Selective extraction of bioactive compounds from plants using recent extraction techniques: A review

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Abstract

Plant extraction has existed for a long time and is still of interest. Due to technological improvements, it is now possible to obtain extracts with higher yields. While global yield is a major parameter because it assesses the extraction performance, it can be of interest to focus on the extraction of particular compounds (specific metabolites) to enrich the sample and to avoid the extraction of unwanted ones, for instance the primary metabolites (carbohydrates, triacylglycerols). The objective then is to improve extraction selectivity is then considered.

In solid-liquid extraction, which is often called maceration, the solvent has a major impact on selectivity. Its polarity has a direct influence on the solutes extracted, related to the chemical structure of the compounds, and modelling compound/solvent interactions by using various polarity or interaction scales is a great challenge to favor the choice of the appropriate extracting liquid.

Technical advances have allowed the development of recent, and sometimes green, extraction techniques, such as Microwave-Assisted Extraction (MAE), Ultrasound-Assisted Extraction (UAE), Pressurized Liquid Extraction (PLE) and Supercritical Fluid Extraction (SFE). This review focuses on the specificity of these recent techniques and the influence of their physical parameters (i.e. pressure, intensity, etc.). In addition to the solvent selection, which is of prime interest, the physical parameters applied by the different techniques influence the extraction results in different ways. Besides, SFE is a versatile and green technique suitable to achieve selectivity for some compounds. Due to its properties, SC-CO_2 allows tailoring conditions to improve the selectivity.

1 Introduction

Primary and secondary metabolites can be extracted from plants by different techniques. For non-volatile compounds, the oldest technique is simply to bring the plant into contact with a solvent (water, alcohol, oil...). This technique is called solid-liquid extraction, or more commonly maceration. For several years now, so-called "modern" extraction techniques have been developed. The enhancement of performance comes from the use of “assisted” technology (i.e. ultrasonic waves, pressure, microwaves) which may reduce the duration of the process and induce energy and solvent saving through various intensification mechanisms. This physical treatment can also impact the extraction mechanism, possibly increasing extraction yields and causing different extraction selectivities compared to simple maceration.

To determine the best operating parameters, process optimization is frequently based on the global yield. However, in some cases, it is necessary to extract one family or one compound over another. Selectivity is then considered to find the best conditions. It can be used to enrich an extract with target compounds [1], or to avoid unwanted compounds such as pollutants [2–5]. In the latter case, purity is the optimized parameter.

The aim of this review is to investigate the different parameters that can induce extraction selectivity in numerous extraction methods.

First, the nature of the solvent is investigated as the right choice of solvent can by itself induce selectivity. In a second part, the review focuses on different techniques and their respective parameters to examine their role in selective extraction. Three extraction methods are described: Ultrasound-Assisted Extraction (UAE), Microwave-Assisted Extraction (MAE) and Pressurized Liquid Extraction (PLE). For example, the impact of frequency and power on selectivity is studied for UAE, pressure for PLE and so on. In the last part, the use of supercritical carbon dioxide (SC-CO_2) in Supercritical Fluid Extraction (SFE) is detailed. This fluid is well known for its selectivity properties. For this reason, this extraction method will be dealt with at greater length than the other three. Carbon dioxide modulation is studied and other parameters such as the use of separators or extraction vessel geometry are presented.

2 Extraction solvent

2.1 Solubility models

Whatever the extraction method used, the chemical nature of the extraction solvent is of primary importance to favor the compound solubility, i.e. the extraction recovery and the extraction selectivity.

The knowledge of these chemical properties, which are the basis of the interactions developed between the solvent and the compounds, guides the selection of an adequate solvent, to maximize the yield or purity of the target molecules. Various scales of solvent and compound chemical properties can help in this choice. For instance, the Rohrschneider polarity P' describes with one general value the ability of the molecules to dissolve in water or in alkanes. Other models such as the solvation parameter model, with the five Abraham descriptors (E, S, A, B, V), or the Cosmo-RS model, with five COSMOments (sig2, sig3, Hb don3, HB acc3, CSA), both detail five interaction types as reviewed elsewhere [6].

One polarity scale is commonly used to evaluate and compare polarities: log P. Also known as log $K_{o/w}$, this parameter is measured as the partition of the target analyte between two solvents (octanol and water). Similar to the Rohrschneider polarity parameter P', one value describes the best solubility of the compound in the polar (aqueous) or non-polar (octanol) solvent. Concentrations in each phase are measured and log $K_{o/w}$ is calculated using the following equation:

$$Log\ K_{O/W} = Log\ (\frac{C_{octanol}}{C_{water}})$$

where $C_{octanol}$ and C_{water} are the concentrations of the compound measured in each phase. *In silico* models also allow the direct calculation of this parameter computationally. In order to give an idea of the polarity of different compounds, Figure 1 locates different compound families as a function of their log P, and Tables S1-S15 summarize all the data for the molecules cited as examples in this review (chemical structures and log P). Log P values were calculated using the MolDesc platform designed by the Institute of Organic and Analytical Chemistry (ICOA) in Orleans – FRANCE (http://moldesc.icoa.fr/). This information can be used as a first-line value in order to estimate the polarity of the solvents and compounds discussed in this review.

The Hansen solubility parameter scale is another frequently used model. It is based on three parameters δd, δp and δh, which respectively describe dispersion, dipolar and hydrogen bond interactions. This scale may appear less accurate than the solvation parameter model (or linear solvation energy relationship - LSER) or the Cosmo-RS models, because of the smaller number of parameters (three against five). However, the possibility to calculate these three Hansen parameters simply from structural fragments of compounds makes it a popular scale. Numerous studies present its use both for the extraction of natural compounds, and to substitute classical and sometimes toxic solvents by green ones [7–20].

Among the various types of presentations used to assist in the choice of solvent such as a Hansen sphere or Teas triangle, the spider diagram is a useful figure to locate each solvent in relation to its three parameter values on a planar projection. Figure 2 shows the location of classical solvents (blue bubbles) used for extraction, as further discussed below, namely water, methanol, ethanol, dimethylformamide (DMF), hexane, acetone and acetonitrile. On this diagram the bubble size is related to the total Hansen parameter. As expected, water is located at the top of the spider diagram because of the high value of the hydrogen bond δh parameter; hexane is at the bottom right, having a high (and unique) dispersive contribution (δd); while acetonitrile is at the bottom left, because of its great dipole-dipole interactions (δp). The classical solvents presented on this diagram are well spread over the diagram space, showing the varied choices, which can be related to the diverse chemical structures of natural compounds. However, due to ecological and toxicity issues, these classical solvents are increasingly substituted by “green” ones. On the basis of previous work suggesting these replacements [7,8,20], one can see the location of green solvents (green bubbles) that can be used instead of classical ones (blue bubbles). Clearly, water is a green solvent, whereas glycerol and 1,3 butane-diol can replace methanol; limonene, methyltetrahydrofurane (MeTHF) or 1,3,3,3 trifluropropene (HFO-1234ze) replace hexane, etc. Some ionic liquids are also used as green solvents, for instance B_{min} Tf2N seems able to substitute DMF. Carbon dioxide is also often used for green extraction. As shown on figure 2, the location of carbon dioxide at 10 MPa varies according to the temperature (25-40°C) [10–18]. Because of the fluid compressibility, CO_2 density is in part related to temperature, which can modify the Hansen parameter values. Moreover, as further discussed, the calculation of these Hansen parameters depends on the equations and data used,

which can lead to differences in the results, explaining some differences between the published values.

Figure 3 shows the location of some bioactive natural compounds on the basis of their Hansen parameters. Four of these compounds (rutin, quercetin, oleuropein and chlorophyll) display a high value both for the polar (δp) and hydrogen bond (δh) values and are located on the left of the occupied space, whereas three other compounds (epicathechin, naringin, catechin) display a high δh value and are located on the top and the right side of the spider diagram. The five compounds having a flavonoid skeleton with numerous hydroxyl groups that can scavenge free radicals in order to prevent damage on a cellular level (catechin, epicatechin, rutin, naringin, quercetin), appear to be best extracted with water or protic solvents, for instance ethanol, glycerol or 1,3 butanediol (fig.2). For naringin, a natural antioxidant which is used as a food additive to treat obesity and diabetes, its solubility appears to be higher in aqueous glycerol than in water, as the Hansen parameters of naringin are closest to that of glycerol [14]. However, the change from water to aqueous glycerol did not provide selective extraction of polyphenols from grape fruits (i.e. anthocyanins are more soluble in water than in aqueous glycerol). Several natural carotenoid pigments (β-carotene, astaxanthin, fucoxanthin, curcumin) are located in the same area, together with α-tocopherol, β-sitosterol and resveratrol. All these compounds have biological activities, such as anti-inflammatory, anti-oxidant or anti-carcinogenic properties, whereas triterpene betulin acts as an antiviral agent [12].

