercrit. Fluids* **2019**, *155*, 104658. https://doi.org/10.1016/J.SUPFLU.2019.104658.
142. Restrepo-Serna, D.L.; Cardona Alzate, C.A. Economic Pre-Feasibility of Supercritical Fluid Extraction of Antioxidants from Fruit Residues. *Sustain. Chem. Pharm.* **2022**, *25*, 100600. https://doi.org/10.1016/J.SCP.2022.100600.
143. Jha, A.K.; Sit, N. Comparison of Response Surface Methodology (RSM) and Artificial Neural Network (ANN) Modelling for Supercritical Fluid Extraction of Phytochemicals from Terminalia Chebula Pulp and Optimization Using RSM Coupled with Desirability Function (DF) and Genetic. *Ind. Crops Prod.* **2021**, *170*, 113769. https://doi.org/10.1016/j.indcrop.2021.113769.
144. Šalić, A.; Tušek, A.; Fabek, D.; Rukavina, I.; Zelić, B. Aqueous Two-Phase Extraction of Polyphenols Using a Microchannel System—Process Optimization and Intensification. *Food Technol. Biotechnol.* **2011**, *49*, 495–501.
145. Liu, C.; Liu, S.; Zhang, L.; Wang, X.; Ma, L. Partition Behavior in Aqueous Two-Phase System and Antioxidant Activity of Flavonoids from Ginkgo Biloba. *Appl. Sci.* **2018**, *8*, 2058. https://doi.org/10.3390/app8112058.
146. Chong, K.Y.; Stefanova, R.; Zhang, J.; Brooks, M.S.L. Aqueous Two-Phase Extraction of Bioactive Compounds from Haskap Leaves (Lonicera Caerulea): Comparison of Salt/Ethanol and Sugar/Propanol Systems. *Sep. Purif. Technol.* **2020**, *252*, 117399. https://doi.org/10.1016/j.seppur.2020.117399.
147. Zhu, J.; Kou, X.; Wu, C.; Fan, G.; Li, T.; Dou, J.; Shen, D. Enhanced Extraction of Bioactive Natural Products Using Ultrasound-Assisted Aqueous Two-Phase System: Application to Flavonoids Extraction from Jujube Peels. *Food Chem.* **2022**, *395*, 133530. https://doi.org/10.1016/j.foodchem.2022.133530.
148. Xu, Y.Y.; Qiu, Y.; Ren, H.; Ju, D.H.; Jia, H.L. Optimization of Ultrasound-Assisted Aqueous Two-Phase System Extraction of Polyphenolic Compounds from Aronia Melanocarpa Pomace by Response Surface Methodology. *Prep. Biochem. Biotechnol.* **2017**, *47*, 312–321. https://doi.org/10.1080/10826068.2016.1244684.
149. Zhou, H.; Feng, X.; Yan, Y.; Meng, X.; Wu, C.; Kang, Y.; Li, Y. Optimization of an Ultrasonic-Assisted Aqueous Two-Phase Extraction Method for Four Flavonoids from Lysionotus Pauciflorus. *Prep. Biochem. Biotechnol.* **2022**, *52*, 770–782. https://doi.org/10.1080/10826068.2021.1992783.
150. Liang, J.; Zhang, H.; Zhu, C. Optimization of Ultrasonic-Assisted Aqueous Two-Phase Extraction of Flavonoids from Hawthorn Leaves Using Response Surface Methodology. *J. Phys. Conf. Ser.* **2022**, *2329*, 012041. https://doi.org/10.1088/1742-6596/2329/1/012041.
151. Li, L.; Zhang, T.; Xing, J.; Xue, B.; Luo, Z.; Liu, Z. Ethanol/Ammonium Sulfate Ultrasonic-assisted Liquid–Liquid Extraction of Flavonoids from Tibetan Sea-buckthorn Fruit. *J. Food Process. Preserv.* **2022**, *46*, e16602. https://doi.org/10.1111/jfpp.16602.
152. Skarpalezos, D.; Detsi, A. Deep Eutectic Solvents as Extraction Media for Valuable Flavonoids from Natural Sources. *Appl. Sci.* **2019**, *9*, 4169. https://doi.org/10.3390/app9194169.