Figure 4 shows the location of some natural products and extraction solvents studied. First, and as discussed previously, depending on the calculation method, the values obtained can differ dramatically. For instance, the location of rosmarinic acid (RA) [18,21] can be close to ethanol or 1,3 butanediol when using the Stefanis method [22] whereas it is close to glycerol carbonate when using the Just method [23]. The differences between these calculation methods were recently discussed by Mathieu [24], who reported the superiority of the Stefanis model for polar compounds, as it takes into account local effects associated with conjugation.

Artemisin, a sesquiterpenoid known for its antimalarial activity, which is located lower on the diagram (fig.4), displays a very high solubility in dichloromethane (DCM) (1195 mg/mL), a rather high solubility in dimethylsulfoxide (DMSO) (103.7 mg/mL) and a satisfactory one in ethyl acetate (39.4 mg/mL) [9]. However, the diagram

shows that the location of artemisin toward these three solvents is not fully in accordance with the experimental solubility measurements. Similarly, the solubility of kahweol and cafestol toward varied solvents has been studied [12]. The normalized values range from 100% for the best extraction obtained in methyl-t-butylether (MTBE), to 0% for ethyl acetate, reaching 88% for DCM and 1.3% for hexane. Although these four solvents seem to be at equivalent distances from the two diterpenes, the experimental solubility values are quite different. Another study was done on the extraction of phenolic compounds (tyrosol, hydroxytyrosol) and phytosterol (β-sitosterol) from olive oil. As expected, the addition of a hydroxyl group to tyrosol improved the δh parameter of hydroxytyrosol, but despite these high δh values, both were only slightly soluble in water [16]. When looking at the respective solubility of these compounds towards green solvents such as ethanol, ethyl lactate, ethyl acetate and limonene, the use of ethanol allows the selective extraction of phenolic compounds, and the use of limonene the selective extraction of β-sitosterol. The other two solvents, ethyl lactate and acetate, could be used for the simultaneous extraction of interesting compounds [16]. The extraction recovery for fucoxanthin was studied in four green solvents, ethanol, ethyl acetate, ethyl lactate and limonene [20]. The best recovery was obtained with ethyl acetate, and the worst with limonene, despite its very close location to fucoxanthin on figure 4. The authors mentioned that the Hansen parameters were related to solubility, but not to the extraction kinetics, which depend on the matrices. Consequently, the use of Hansen parameters should be restricted to initial evaluation for the solvent selection. Nevertheless, when looking at the extraction selectivity between carotenoids and chlorophylls, the values were 0.52 for ethanol, 0.54 for ethyl lactate, 1.22 for ethyl acetate and 3.54 for limonene (at 40°C), showing the satisfactory relationship between the Hansen parameter location and this relative value.

All these models help to describe the polarities of different molecules based on different calculations. However, a common feature of all these models is that they evaluate a molecule without taking its environment into account. In the case of plant extraction, it is not clear that a solvent, which may solubilize a compound predicted by a previous model, will extract this same compound during plant extraction: other mechanisms can interfere during extraction such as co-extraction of other molecules, intra-particle diffusional resistance, etc.

2.2 Solvent selectivity

In solid-liquid extraction, solutes migrate from the solid (plant sample) to the liquid (extraction solvent) depending on the physicochemical properties of the solutes and solvent. It is therefore natural that the extraction solvent should play an important role during extraction and affect selectivity. Several studies have highlighted the selectivity of different solvents as a function of the targeted compounds. These solvents and their selectivity properties can be applied to any kind of extraction processes. This first part of the review focuses on solvent effects independently of other physicochemical effects induced by the extraction technique itself such as temperature, pressure, etc.

To illustrate the solvent effects, Santovo *et al*. [25] extracted antimicrobial molecules from freeze-dried *Haematococcus pluvialis* microalgae using PLE. Hexane and ethanol were used and compared. They confirmed that hexane (Log P = 2.6) favors the extraction of alkanes (i.e. octane Log P = 3.4) and methyl esters (i.e. Hexadecanoic acid ethyl ester Log P = 6.0) without carboxylic acids, while ethanol (Log P = 0.0) extracts carboxylic acids (i.e. butanoic acid Log P = 0.9) without any alkanes or methyl esters. Otero *et al*. [26] demonstrated that ethyl acetate is a better solvent to extract fatty acids from freeze dried Galician Algae compared to less polar (hexane) and more polar (ethanol, and ethanol/water) solvents using PLE. The fatty acid content (expressed as mg per g of extract) was higher using ethyl acetate (693.20 mg/g) than hexane (426.12 mg/g) or ethanol (554.42 mg/g). However, it highlighted the fact that solubility is not a binary term (solutes are neither completely soluble nor not soluble at all).

Ethanol and hexane were also compared with respect to pigment content. Jaime *et al*. [27] studied the impact of these solvents through the extraction yield of different pigments such as chlorophylls and carotenoids from *Haematococcus pluvialis* microalgae by PLE. Both pigment families were found in ethanol and hexane extracts. This shows that even with a high log P gap, some compounds are soluble in any solvent. Differences were observed with xanthophylls such as lutein, which was more abundant in the ethanol extract than in the hexane extract (61.0% normalized area in ethanol *vs* 38.2% in hexane). The contrary was observed with carotenes such as β-carotene (5.4% in ethanol *vs* 8.4% in hexane). This can be explained by the fact that xanthophyll compounds are more polar than carotenes due to the presence of

oxygenated functions (ketone, epoxy, hydroxyl). Saha *et al*. [28] studied different solvent compositions (using acetone LogP = -0.24, hexane and ethanol) on the extraction of lutein and β-carotene from orange carrot using PLE. Acetone mixtures led to extracts with a lower content of both carotenoids. However, ethanol mixed with hexane demonstrated a higher recovery of lutein and β-carotene. Macìas-Sànchez *et al*. [29] extracted the same pigments by UAE from *Dunaliella salina* micro-algae using two other solvents, methanol and DMF (LogP = -0.83). The carotenoid/chlorophyll ratio was measured. Between these two solvents, the ratios were respectively around 5 and 8, demonstrating a higher carotenoid selectivity with DMF, which is less polar than methanol. This selectivity was also investigated by Sànchez-Camargo *et al*. [10] on *Phaeodactylum tricornutum* diatom by PLE. Among varied solvents, some considered as greener were tested such as d-limonene or ethyl lactate. They demonstrated a higher carotenoid/chlorophyll ratio, showing higher selectivity. The minimum ratio was obtained using ethanol (0.52) while the maximum was obtained with d-limonene at (1.73).

Selectivity can also be observed for more polar molecules. Bellumori *et al.* [30] extracted rosemary leaves with MAE and UAE and different solvents. They showed that hexane was more selective for terpenoids (mainly carnosic acid), while selectivity for phenolic compounds such as rosmarinic acid was improved using ethanol. This was confirmed by Oliveira *et al.* [31] using different extraction solvents from water to acetone with maceration. Water favored the extraction of rosmarinic acid, while acetone favored carnosic acid extraction. Zachovà *et al*. [32] examined the extraction of stilbenes (i.e. resveratrol, …) from grape cane with methanol, acetone and ethanol. They demonstrated that ethanol was more selective than methanol by extracting similar amounts of stilbenes with a lower global yield. With an 18% lower yield compared to ethanol, acetone was the most selective solvent, extracting 2.4 times more concentrated stilbene. Boukhris *et al*. [33] developed a two-step PLE to extract germacranolides and phenolic compounds from *Anvillea radiata*. A first extraction with chloroform extracted germacranolides and a second step with methanol extracted phenolic compounds. To conclude, the above studies confirmed that selectivity can be obtained using non-polar and polar solvents, or by mixing them to obtain other extraction solvents with intermediate global polarity.

In the last decades, new kinds of solvent have been developed. Ionic liquids (IL) were some of the first. They were discovered at the end of the XIXth century, but found application only from the 1970s on (first used as electrolytes in batteries). They consist in blending two ionic compounds with opposite charges. This blend creates a mixture with different physicochemical properties from those of the compounds used. For example, this difference can be visibly seen by mixing two solids and obtaining a liquid mixture. This kind of solvent has been used in plant extraction and shows interesting selectivity. Liu *et al*. [34] studied the use of an ionic liquid ($[HO_3S(CH_2)_4mim]HSO_4$) at different concentrations in water: from 0.2 to 1.6 M for the extraction of phenolic acids from *Eucalyptus globulus* leaves by MAE. The ionic solvent $[HO_3S(CH_2)_4mim]HSO_4$ at 1.0 M in water improved extraction by playing a catalytic role in the formation of ellagic and gallic acids from hydrolysable tannins such as tellimagrandin II. Selectivity was observed by changing the concentration of the ionic solvent, inducing different catalysis mechanisms that resulted in different ellagic and gallic acid compositions. Similar results were obtained by Sukor *et al*. [35] who used BmimTf2N for the extraction of gallic and tannic acids from oak galls during UAE. Different concentrations from 0.05 to 0.20 M led to different acid contents. Compared to other classical solvents, for example methanol, ionic liquids doubled the extraction yield of these phenolic compounds. These studies confirm the interest in these IL compared to more classical solvents such as methanol. This catalytic agent allows the extraction of compounds that are not extractable with other selective solvents.

Another family of solvents was developed historically from IL, Deep Eutectic Solvents (DES). DES are more recent, as they appeared at the beginning of the 2000s. The principle is close to that of IL. However, the compounds are not ionic and the interactions result from hydrogen bonding. To create a DES, one hydrogen-bonding donor and one hydrogen-acceptor are required. This results in a eutectic mixture with a lower melting point. Bubalo *et al*. [36] developed different DES for the extraction of phenols from grape skin using MAE and UAE. Choline chloride was used as hydrogen acceptor while different hydrogen donors were tested (i.e. glycerol, oxalic acid, malic acid, sorbose). Results showed that the selectivity could be tailored as a function of the different DES used. This was especially the case for the recovery of p-coumaroylmonoglucosides (i.e. malvidin-3-O-(6-p-coumaroyl)glucoside) using a choline chloride:glycerol 1:2 (molar ratio) mixture compared to other compounds such

as anthocyanin-3-O-monoglucosides (i.e. petunidin-3-O-glucosides). Shang *et al*. [37] studied the extraction of *Cyclocarya paliurus* (Batal.) Iljinskaja leaves by UAE with respect to different flavonoid yields. They showed that alcohol- and amine-based DES are better for the extraction of these flavonoids than sugar- and acid-based DES. This can be explained by the fact that these compounds are better extracted by an alkaline solvent. It is then possible to selectively extract these flavonoids (kaempferol, kaempferol-7-O-α-L-rhamnoside, quercetin, quercetin-3-O-β-D-glucuronide, and kaempferol-3-O-β-D-glucuronide) from other compounds, which are better extracted in acidic solvents (i.e. anthocyanins, which are described next). Another name can be used for this kind of solvent: NaDES when only “natural” compounds are used such as carbohydrates (glucose, sorbitol…), acids (citric acid, amino acids, …), etc. Guo *et al*. [38] worked on the extraction of anthocyanins (i.e. cyanidin-3-O-glucoside) from mulberry using NaDES. These compounds are sensitive to pH changes, and by using different kinds of solvents (acidic and alkaline), the authors demonstrated that anthocyanins are better extracted using acidic mixtures. The impact of pH itself on selectivity is further detailed later in this paper.

In order to change the extraction solvent viscosity, or to increase its polarity, water can be added to other solvents. Pagano *et al*. [39] confirmed the use of a water mixture with ethyl lactate and ethanol on *Ocimum basilicum* L by PLE to recover polyphenolic acids (rosmarinic and caffeic acids). Ethyl lactate mixtures seemed inadequate to extract these compounds. However, adding water had a positive impact for acids. The highest content expressed in mg per g of extract was obtained using 25% of water in ethanol for rosmarinic acid (17.78 mg/g) while the caffeic acid content was higher with pure ethanol (2.42 mg/g). The caffeic acid/rosmarinic acid ratio was calculated and was higher with pure ethanol, showing that pure ethanol is the most selective solvent to extract caffeic acid over rosmarinic acid.

The impact of water was also investigated on pigments. Rudke *et al*. [40] showed a negative influence of water on carotenoid extraction from buriti (*Mauritia flexuosa L*.) using ethanol-water mixtures in PLE. In addition, carotenoids were little impacted by temperature changes. However, the phenolic content seemed less affected by solvent change than by temperature. Based on these results, it is then possible to increase selectivity for the extraction of carotenoids over polyphenols and *vice versa* using temperature (this parameter is discussed further in this review).

Regarding more polar pigments such as tannins, Bosso *et al*. [41] showed a positive impact of an ethanol:water mixture for the extraction of condensed tannins and flavonoids by UAE. But when using pure solvent (water or ethanol), the tannin content decreased drastically and reached a minimum of 8.0 mg/g dry sample weight with EtOH:Water 50/50 v/v, and around 0.5 mg/g with EtOH and water. A maximum flavonoid yield was also reached using ethanol-water mixtures. But using pure ethanol, the decrease was not as significant as that observed for tannins. Using pure ethanol was then a more selective way to extract flavonoids over condensed tannins.

Carrero-Carralero *et al*. [42] extracted bioactive carbohydrates (*i.e*. inositols) from mung bean (*Vigna radiate*) and studied the impact of different extraction solvent mixtures between ethanol, methanol and water by MAE. Water extracted more carbohydrates and other non-bioactive compounds. However, despite the higher yield, water was less selective than alcohol mixtures as it also extracted non-bioactive carbohydrates, thereby producing bioactive extracts of lower purity.

As shown previously, pH affects extraction yields due to different forms of ionizable analytes. Machado *et al*. [43] compared different extracts obtained with an ethanol:water mixture to a mixture with an acidic pH (pH=2). The acidic solvent improved the global yield, but it did not improve the yield of phenolic and anthocyanin content. As a result, selectivity towards these compounds was lower. pH can also impact the plant matrix, as acidic conditions improve the breakdown of different cell walls. Qu *et al*. [44] studied the impact of pH on the extraction of seed oil from yellow horn. Reducing pH seemed to improve the oil release by changing the stability of oil bodies in the cell walls, thereby helping the release of lipids. However, for more acidic conditions (from pH=4 to 3), the extraction yield was no longer improved and this is possibly explained by the proteins that coalesced, which stopped oil release by blocking it in cells. This highlights the fact that pH can affect selectivity by changing the plant cell organization, thereby modifying the release of compounds (in the present case, lipids).

In addition to water, additives can also tune extraction selectivity. It is possible to use aqueous two-phase systems (ATPS) for plant extraction. ATPS are generally composed of alcohol and water with inorganic salts. Depending on their charge density and hydration capacity, salts can change solvent properties. For instance, water and ethanol are miscible. By adding salts, their hydration by water will reduce

miscibility between ethanol and water. Ethanol is then excluded from the upper part of the mixture. For example, Guo *et al*. [45] used different salts ($(NH_4)_2SO_4$, KH_2PO_4, $CaCl_2$, NaCl and sodium citrate) to extract lignans (schizandrin, schisantherin A and deoxyschizandrin) from *Schisandra chinensis* (turcs.) Baill seeds by UAE. The ATPS excluded ethanol in the upper part but also other water-free molecules, and in the present case, lignans. Excluding lignans during the process enhanced extraction by maintaining a maximum concentration gradient between plant and solvent, thereby favoring their solubilization. Although yields were similar to classic ethanol extraction, purities increased: the purity of the three target compounds doubled with UAE-ATPS compared to classic UAE-ethanol extraction. This technique was also used by Cheng *et al*. [46] to extract polysaccharides from *Gentiana scabra Bunge* by MAE. This two-phase system allowed the selective recovery of polysaccharides in the upper part, enhancing the purity, and hence the selectivity. Polysaccharides that are soluble in ethanol (homopolysaccharides made of glucose for example) were better extracted in the upper phase while those soluble in water (heteropolysaccharides made of arabinose, galacturonic acid for example) remained in the bottom phase. This is a selective way of extracting different groups of polysaccharides.