153. Alañón, M.E.; Ivanović, M.; Gómez-Caravaca, A.M.; Arráez-Román, D.; Segura-Carretero, A. Choline Chloride Derivative-Based Deep Eutectic Liquids as Novel Green Alternative Solvents for Extraction of Phenolic Compounds from Olive Leaf. *Arab. J. Chem.* **2020**, *13*, 1685–1701. https://doi.org/10.1016/j.arabjc.2018.01.003.
154. Ivanović, M.; Razboršek, M.I.; Kolar, M. Innovative Extraction Techniques Using Deep Eutectic Solvents and Analytical Methods for the Isolation and Characterization of Natural Bioactive Compounds from Plant Material. *Plants* **2020**, *9*, 1428.
155. Kalyniukova, A.; Holuša, J.; Musiolek, D.; Sedlakova-Kadukova, J.; Płotka-Wasylka, J.; Andruch, V. Application of Deep Eutectic Solvents for Separation and Determination of Bioactive Compounds in Medicinal Plants. *Ind. Crops Prod.* **2021**, *172*, 114047.
156. Socas-Rodríguez, B.; Torres-Cornejo, M.V.; Álvarez-Rivera, G.; Mendiola, J.A. Deep Eutectic Solvents for the Extraction of Bioactive Compounds from Natural Sources and Agricultural By-Products. *Appl. Sci.* **2021**, *11*, 4897. https://doi.org/10.3390/app11114897.
157. Wang, T.; Li, Q. DES Based Efficient Extraction Method for Bioactive Coumarins from Angelica Dahurica (Hoffm.) Benth. & Hook.f. Ex Franch. & Sav. *Separations* **2021**, *9*, 5. https://doi.org/10.3390/separations9010005.
158. Dai, Y.; Witkamp, G.J.; Verpoorte, R.; Choi, Y.H. Tailoring Properties of Natural Deep Eutectic Solvents with Water to Facilitate Their Applications. *Food Chem.* **2015**, *187*, 14–19. https://doi.org/10.1016/j.foodchem.2015.03.123.

159. Nam, M.W.; Zhao, J.; Lee, M.S.; Jeong, J.H.; Lee, J. Enhanced Extraction of Bioactive Natural Products Using Tailor-Made Deep Eutectic Solvents: Application to Flavonoid Extraction from Flos Sophorae. *Green Chem.* **2015**, *17*, 1718–1727. https://doi.org/10.1039/c4gc01556h.
160. Bubalo, M.C.; Ćurko, N.; Tomašević, M.; Ganić, K.K.; Redovniković, I.R. Green Extraction of Grape Skin Phenolics by Using Deep Eutectic Solvents. *Food Chem.* **2016**, *200*, 159–166. https://doi.org/10.1016/j.foodchem.2016.01.040.
161. Pätzold, M.; Siebenhaller, S.; Kara, S.; Liese, A.; Syldatk, C.; Holtmann, D. Deep Eutectic Solvents as Efficient Solvents in Biocatalysis. *Trends Biotechnol.* **2019**, *37*, 943–959.
162. Xia, G.H.; Li, X.H.; Jiang, Y.H. Deep Eutectic Solvents as Green Media for Flavonoids Extraction from the Rhizomes of Polygonatum Odoratum. *Alex. Eng. J.* **2021**, *60*, 1991–2000. https://doi.org/10.1016/j.aej.2020.12.008.
163. Bajkacz, S.; Adamek, J. Development of a Method Based on Natural Deep Eutectic Solvents for Extraction of Flavonoids from Food Samples. *Food Anal. Methods* **2018**, *11*, 1330–1344. https://doi.org/10.1007/s12161-017-1118-5.
164. Shang, X.; Tan, J.N.; Du, Y.; Liu, X.; Zhang, Z. Environmentally-Friendly Extraction of Flavonoids from Cyclocarya Paliurus (Batal.) Iljinskaja Leaves with Deep Eutectic Solvents and Evaluation of Their Antioxidant Activities. *Molecules* **2018**, *23*, 2110. https://doi.org/10.3390/molecules23092110.