The solvent plays a major role in solid-liquid extraction. Its polarity directly influences the compounds extracted, from non-polar ones with the extraction of alkanes using hexane [25] to the extraction of carbohydrates using water [42]. In addition, green solvents such as NaDES proved to be effective for the extraction of anthocyans [38]. However, in the last few decades, new modern extraction techniques have been developed in order to improve extraction both in terms of efficacy and in the way they are obtained: greener, safer and more cost-effectively. Different physical effects are put to advantage to intensify the extraction process and four techniques will be detailed in this review.

3 Selectivity in modern liquid extraction techniques

Ultrasound-assisted extraction (UAE), microwave-assisted extraction (MAE) and pressurized fluid extraction (PLE) can provide selectivity either during a pre-processing step, or during an extraction process, or both. In this review, selectivity during extraction steps is examined for different techniques.

3.1 Ultrasound Assisted Extraction (UAE)

Ultrasounds were discovered at the end of the XIXth century. These acoustic waves have been applied to food processing as a new green technology, but also in the pharmaceutical, nutraceutical and cosmetic fields.

The use of ultrasound enhances the extraction mechanism. These waves, at certain frequencies and amplitudes, create cavitation bubbles which, when they reach a non-stable point, release high temperature and high pressure by imploding. This phenomenon can break cell walls and favor the release of metabolites. Several parameters can modulate ultrasonic waves. The two main ones are the frequency (Hz) and the amplitude (MPa). Power (W) is the amplitude over time and intensity is power over surface area (W/m). These parameters change ultrasonic waves and can interact differently with plant samples.

The frequency of ultrasound waves is an important factor. However, no article was found demonstrating significant extraction selectivity by modifying the frequency. Chen *et al*. [47] studied the impact of different factors such as solvent, temperature but also ultrasonic frequency (from 2 to 8 kHz) on the extraction of betulin from white birch bark. However, frequency seemed to have a less significant effect than the solvent on betulin purity.

Ultrasound power, on the contrary, has shown a significant effect on selectivity. Alvez-Filho *et al*. [48] focused on the extraction of chlorogenic acids from sweet potato peels. Different power densities from 0 to 50 W/L (equivalent to 500 W in this case) were applied during the extraction and revealed that some compound yields such as 4,5-dicaffeoylquinic, 3-caffeoyl-4-feruloylquinic, and 3-caffeoylquinic acids improved with intensity. These compounds result from hydrolysis reactions on other molecules such as tricaffeoylquinic acid. This reaction is due to the formation of OH radicals, caused by ultrasonic waves, which produce H_2O_2. Hydrogen peroxide and hydroxyl radicals can induce a hydrolysis reaction. This article highlighted the fact that ultrasound-assisted extraction can be used to extract or modify solutes by adjusting the power, resulting in a selective process. Sousa *et al*. [49] observed similar results in an earlier study on gallic acid formation from other polyphenols extracted from *Phyllanthus amarus* using of different intensityrange (99 to 301 W/cm^3). They demonstrated that a higher gallic acid content was obtained with the highest intensity during the longest extraction time tested (9 min). Hydrolysis

reactions were also observed on polysaccharide extraction from tea flower by Wei *et al*. [50]. Ultrasonic waves seem to be able to cut polysaccharide chains into small pieces, affecting the selectivity of the process. The same effect on polysaccharide was studied by Zhu *et al*. [51] on pomegranate peel, varying the power from 100 to 200 W.

Differences can also be seen with different instruments. Jacotet-Navarro *et al*. [52] compared three ultrasonic devices (bath, reactor and probe) by extracting rosmarinic, carnosic and ursolic acid from rosemary leaves. Differences were observed regarding the yield of these compounds and their purities. These differences were due to the different ultrasonic power provided by each device.

Independently of ultrasound waves' characteristics, it is also possible to use temperature in order to optimize the extraction process. Ramić *et al*. [53] studied the impact of different parameters such as temperature (30 to 70°C) and ultrasonic power (72 to 216 W) on the extraction of polyphenolic compounds from *Aronia melanocarpa* by-products. Optimized conditions were found for different groups: Total Phenolic (TP), Total Flavonoid (TF), Monomeric Anthocyanins (MA) and Total Proanthocyanidin content (TPA). The optimal temperature for all families was 70°C while the best ultrasonic power was around 200 W. However, the effect of ultrasonic power did not appear to be very significant compared to temperature. MA content decreased with high temperature (70°C) and long extraction time (90 min), suggesting degradation effects. Other compound families (TP and TF) showed an increasing extraction yield with temperature, indicating good thermal stability. It is therefore possible to selectively extract TP, TF and TPA from MA by using high and optimized temperatures with a long extraction time (90 min).

Chemat *et al*. [54] compared the impact of temperature on the yield and purity of artemisinin from *Artemisia annua* L. between conventional extraction and UAE. They showed that UAE with high temperature increased the extraction yield, but that the purity of artemisinin decreased due to the enhanced extraction of other compounds. Similar results were obtained by Lavoie *et al*. [55] with the extraction of betulinic acid from *Betula alleghaniensis* and *B. papyrifera*. The concentration of this compound increased with temperature. However, the extraction was more selective at low temperature, yielding purer extracts that were not contaminated with squalene.

To conclude, ultrasonic waves enhance plant extraction by facilitating cell wall breakdown and compound release. However, other mechanisms induced by different intensities [48] (chlorogenic acids from sweet potato peels), temperatures [53] (polyphenolic compounds from *Aronia melanocarpa* by-products) or devices [52] (by the comparison of bath, reactor and probe for the extraction of rosmarinic, carnosic and ursolic acid from rosemary leaves) can affect extraction and even selectivity. For example, thermal degradation and hydrolysis can chemically modify the solutes, making it possible to selectively obtain solutes. All the above-mentioned articles demonstrate how ultrasonic waves can change the extraction process, resulting in different selectivities.

3.2 Microwave Assisted Extraction (MAE)

Microwave-Assisted Extraction (MAE) uses microwave technology in order to heat a solid and liquid mixture. Heating is induced by microwave irradiation absorbed by molecules depending on their dielectric constant. Polar molecules with a high dielectric constant (*i.e.* water with a dielectric constant of 78.5 at 25°C, ethanol with 24.3 at 25°C) are able to absorb this energy and re-emit it, resulting in heating the system, whereas solvents with a low dielectric constant such as hexane (1.87 at 25°C) are insensitive to microwaves.

The main parameter for microwave-assisted extraction is temperature. It is possible to change the temperature by changing the irradiation duration and power. In practice, the temperature can be set by regulating the irradiation power in order to maintain the right temperature. Conversely, it is also possible to use power intensity directly.

Power must be considered a key parameter in order to optimize extraction when using MAE. Chen *et al*. [56] extracted trans-resveratrol from tree peony seed oil-extracted residues. Changing the microwave irradiation power impacted the yield of resveratrol: increasing the power from 120 to 385 W increased the yield (from 1.2 µmol/g to 2.9 µmol/g) with a similar purity level (between 80 and 90%). This can be due to increased diffusivity of the solvent, induced by the irradiation energy coming from the plant matrix to the solvent [57]. However, from 385 to 700 W, the yield decreased. Excessive irradiation can cause internal over-heating, leading to carbonization and then other reactions such as isomerization and/or degradation of the product. Kaur *et al*. [58] observed a similar behavior of swertiamarin, amarogentin

493 and mangiferin content as a function of irradiation power. The best yield was
494 observed around 500 W for the first two compounds, or 550 W for the third one.

495 As in UAE, temperature itself can selectively impact the extraction of
496 compounds. Ruiz-Aceituno *et al*. [59] selectively extracted different sugars (inositols
497 and inulin) from artichoke external bracts using temperature and MAE. The highest
498 inositol yields were obtained at low temperature (50°C) while inulin was better
499 extracted at 120°C. Moreira *et al*. [60] studied the impact of solvent using different
500 alcohol-water mixtures on polyphenol extraction from apple tree wood. They showed
501 that, at 100°C, mixtures increased the total phenolic content compared to pure
502 methanol, ethanol or water. This can be attributed to the high dielectric constant of
503 water, which increases energy absorption by the solvent mixture and thus, by
504 increasing the temperature inside the sample, leads to an easier release of
505 compounds. This variation of power with different ethanol-water compositions was
506 studied by Koyu *et al*. [61]. Water is a good solvent for the absorption of microwaves
507 due to its high dielectric constant. It was observed that mixtures containing high
508 amounts of water (*e.g*. 65%) required higher microwave irradiation power (500 W)
509 than mixtures with lower amounts of water (30%, 300 W) in order to extract the same
510 anthocyanin content. This can be explained by the fact that solvents that absorb
511 fewer microwaves can induce more waves in the sample and ultimately improve
512 extraction.

513 It is also possible to irradiate the plant samples directly and use residual water
514 as the extraction solvent. Michel *et al*. [62] evaluated this technique for the extraction
515 of antioxidants from sea buckthorn (*Hippophaë rhamnoides L.*) berries. This
516 technique was considered as a good alternative for the extraction of polar
517 antioxidants (i.e. quercetin and isorhamnetin) which are usually not extracted with
518 other techniques such as aqueous maceration or simple pressing. In addition, this
519 technology can be used for other processes such as hydrodistillation (HD). Using
520 only residual water, Lucchesi *et al*. [63] extracted essential oil from *Elletaria*
521 *cardamomum L.* They observed that, compared to classical hydrodistillation,
522 oxygenated compounds were better extracted using solvent-free microwave
523 extraction. The absence of solvent likely reduces thermal and hydrolysis reactions
524 that may degrade oxygenated compounds.

To conclude, MAE can induce selectivity through irradiation power, which can play a role as seen for the extraction of trans-resveratrol from tree peony seed oil-extracted residues [56]. Temperature (induced by irradiation) also influences selectivity for the extraction of different sugars (inositols and inulin) from artichoke external bracts [59]. All the results obtained may come from selective heating due to solvent composition or plant matrix.

3.3 Pressurized Liquid Extraction (PLE)

In many studies, this technique has been used to extract pollutants from natural matrices such as soils, but others have focused on the extraction of metabolites from plants. This technique applies pressure in order to heat the extraction solvent above its boiling point. Thus, it enhances extraction efficiency by reaching higher temperatures than conventional extraction (maceration, soxhlet, etc.). Higher temperatures lead to a higher solvent solubility capacity, to a lower viscosity improving penetration of the solvent into plant cells, and to a reduction in solute-matrix interactions. All these effects lead to an improvement in the extraction yield, and may then lead to a decrease in selectivity.

The role of temperature (from 80 to 125°C) on extraction selectivity was reported by Dunford *et al*. [64] when extracting policosanol (a long-chain alcohol) from wheat straw, germ and bran. A higher temperature resulted in no significant change in policosanol extraction but in a higher global yield, resulting in a decrease in selectivity. An increase in the extraction yield of p-coumaric acid, trans-ferulic acid, rutin and hesperidin related to a temperature increase (62 and 90°C) was also observed by Gòmez-Mejìa *et al*. [65] when extracting polyphenols from citrus peel waste. Hossain *et al*. [66] observed different trends as a function of temperature (66 to 129°C) with antioxidants from rosemary. Some compounds were positively affected by temperature (caffeic acid, gallic acids) while others were negatively affected (rosmarinic acid, luteolin-7-oglucoside, apigenin-7-oglucoside, carnosic acid and carnosol). This study confirms that temperature does not always increase extraction yield for polyphenols. Rudke *et al*. [40] studied the impact of different parameters on the extraction of phenolic compounds and carotenoids from buriti (Mauritia flexuosa L.) shell. The impact of temperature (30 to 70°C) differed between these two compound families. Total polyphenol yield was improved at higher temperatures while carotenoids were not strongly impacted by this parameter.

However, because carotenoids are sensitive to high temperature, the yield increase resulting from temperature was maybe hidden by a yield decrease due to degradation, finally resulting in no change observed. Alvarez-Casas *et al*. [67] observed similar degradation results on different polyphenols through the extraction from white grape marc. Some compounds such as gallic acid and catechin were negatively impacted by high temperature (above 100°C) while total phenolic and flavonoid contents were increased, even at the highest temperature. Similar effects were observed by Dobiáš *et al*. [68] for the extraction of esculetin, rutin, scopoletin, 7-hydroxy-coumarin and quercetin from different plant samples. While compound yields improved as a function of temperature, quercetin content decreased from 80° to 100°C.

Benito-Román *et al*. [69] optimized the extraction of β-glucans and phenols at high temperature (from 135 to 175°C) from waxy barley. Temperature had a negative impact on glucan yield and a positive one on total phenolic yield. However, high temperature can lead to a fragmentation of this polysaccharide, explaining the observed decrease in glucan recovery. Ruiz-Aceituno *et al*. [70] extracted different sugars from pine nuts. They highlighted the fact that between different sugars (i.e. inositols, pinitol, …), different behaviors regarding temperature were observed, with some being positively affected, while others were negatively affected. All the above studies showed that it is not easy to predict the impact of temperature, although temperature can improve selectivity.

Pressurized hot water extraction (PHWE) or subcritical water extraction (SWE), which are considered as new “green” extraction techniques, are based on the dramatic change in the dielectric constant of water at high temperature (figure 5 reproduced from [71]). High temperature favors the movement of water molecules that reduces intermolecular hydrogen bonding, and induces a lower polarity. Selectivity behavior of heated water was reported by Ko *et al*. [72] for the extraction of flavonoids from different plant samples using SWE. The maximum extraction temperature for quercetin was 170°C, while the extraction of quercitrin, which contains more hydroxyl groups due to one glycoside substituent, was optimal at 110°C, indicating that it was more soluble when the polarity of water was higher (at the moderately high temperature of 110°C). However, another study by Kumar *et al*. [73] focusing on the same compounds did not show such a clear effect of

591 temperature. This might be due to a shorter extraction time in the latter case. Time is
592 also an important factor, especially at high temperature because it can increase
593 degradation reactions which may occur directly in the extraction cell. Kwon *et al*. [74]
594 observed this degradation effect at high temperature on curcuminoids from Curcuma
595 long L using ethanol-water mixtures. An increase in temperature (from 110 to 135°C)
596 improved curcuminoid content, but an extraction time above 7 min led to a decrease.

597 Pressurized extraction (PLE and PHWE) applies temperature and pressure but
598 in a system that is mainly static for technological reasons. This mode keeps the
599 extraction solvent in contact with the matrix for a certain time, and then a portion of
600 solvent is refreshed ("flush" volume expressed in percentage). Zaghdoudi *et al*. [75]
601 studied the impact of extraction cycles (1 and 5) on carotenoid extraction from
602 Tunisian kaki, peach and apricot at 40°C and with an extraction solvent composed of
603 methanol:methyl-tetrahydrofuran 20:80 v/v. The study demonstrated that different
604 carotenoids are not affected in the same way when the number of cycles changes.
605 Some compounds, such as lutein, were not affected, whereas others (carotene,
606 zeaxanthin, cryptoxanthin) showed a yield decrease with a higher number of cycles.
607 Before each new cycle, part of the solvent is renewed. This induces changes in the
608 compounds, which prefer to migrate to a fresh solvent than to a solvent already
609 containing solutes. This difference can lead to selectivity.

610 In conclusion, temperature can be considered as the main optimizing parameter
611 for PLE. Temperature may impact the selective extraction of the compounds
612 positively or negatively, depending on their chemical structure, as observed in many
613 of the papers discussed in this part. In addition, even if pressure allows the use of
614 temperatures higher than the solvent boiling point, it is not always necessary to apply
615 excess heat. What is more, the role of the number of cycles, which induces a
616 pseudo-dynamic extraction, on the selectivity of extraction has been little studied.