165. Meng, Z.; Zhao, J.; Duan, H.; Guan, Y.; Zhao, L. Green and Efficient Extraction of Four Bioactive Flavonoids from Pollen Typhae by Ultrasound-Assisted Deep Eutectic Solvents Extraction. *J. Pharm. Biomed. Anal.* **2018**, *161*, 246–253. https://doi.org/10.1016/j.jpba.2018.08.048.
166. Rashid, R.; Mohd Wani, S.; Manzoor, S.; Masoodi, F.A.; Masarat Dar, M. Green Extraction of Bioactive Compounds from Apple Pomace by Ultrasound Assisted Natural Deep Eutectic Solvent Extraction: Optimisation, Comparison and Bioactivity. *Food Chem.* **2022**, *398*, 133871. https://doi.org/10.1016/j.foodchem.2022.133871.
167. Lei, J.; Wang, Y.; Li, W.; Fu, S.; Zhou, J.; Lu, D.; Wang, C.; Sheng, X.; Zhang, M.; Xiao, S.; et al. Natural Green Deep Eutectic Solvents-Based Eco-Friendly and Efficient Extraction of Flavonoids from Selaginella Moellendorffii: Process Optimization, Composition Identification and Biological Activity. *Sep. Purif. Technol.* **2022**, *283*, 120203. https://doi.org/10.1016/J.SEPPUR.2021.120203.
168. Liu, J.Z.; Lyu, H.C.; Fu, Y.J.; Jiang, J.C.; Cui, Q. Simultaneous Extraction of Natural Organic Acid and Flavonoid Antioxidants from *Hibiscus Manihot* L. Flower by Tailor-Made Deep Eutectic Solvent. *LWT* **2022**, *163*, 113533. https://doi.org/10.1016/j.lwt.2022.113533.
169. Yu, Q.; Wang, F.; Jian, Y.; Chernyshev, V.M.; Zhang, Y.; Wang, Z.; Yuan, Z.; Chen, X. Extraction of Flavonoids from Glycyrrhiza Residues Using Deep Eutectic Solvents and Its Molecular Mechanism. *J. Mol. Liq.* **2022**, *363*, 119848. https://doi.org/10.1016/j.molliq.2022.119848.
170. Zhang, Y.; Bian, S.; Hu, J.; Liu, G.; Peng, S.; Chen, H.; Jiang, Z.; Wang, T.; Ye, Q.; Zhu, H. Natural Deep Eutectic Solvent-Based Microwave-Assisted Extraction of Total Flavonoid Compounds from Spent Sweet Potato (*Ipomoea Batatas* L.) Leaves: Optimization and Antioxidant and Bacteriostatic Activity. *Molecules* **2022**, *27*, 5985. https://doi.org/10.3390/molecules27185985.
171. Pham, T.N.; Lam, T.D.; Nguyen, M.T.; Le, X.T.; Vo, D.V.N.; Toan, T.Q.; Vo, T.S. Effect of Various Factors on Extraction Efficiency of Total Anthocyanins from Butterfly Pea (*Clitoria Ternatea* L. Flowers) in Southern Vietnam. *IOP Conf. Ser. Mater. Sci. Eng.* **2019**, *544*, 012013. https://doi.org/10.1088/1757-899X/544/1/012013.
172. Jurinjak Tušek, A.; Benković, M.; Valinger, D.; Jurina, T.; Belščak-Cvitanović, A.; Gajdoš Kljusurić, J. Optimizing Bioactive Compounds Extraction from Different Medicinal Plants and Prediction through Nonlinear and Linear Models. *Ind. Crops Prod.* **2018**, *126*, 449–458. https://doi.org/10.1016/j.indcrop.2018.10.040.
173. Šain, A.; Matešić, N.; Jurina, T.; Jurinjak Tušek, A.; Benković, M.; Valinger, D.; Gajdoš Kljusurić, J. Optimization of ethanol/water solvent extraction of bioactive components originating from industrial hemp (*Cannabis Sativa* L.). *Hrana Zdr. Boles.* **2020**, *9*, 30–39.
174. Kumari, M.; Gupta, S.K. Response Surface Methodological (RSM) Approach for Optimizing the Removal of Trihalomethanes (THMs) and Its Precursor's by Surfactant Modified Magnetic Nanoadsorbents (SMNP)—An Endeavor to Diminish Probable Cancer Risk. *Sci. Rep.* **2019**, *9*, 18339. https://doi.org/10.1038/s41598-019-54902-8.
175. Leyva-Jiménez, F.-J.; Fernández-Ochoa, .; Cádiz-Gurrea, M.D.L.L.; Lozano-Sánchez, J.; Oliver-Simancas, R.; Alañón, M.E.; Castangia, I.; Segura-Carretero, A.; Arráez-Román, D. Application of Response Surface Methodologies to Optimize High-Added Value Products Developments: Cosmetic Formulations as an Example. *Antioxidants* **2022**, *11*, 1552. https://doi.org/10.3390/antiox11081552.
176. Kim, J.H.; Shin, H.K.; Seo, C.S. Optimization of the Extraction Process for the Seven Bioactive Compounds in Yukmijihwang-Tang, an Herbal Formula, Using Response Surface Methodology. *Pharmacogn. Mag.* **2014**, *10*, S606–S613. https://doi.org/10.4103/0973-1296.139798.
177. Shukla, L.; Nishkam, A. Performance Optimization, Prediction, and Adequacy by Response Surfaces Methodology with Allusion to DRF Technique. *ISRN Text.* **2014**, *2014*, 34041. https://doi.org/10.1155/2014/634041.
178. Dasankoppa, F.S.; Sholapur, H.N.; Byahatti, A.; Abbas, Z.; Komal, S.K.; Subrata, K. Application of Response Surface Optimization Methodology in Designing Ordispersible Tablets of Antdiabetic Drug. *J. Young Pharm.* **2020**, *12*, 173–177. https://doi.org/10.5530/jyp.2020.12.35.
179. Hazir, E.; Koc, K.H.; Hiziroglu, S. Optimization Of Sanding Parameters Using Response Surface Methodology. *Maderas Cienc. Tecnol.* **2017**, *19*, 407–416. https://doi.org/10.4067/S0718-221X2017005000101.

180. Ranade, S.S.; Thiagarajan, P. Selection of a Design for Response Surface. *IOP Conf. Ser. Mater. Sci. Eng.* **2017**, *263*, 022043. https://doi.org/10.1088/1757-899X/263/2/022043.
181. Johnson, R.T.; Montgomery, D.C. Choice of Second-Order Response Surface Designs for Logistic and Poisson Regression Models. *Int. J. Exp. Des. Process Optim.* **2009**, *1*, 2. https://doi.org/10.1504/ijedpo.2009.028954.
182. Chen, X.; Jia, X.; Yang, S.; Zhang, G.; Li, A.; Du, P.; Liu, L.; Li, C. Optimization of Ultrasonic-Assisted Extraction of Flavonoids, Polysaccharides, and Eleutherosides from Acanthopanax Senticosus Using Response Surface Methodology in Development of Health Wine. *LWT* **2022**, *165*, 113725. https://doi.org/10.1016/j.lwt.2022.113725.
183. Shahidi, S.A. Effect of Solvent Type on Ultrasound-Assisted Extraction of Antioxidant Compounds from Ficaria Kochii: Optimization by Response Surface Methodology. *Food Chem. Toxicol.* **2022**, *163*, 112981. https://doi.org/10.1016/j.fct.2022.112981.
184. Yu, M.; Wang, B.; Qi, Z.; Xin, G.; Li, W. Response Surface Method Was Used to Optimize the Ultrasonic Assisted Extraction of Flavonoids from Crinum Asiaticum. *Saudi J. Biol. Sci.* **2019**, *26*, 2079–2084. https://doi.org/10.1016/j.sjbs.2019.09.018.
185. Wani, K.M.; Uppaluri, R.V.S. Efficacy of Ultrasound-Assisted Extraction of Bioactive Constituents from Psidium Guajava Leaves. *Appl. Food Res.* **2022**, *2*, 100096. https://doi.org/10.1016/j.afres.2022.100096.