617 This part has described three techniques (UAE, MAE and PLE) based on
618 selectivity results. Each of them has advantages due to their technical parameters
619 such as: power of ultrasonic waves, power intensity for microwaves and temperature
620 for pressurised extraction. They all also have advantages over classical extraction
621 methods, beyond the apparatus required, based on their lower solvent consumption,
622 speed of extraction and energy consumption. Nevertheless, the main parameter
623 influencing selectivity is not the physical parameters but rather the chemical nature of

624 the extraction solvent. Consequently, and because of this major effect of the solvent,
625 it is difficult to favor one technique over another in terms of selectivity. The easiness
626 of the scale-up of these techniques for industrial processes should also be taken into
627 account.

628

629 ## 4. Supercritical Fluid Extraction (SFE)

630 Supercritical fluid extraction has been widely studied and is usually considered
631 a green extraction technique [76,77] owing to the use of a green and renewable
632 solvent: carbon dioxide. While other fluids can be used in plant extraction (such as
633 propane), CO_2 has more advantages such as non-toxicity and thermodynamic
634 parameters, which facilitate its use in the supercritical state (above 31.1°C and 7.4
635 MPa). This review will thus focus on supercritical extraction using carbon dioxide.

636 Figure 6 presents a scheme of a supercritical fluid extractor. In green, the
637 parameters that can lead to selectivity changes are highlighted. All these selective
638 points are discussed in this review.

639 A first part focuses on supercritical carbon dioxide (Sc-CO_2) interactions, *i.e.* on
640 solubility. Parameters such as pressure, temperature and modifier can change these
641 Sc-CO_2 properties. The extraction of non-polar molecules (lipids, terpenes, etc.) is
642 examined first, followed by successively more polar molecules.

643 A second part describes more technical aspects, such as the different extraction
644 modes (static, dynamic), the vessel geometry and sequential extraction.

645 ### 4.1 Solvent selectivity in SFE

646 Supercritical carbon dioxide is a particular extraction solvent. Due to its
647 compressibility, it is sensitive to pressure and temperature changes. Density can
648 change with pressure (an increase in pressure leads to an increase in density) and
649 with temperature (an increase in temperature leads to a decrease in density). Density
650 change may modify interactions with the compounds, and thus their extraction. In
651 addition, a co-solvent, often called modifier, can be added in order to modulate the
652 polarity of Sc-CO_2. For instance, adding an alcoholic modifier (such as ethanol) to
653 carbon dioxide increases the polarity of the extraction fluid.

4.1.1 Lipophilic compounds

Due to the low polarity of carbon dioxide, supercritical fluid extraction has been widely applied to oils and more particularly lipids. Lipids are a large family with different subcategories (for example glycerides, phospholipids, waxes…). Sc-CO_2 SFE has been involved in oil removal processes in order to replace the classical process using n-hexane. Markom *et al*. [78] optimized process parameters to recover crude palm oil. After varying temperature (40°C to 60°C) and pressure (11 to 20 MPa), they studied the extraction kinetics and monitored fatty acid (FA) chain lengths (C12 to C20, saturated and unsaturated) in the glycerides extracted. For any conditions and any related density, light fatty acids such as C12:0 and C14:0 were extracted at the beginning of the process while heavier chains were extracted later. The FA chain length was the most influential parameter for selectivity compared to unsaturation number. It was then possible to collect lighter or heavier fractions of glycerides based on their extraction kinetic differences. Moreover, using a slower extraction kinetic and the right CO_2 density can induce a longer extraction process, making it easier to collect separate fractions (with light or heavy compounds).

In the field of oils and fats, Free Fatty Acid (FFA) content is an important property of oils. It can affect flavor perceived as a metallic taste. FFA come from a lipolysis reaction directly in oil/fat samples. The content of FFA was studied by King *et al.* [79] as a function of different pressures and temperatures. In conditions where the Sc-CO_2 density was the lowest (40°C and 13.8 MPa), larger amounts of FFA were extracted. Then, FFA content in the extracted oil decreased when the temperature increased (up to 100°C). Pressure and temperature had a selective impact on FFA content. To conclude, FFA can be considered as light lipids and thus, require low-density Sc-CO_2 to be extracted. They are similar to short chain glycerides.

Dos Santos Garcia *et al*. [80] worked on the extraction of *Mucuna* seed oil in order to produce defatted meal. Their study also focused on the extraction of L-DOPA (3,4-dihydroxyphenylalanine), an amino acid with antioxidant properties. The aim was to obtain an alternative to other conservatives, such as butylated-hydroxy-toluene (BHT), butylated-hydroxy-anisole (BHA), or tocopherols, which are usually added to avoid oxidation. *Mucuna* seeds are known to be a high-yielding source of L-DOPA. Variation in the pressure (15 to 25 MPa) and temperature (40 to 60°C)

687 showed that both L-DOPA and oil yield increased with CO_2 density. However,
688 temperature had no visible impact on the chemical distribution of fatty acids. In a
689 different paper, Salvador *et al*. [81] focused on the extraction of oil from pecan nut
690 cake. After carrying out different extractions with various pressure and temperature
691 settings, it appeared that a lower pressure (10 MPa), and therefore a lower density of
692 Sc-CO_2, may advantage the extraction of saturated fatty acids. No significant change
693 in the ratio between saturated and unsaturated fatty acids was observed with
694 pressure changes (from 15 to 30 MPa). From a certain pressure (especially 15 MPa),
695 pressure did not seem to have much impact on the fatty acid profile of extracted oils.
696 However, the use of a modifier showed greater differences. Couto *et al*. [82]
697 compared the oils extracted with and without modifier (ethanol at 6.5 wt%). The ratio
698 of saturated (S) and unsaturated (U) fatty acids was calculated with experiments
699 using the same pressure and temperature (20 MPa and 50°C). Results showed that
700 using a modifier improved the recovery of saturated acids (such as lauric, myristic or
701 arachidonic acids) over unsaturated ones. The S/U ratio was around 0.9 without
702 modifier and below 0.5 with 6.5% of ethanol.

703 Docosahexaenoic acid (DHA) is an omega-3 fatty acid present in different oils
704 (from plant and fish). It is known for its beneficial properties especially for health
705 (brain functions, pregnancy …). Tang *et al*. [83] focused on the selectivity of DHA
706 applied to oil-rich microalgae. Different modifiers such as petroleum ether, acetone,
707 methanol and ethanol were tested. Using ethanol or methanol as modifier increased
708 the content of unsaturated lipids extracted (from 30 to 100%) and thus the selectivity
709 *vs.* saturated lipids. Increased pressure (up to 35 MPa) resulted in a higher extraction
710 efficacy but too high a pressure (above 35 MPa) caused the extraction of impurities.
711 In a second step, temperature was also optimized. Temperature increase improved
712 mass transfer by increasing the vapor pressure of solutes. However, from 40°C,
713 increasing temperature decreased the Sc-CO_2 density and hence the solubility of
714 compounds. This indicates that pressure, temperature and modifier can all modify
715 Sc-CO_2 behavior in order to selectively extract DHA, but it also reveals the
716 complexity of the influence of these three parameters.

717 Phospholipids are part of the polar lipid family. Montanari *et al.* [84] investigated
718 selectivity applied to phospholipids in soybeans using Sc-CO_2. Increasing the
719 pressure (up to 68.9 MPa) increased the total phospholipid content. However, when a

720 lower pressure (16.6 MPa) was applied, differences between the phospholipid
721 families (phosphatidylcholine, phosphatidyl-ethanolamine, a-phosphatidylinositol)
722 were observed. The percentage of phosphatidylcholine decreased from above 70%
723 of total phospholipids down to 20%. Conversely, the proportions of phosphatidyl-
724 ethanolamine and a-phosphatidylinositol increased. No significant change was
725 observed when temperature (60°C to 80°C) was tested. In addition, it was necessary
726 to add a modifier (here 10% ethanol) to Sc-CO_2 in order to extract phospholipids.