186. Zhang, X.; Su, J.; Chu, X.; Wang, X. A Green Method of Extracting and Recovering Flavonoids from Acanthopanax Senticosus Using Deep Eutectic Solvents. *Molecules* **2022**, *27*, 923. https://doi.org/10.3390/molecules27030923.
187. Jamshaid, S.; Ahmed, D. Optimization of Ultrasound-Assisted Extraction of Valuable Compounds from Fruit of Melia Azedarach with Glycerol-Choline Chloride Deep Eutectic Solvent. *Sustain. Chem. Pharm.* **2022**, *29*, 100827. https://doi.org/10.1016/j.scp.2022.100827.
188. Oktaviyanti, N.D.; Kartini, K.; Hadiyat, M.A.; Rachmawati, E.; Wijaya, A.C.; Hayun, H.; Mun'Im, A. A Green Extraction Design for Enhancing Flavonoid Compounds from Ixora Javanica Flowers Using a Deep Eutectic Solvent: Green Extraction of Ixora Javanica. *R. Soc. Open Sci.* **2020**, *7*, 201116. https://doi.org/10.1098/rsos.201116.
189. Hao, C.; Chen, L.; Dong, H.; Xing, W.; Xue, F.; Cheng, Y. Extraction of Flavonoids from Scutellariae Radix Using Ultrasound-Assisted Deep Eutectic Solvents and Evaluation of Their Anti-Inflammatory Activities. *ACS Omega* **2020**, *5*, 23140–23147. https://doi.org/10.1021/acsomega.0c02898.
190. Sharma, B.R.; Kumar, V.; Kumar, S.; Panesar, P.S. Microwave Assisted Extraction of Phytochemicals from Ficus Racemosa. *Curr. Res. Green Sustain. Chem.* **2020**, *3*, 100020. https://doi.org/10.1016/j.crgsc.2020.100020.
191. He, Q.; Li, Y.; Zhang, P.; Zhang, A.; Wu, H. Optimisation of Microwave-Assisted Extraction of Flavonoids and Phenolics from Celery (*Apium Graveolens* L.) Leaves by Response Surface Methodology. *Czech J. Food Sci.* **2016**, *34*, 341–349. https://doi.org/10.17221/266/2015-CJFS.
192. Niu, Q.; Gao, Y.; Liu, P. Optimization of Microwave-Assisted Extraction, Antioxidant Capacity, and Characterization of Total Flavonoids from the Leaves of Alpinia Oxyphylla Miq. *Prep. Biochem. Biotechnol.* **2020**, *50*, 82–90. https://doi.org/10.1080/10826068.2019.1663535.
193. Xu, B.; Tao, R.; Huang, Z.; Zhu, D.; Liu, J. Process Optimization of Microwave-Assisted Extraction of Flavonoids from Salvia Plebeian Using Response Surface Methodology.*J. Phys. Conf. Ser.* **2020**, *1578*, 012222.
194. Weremfo, A.; Adulley, F.; Adarkwah-Yiadom, M. Simultaneous Optimization of Microwave-Assisted Extraction of Phenolic Compounds and Antioxidant Activity of Avocado (Persea Americana Mill.) Seeds Using Response Surface Methodology. *J. Anal. Methods Chem.* **2020**, *2020*, 7541927. https://doi.org/10.1155/2020/7541927.
195. Bubba, D.; Ašperger, D.; Gavrani´cgavrani´c, M.; Prišlin, B.; Renduli´crenduli´c, N.; Šikuten, I.; Markovi´c, Z.M.; Babi´c, B.B.; Maleti´c, E.M.; Karoglan, J.; et al. Optimization of Microwave-Assisted Extraction and Matrix Solid-Phase Dispersion for the Extraction of Polyphenolic Compounds from Grape Skin. *Separations* **2022**, *9*, 235. https://doi.org/10.3390/SEPARATIONS9090235.
196. Pereira, D.T.V.; Zabot, G.L.; Reyes, F.G.R.; Iglesias, A.H.; Martínez, J. Integration of Pressurized Liquids and Ultrasound in the Extraction of Bioactive Compounds from Passion Fruit Rinds: Impact on Phenolic Yield, Extraction Kinetics and Technical-Economic Evaluation. *Innov. Food Sci. Emerg. Technol.* **2021**, *67*, 102549. https://doi.org/10.1016/j.ifset.2020.102549.
197. Ouédraogo, J.C.W.; Dicko, C.; Kini, F.B.; Bonzi-Coulibaly, Y.L.; Dey, E.S. Enhanced Extraction of Flavonoids from Odontonema Strictum Leaves with Antioxidant Activity Using Supercritical Carbon Dioxide Fluid Combined with Ethanol. *J. Supercrit. Fluids* **2018**, *131*, 66–71. https://doi.org/10.1016/j.supflu.2017.08.017.
198. Liu, J.; Liu, J.; Lin, S.; Wang, Z.; Wang, C.; Wang, E.; Zhang, Y. Supercritical Fluid Extraction of Flavonoids from Maydis Stigma and Its Nitrite-Scavenging Ability. *Food Bioprod. Process.* **2011**, *89*, 333–339. https://doi.org/10.1016/j.fbp.2010.08.004.
199. Liu, X.Y.; Ou, H.; Zuo, J.; Gregersen, H. Supercritical CO2 Extraction of Total Flavonoids from Iberis Amara Assisted by Ultrasound. *J. Supercrit. Fluids* **2022**, *184*, 105581. https://doi.org/10.1016/j.supflu.2022.105581.
200. Arias, J.; Mejía, J.; Córdoba, Y.; Martínez, J.R.; Stashenko, E.; del Valle, J.M. Optimization of Flavonoids Extraction from Lippia Graveolens and Lippia Origanoides Chemotypes with Ethanol-Modified Supercritical CO2 after Steam Distillation. *Ind. Crops Prod.* **2020**, *146*, 112170. https://doi.org/10.1016/j.indcrop.2020.112170.
201. Ochoa-Velasco, C.E.; Ruiz-López, I.I. Mass Transfer Modeling of the Antioxidant Extraction of Roselle Flower (*Hibiscus Sabdariffa*). *J. Food Sci. Technol.* **2019**, *56*, 1008–1015. https://doi.org/10.1007/s13197-018-03567-8.
202. Fedoryshyn, O.; Kniazieva, K.; Mylyanych, A.; Petrina, R. Kinetics of Extraction of Phenolic Compounds and Flavonoids from Carlina Acaulis. *Int. Q. J. Econ. Technol. Model. Process.* **2020**, *09*, 3–10.

203. Galgano, F.; Tolve, R.; Scarpa, T.; Caruso, M.C.; Lucini, L.; Senizza, B.; Condelli, N. Extraction Kinetics of Total Polyphenols, Flavonoids, and Condensed Tannins of Lentil Seed Coat: Comparison of Solvent and Extraction Methods. *Foods* **2021**, *10*, 1810. https://doi.org/10.3390/foods10081810.
204. Mitic, M.; Jankovic, S.; Mitic, S.; Kocic, G.; Maskovic, P.; Dukic, D. Optimization and Kinetic Modelling of Total Phenols and Flavonoids Extraction from Tilia Cordata m. Flowers. *S. Afr. J. Chem.* **2021**, *75*, 64–72. https://doi.org/10.17159/0379-4350/2021/v75a7.
205. Piwowarska, N.; González-Alvarez, J. Extraction of Antioxidants from Forestry Biomass: Kinetics and Optimization of Extraction Conditions. *Biomass Bioenergy* **2012**, *43*, 42–51. https://doi.org/10.1016/j.biombioe.2012.03.031.
206. Gerke, I.B.B.; Hamerski, F.; de Paula Scheer, A.; da Silva, V.R. Solid–Liquid Extraction of Bioactive Compounds from Yerba Mate (Ilex Paraguariensis) Leaves: Experimental Study, Kinetics and Modeling. *J. Food Process Eng.* **2018**, *41*, e12892. https://doi.org/10.1111/jfpe.12892.
207. Kusuma, H.S.; Mahfud, M. The Extraction of Essential Oils from Patchouli Leaves (Pogostemon Cablin Benth) Using a Microwave Air-Hydrodistillation Method as a New Green Technique. *RSC Adv.* **2017**, *7*, 1336–1347. https://doi.org/10.1039/C6RA25894H.