727 In oil refining, the non-saponifiable fraction has interesting uses especially in
728 cosmetics. It is composed of fatty esters (waxes), sterols, squalene, triterpenes, etc.
729 Felföoldi-Gàva *et al*. [85] studied the influence of modifier (ethanol at 0, 5 and 10%),
730 pressure (30 to 45 MPa) and temperature (40 to 60°C). It was observed that the non-
731 saponifiable content can be decreased by increasing the temperature or increasing
732 the modifier percentage. As expected, increasing the polarity of the extraction solvent
733 by adding ethanol to Sc-CO_2 favored the extraction of polar lipids against less polar
734 compounds. Martins *et al*. [86] optimized SFE parameters in order to extract sterols
735 from *Eichhornia crassipes* biomass, which is classified as an invasive plant. They
736 focused on 4 sterols: stigmasterol, β-sitosterol and methylcholesterol. The modifier
737 (ethanol) had more impact on sterol yields than on the total yield, whereas pressure
738 and temperature did not seem to be selectively significant. However, the β-sitosterol
739 content had a different behavior and was better extracted at high pressure (30 MPa).
740 In this case, it was the most abundant compound, so these conditions were selected.
741 Sovova *et al*. [87] studied the extraction of 20-hydroxyecdysone from *Leuzea*
742 *carthamoides* DC. They observed that this steroid was preferably extracted at the
743 highest pressure tested (27-28 MPa at 60°C), confirming that this kind of molecule
744 requires high pressure, and therefore a high Sc-CO_2 density, to be extracted.

745 de Melo *et al*. [88] studied the recovery of stigmasterol from water hyacinth
746 using Sc-CO_2. The influence of temperature was observed at constant pressure (20
747 MPa). Between 40°C and 60°C, the lower temperature provided the best extraction
748 yield due to a higher Sc-CO_2 density. Besides, selectivity was calculated from
749 stigmasterol content and total extract content as a function of extraction time. In this
750 case, a selectivity value above 1 indicated a favorable extraction of this compound.
751 As expected due to the lower yield, selectivity at 40°C was better than at 60°C.
752 Moreover, at this temperature of 40°C, the extraction selectivity varied with time (for

753 instance between 1 h and 5 h extraction). This means that the first fractions obtained
754 during the first hour were not selective. These results indicate that the extraction
755 kinetic plays a key role in selectivity.

756 Dias *et al*. [89] studied the selective extraction of spilanthol (a fatty acid amide)
757 from *Spilanthes acmella* flowers. Different temperatures (50 to 70°C) and pressure
758 values (15 to 49 MPa) were tested. The selectivity was calculated as the ratio of
759 spilanthol content over total content. The best selectivity was obtained at the highest
760 temperature tested (70°C), while the best pressure was the intermediate point tested
761 (32 MPa). This demonstrates the complexity of plant extraction. Notwithstanding this
762 difficulty, selectivity (spilanthol/yield ratio) and spilanthol yield were both multiplied by
763 5 in the optimized conditions compared to initial temperature (50°C).

764 Supercritical fluid extraction using Sc-CO_2 is a suitable technique for lipid
765 extraction. This review has highlighted some selective ways to extract specific lipid
766 families from non-polar ones (i.e. waxes) to more polar ones (i.e. phospholipids). This
767 selectivity comes from Sc-CO_2 density changes, and sometimes also from the
768 addition of a modifier. Non-polar compounds (i.e. waxes) are extracted at high
769 density while more polar compounds (i.e. FFA, short chain glycerides) are better
770 extracted using low density. More polar compounds (i.e. phospholipids) also require a
771 polar modifier in order to be extracted.

772 Also known as vitamin K, tocopherols are fat-soluble compounds, which can be
773 extracted from oils by SFE. Montañés *et al*. [90] studied the extraction of apple seed
774 oil and its tocopherol content, between 43 and 63°C, and 300 to 130 MPa (a very
775 high pressure). Increasing the temperature (from 53 to 63°C) led to a decrease in
776 tocopherol content, except for δ-tocopherol, due to compound degradation.
777 Nevertheless, the high pressure improved extraction yield both for oil and tocopherol
778 [90].

779 SFE using Sc-CO_2 can also be used to selectively extract other metabolites
780 such as terpenes. These metabolites are composed of isoprene units (C_5H_8).
781 Terpenes are rather non-polar molecules. Isoprene units are organized in a linear or
782 cyclic way, either oxygenated or not, and compose different families ranging from
783 monoterpenes such as limonene, to tetra-terpenes such as carotenes, and even to
784 natural rubber.

785 Pavlic *et al*. [91] studied the influence of pressure and temperature on
786 monoterpene content from sage herbal dust. Monoterpene content increased with
787 pressure (from 10 to 20 MPa at 50°C), related to a density increase. But this content
788 decreased for pressures above 20 MPa up to 30 MPa, due to a loss of selectivity
789 toward monoterpenes. Regarding temperature, selectivity decreased when the
790 temperature increased (from 40°C to 50°C), due to a decrease in density. However,
791 selectivity increased again from 50°C to 60°C due to the increase in the vapor
792 pressure of the analytes. Reverchon *et al*. [92] investigated the SFE of jasmine
793 concrete, a product used in fragrances and necessary for the production of various
794 other fragrances. This product undergoes fractionation steps to remove unwanted
795 compounds (fatty acids, waxes, etc.) in order to obtain a pure product called an
796 absolute. The study showed that under different pressure settings, different ranges of
797 compounds were extracted. The lowest pressure applied was 8 MPa (at 40°C) and it
798 extracted low molecular weight compounds (i.e. linalool, benzyl acetate). A second
799 step using Sc-CO_2 at 8.5 MPa (and the same temperature) was used. This difference
800 may seem insignificant but it has a significant impact on Sc-CO_2 density (25%
801 increase). The second set of conditions extracted heavier compounds such as
802 diterpenes (i.e. phytol), but also undesired compounds such as fatty acid esters (i.e.
803 methyl oleate and ethyl eicosenoate). Then, a last step with Sc-CO_2 at 20 MPa was
804 used in order to extract lipophilic compounds such as waxes (i.e. nonacosane). This
805 work is a perfect illustration of how the selectivity of Sc-CO_2 can be tailored by
806 modulating pressure, and hence its density. Sonsuzer *et al*. [93] also studied the
807 selectivity between different terpene families: monoterpenes, sesquiterpenes and
808 oxygenated monoterpenes, extracted from *Thymbra spicata* oil. They demonstrated
809 that increasing the pressure (from 8 to 12 MPa) decreased the selectivity of
810 monoterpenes. This is explained by the better extraction of the less volatile
811 compounds (sesquiterpenes and oxygenated monoterpene) when the fluid density is
812 higher. Similar results were also observed by Barjaktarovic *et al*. [94] in their study of
813 SFE on *Juniperus communis* L. fruits. Different compound families (i.e.
814 monoterpenes, sesquiterpenes, oxygenated monoterpenes, oxygenated
815 sesquiterpenes and other heavier compounds such as waxes) were studied. Results
816 showed that a lower pressure (8 MPa compared to 10 MPa) gave the best selectivity
817 for the extraction of oxygenated *vs.* non-oxygenated and waxes.

Trabelsi *et al*. [95] extracted terpenes from *Citrus aurantium amara* peels. At a constant temperature and constant percentage of modifier (3 wt% of ethanol), limonene oxide (oxygenated monoterpene), 1,5-heptadiene,3,6-dimethyl, α-caryophyllene (sesquiterpene), 3,9-dodecadien and bicycle[10.1.0]tridec-1-ene were extracted with a pressure above 17 MPa and static time greater than 50 min. They were extracted separately from sabinene, ocimenol (monoterpenes) and α-farnesene (sesquiterpene) which were extracted only at low pressure with a short static time (30 min). Pourmortazavi *et al*. [96] reported similar results regarding the impact of pressure and temperature. However, they investigated the impact of the modifier (methanol, ethanol, dichloromethane and hexane). Hexane (at 5%) was found to be a selective modifier for 1,8-cineole, limonene and δ-3-carene (monoterpenes). While their content was similar to the one obtained with other modifiers at 5%, the number of compounds extracted changed from 22 with other modifiers to 7 with hexane. This demonstrates its good selectivity toward monoterpenes.