208. PELEG, M. An Empirical Model for the Description of Moisture Sorption Curves. *J. Food Sci.* **1988**, *53*, 1216–1217. https://doi.org/10.1111/j.1365-2621.1988.tb13565.x.
209. Jokić, S.; Velić, D.; Bilić, M.; Bucić-Kojić, A.; Planinić, M.; Tomas, S. Modelling of Solid-Liquid Extraction Process of Total Polyphenols from Soybeans. *Czech J. Food Sci.* **2010**, *28*, 206–212. https://doi.org/10.17221/200/2009-CJFS.
210. Bee Lin, C.; Yen Leng, C. Solid-Liquid Extraction Kinetics of Total Phenolic Compounds (TPC) from Red Dates. *MATEC Web Conf.* **2018**, *152*, 01001. https://doi.org/10.1051/matecconf/201815201001.
211. Kaleta, A.; Górnicki, K. Evaluation of Drying Models of Apple (Var. McIntosh) Dried in a Convective Dryer. *Int. J. Food Sci. Technol.* **2010**, *45*, 891–898. https://doi.org/10.1111/j.1365-2621.2010.02230.x.
212. Diamante, L.M.; Ihns, R.; Savage, G.P.; Vanhanen, L. Short Communication: A New Mathematical Model for Thin Layer Drying of Fruits. *Int. J. Food Sci. Technol.* **2010**, *45*, 1956–1962. https://doi.org/10.1111/j.1365-2621.2010.02345.x.
213. Rakshit, M.; Srivastav, P.P.; Bhunia, K. Kinetic Modeling of Ultrasonic-assisted Extraction of Punicalagin from Pomegranate Peel. *J. Food Process Eng.* **2020**, *43*, 1956–1962. https://doi.org/10.1111/jfpe.13533.
214. Tao, Y.; Zhang, Z.; Sun, D.-W. Kinetic Modeling of Ultrasound-Assisted Extraction of Phenolic Compounds from Grape Marc: Influence of Acoustic Energy Density and Temperature. *Ultrason. Sonochem.* **2014**, *21*, 1461–1469. https://doi.org/10.1016/j.ultsonch.2014.01.029.
215. Yiğitarslan, S. Modeling of Solid-Liquid Extraction of Total Phenolics from *Capsicum Annium* L. *J. Turk. Chem. Soc. Sect. B Chem. Eng.* **2017**, *1*, 43–60.
216. Sturzoiu, A.; Stroescu, M. Empirical Models Applied for Kinetics Extraction of β β β β β-Carotene from Rosa Canina. *Rev. Chim.* **2011**, *62*, 344–348.
217. Sridhar, A.; Ponnuchamy, · Muthamilselvi; Ponnusamy, ·; Kumar, S.; Kapoor, A.; Dai-Viet, ·; Vo, N.; Prabhakar, S. Techniques and Modeling of Polyphenol Extraction from Food: A Review. *Environ. Chem. Lett.* **2021**, *19*, 3409–3443. https://doi.org/10.1007/s10311-021-01217-8.
218. Lazar, L.; Talmaciu, A.I.; Volf, I.; Popa, V.I. Kinetic Modeling of the Ultrasound-Assisted Extraction of Polyphenols from Picea Abies Bark. *Ultrason. Sonochem.* **2016**, *32*, 191–197. https://doi.org/10.1016/j.ultsonch.2016.03.009.
219. Yedhu Krishnan, R.; Rajan, K.S. Microwave Assisted Extraction of Flavonoids from Terminalia Bellerica: Study of Kinetics and Thermodynamics. *Sep. Purif. Technol.* **2016**, *157*, 169–178. https://doi.org/10.1016/j.seppur.2015.11.035.
220. Palsikowski, P.A.; Besen, L.M.; Santos, K.A.; da Silva, C.; da Silva, E.A. Supercritical CO2 Oil Extraction from Bauhinia Forficata Link Subsp. Pruinosa Leaves: Composition, Antioxidant Activity and Mathematical Modeling. *J. Supercrit. Fluids* **2019**, *153*, 104588. https://doi.org/10.1016/j.supflu.2019.104588.