Allawzi *et al*. [97] optimized the extraction of Jordanian rosemary essential oil by SFE. The paper also confirmed that a pressure increase (from 7.6 to 9 MPa at 35°C) improved the extraction of monoterpenes (α-pinene and eucalyptol), while methyl esters (i.e. palmitic acid methyl ester, hexadecenoic acid methyl ester) were extracted only at 7.6 MPa. The selectivity between oxygenated terpenes and other terpenes was investigated by Mira *et al*. [98].They carried out SFE on orange peel and showed that the ratios of oxygenated compounds (mainly linalool) over non-oxygenated terpenes was high at the lowest pressure (8 MPa at 20°C) and then decreased when the pressure increased (up to 15 MPa). Then, from a certain pressure (i.e. 15 MPa at 20°C), it increased again but more slightly. It demonstrated that the selectivity of oxygenated compounds over non-oxygenated ones was better when using Sc-CO_2 at low density. The work by Van Opstaele *et al*. [99] confirmed the same behavior. In order to develop hop aromas by SFE, the fraction responsible for floral scent was more significant at low Sc-CO_2 density. One molecule responsible for this floral scent is, among others, linalool. Jokic *et al*. [100] worked on *Salvia officinalis L*. leaves and reported identical conclusions regarding oxygenated monoterpenes.

Glisic *et al*. [101] focused on diterpenes from sage (*Salvia officinalis L*.) and studied 3 different diterpene (D) selectivities: one regarding the selectivity of

monoterpenes and oxygenated monoterpenes ($S_{D/(M+OM)}$), the second with sesquiterpenes and oxygenated sesquiterpenes ($S_{D/(S+OS)}$) and the third with triterpenes, esters and waxes ($S_{D/(T+E+W)}$). These selectivities were plotted as a function of pressure. Increasing the pressure had a different impact on terpenes. For monoterpenes and oxygenated monoterpenes ($S_{D/(M+OM)}$), a pressure increase from 7 to 15 MPa decreased selectivity due to the higher solubility of monoterpenes in low-density Sc-CO_2. Above 15 MPa, this selectivity increased slightly due to an increase in diterpene solubility. In comparison with the other two selectivities (sesquiterpenes $S_{D/(S+OS)}$ and triterpenes $S_{D/(T+E+W)}$), the increase in pressure increased both selectivities, meaning that the solubility of diterpenes increased without increasing that of other heavy compounds. This study confirmed the correlation between the volatility of extracted compounds with Sc-CO_2 density: low-density Sc-CO_2 extracts light terpenes better, while high-density CO_2 improves the recovery of heavier compounds.

Bogdanovic *et al*. [102] optimized SFE in order to obtain diosgenin (sapogenin family) rich extract from fenugreek (*Trigonella foenum-graecum L*.) seeds. Thanks to a response surface methodology, they optimized conditions (24.6 MPa and 43.5°C) in order to increase diosgenin yield with a decrease in total yield, showing the improvement of purity.

Klein *et al*. [103] worked on triterpenoid extraction from uvaia leaves (*Eugenia pyriformis Cambess*.) and particularly on α/β-amyrin. They obtained the purest α/β-amyrin extract using the lowest pressure tested (10 MPa) and the highest temperature (60°C). Higher densities increased yield, but decreased purity. Oliveira *et al*. [104] studied the extraction of *Piper divaricatum* essential oil, focusing on another family of volatile compounds: phenylpropenes. After varying the pressure and temperature parameters, they succeeded in selectively extracting high amounts of eugenyl acetate and β-elemene with low amounts of eugenol and methyl eugenol (at 35 °C and 10 MPa), showing again the selectivity of low density Sc-CO_2.

Morsy *et al*. [105] produced thymol-rich extracts from ajwain (*Carum copticum L*.) and thyme (*Thymus vulgaris L*.). Thymol is a phenol but is also a volatile compound. Different pressure conditions (10.4 and 16.7 MPa at 40°C) were tested and the use of higher pressure improved thymol yield. However, with higher pressures, it was possible to avoid the extraction of unwanted compounds such as

fatty acids (i.e. 9-octadecenoic acid). Because these acids were better extracted at lower pressure (10.4 MPa), thymol selectivity toward fatty acids was improved.

Like lipid extraction, SFE is suitable for terpene extraction, from volatile monoterpenes to non-volatile triterpenes. Low-density Sc-CO_2 favors the selectivity of volatile compounds, whatever their polarity.

4.1.2 Pigments

Pigments are responsible for the color of plants. Carotenoids and chlorophylls are respectively responsible for yellow or green colors. These pigments are important because they are necessary for photosynthesis reactions in plant cells. However, it may be necessary to remove them from plant extracts because of color and stability issues during extraction processes, inducing color changes [106]. Carotenoids often display antioxidant and provitaminic activities that explain the interest in their selective extraction from varied matrices. The studies presented below demonstrate how SFE can selectively extract these compounds.

Carotenoids are divided into two families: carotenes and xanthophylls. The latter group is differentiated by the presence of oxygen atoms, increasing the compound polarity, which may cause them to interact differently with Sc-CO_2. Filho *et al*. [107] studied the impact of pressure (10 to 40 MPa) and temperature (40 and 60°C) of pure Sc-CO_2 on different compounds from the carotene and xanthophyll families. It was shown that oxygen-containing molecules were not, or only weakly, extracted at any setoff pressure and temperature. However, one xanthophyll behaved differently: rubixanthin. This can be explained by the fact that it contains only one hydroxyl group against two for other xanthophylls (*i.e.* cryptoxanthin). Regarding the behavior of carotenes, higher pressure and/or temperature values increased carotene yields. Gomez-Prieto *et al*. [108] confirmed this behavior using *Mentha spicata* L.. In addition, they suggested a sequential extraction of β-carotene and lutein, using first Sc-CO_2 at 40°C and 11.3 MPa for carotene, and then increasing the temperature to 60°C to extract lutein. Contrary to what Filho *et al*. [107] observed, lutein was affected by temperature compared to the other xanthophylls they studied. Chronopoulou *et al*. [109] selectively extracted menaquinon-7 from other carotenoids at low Sc-CO_2 density (10 MPa and 40°C) using *Tetradesmus Obliquus* microalgae. Gomez-Prieto *et al*. [110] extracted trans-lycopene from tomato. At 40°C, changing the density of Sc-CO_2 through pressure

increases (from 7.7 to 28.1 MPa) changed the extraction of the lycopene isomer ratio between *cis* and *trans* forms. At lower density, the extraction of cis-lycopene over the trans form was favored. For densities above 0.65 g/mL (approximately 13.5 MPa), the contrary was observed, showing extraction selectivity between two isomers obtained only with pressure changes.

Wrona *et al*. [111] studied the impact of pressure and temperature on lipids, phenolic and chlorophyll content by carrying out SFE on *Solidago gigantean Ait*. They confirmed that lipidic and phenolic contents increased when pressure increased (up to 80 MPa). But contents decreased when the temperature increased (up to 70°C). However, chlorophyll content was improved using high pressure and temperature. Because pressure had a positive impact on every yield, temperature appeared to be a good factor for the selective extraction of chlorophyll pigments over lipids and phenolic compounds.

Garcia *et al*. [112] studied the influence of temperature (40 to 60°C) and pressure (25 to 35 MPa) on carotenoid and chlorophyll contents. Both families were influenced in the same way: the contents increased with pressure and decreased with temperature. In addition, ethanol was used as modifier at 1 wt% and 5 wt%. The contents of chlorophylls and carotenoids improved with the percentage of modifier. Abrahamsson *et al*. [113] studied the impact of experimental conditions for chlorophyll *a* and carotenoids and confirmed previous observations, especially the impact of modifier (ethanol). However, selectivity can still be improved for these two pigment families. Guedes *et al*. [114] examined the ratio of carotenoids to chlorophyll *a* on *Scenedesmus obliquus* extraction. The maximum ratio was obtained using 25 MPa pressure and 60°C temperature. Even if the chlorophyll content increased as a function of temperature and pressure, carotenoids increased even more, which resulted in a better selectivity. However, this ratio decreased when ethanol was used as modifier due to a great increase in carotenoids and chlorophylls.

Even if SFE using carbon dioxide is an extraction technique of interest for non-polar molecules, it is also possible to selectively extract polar metabolites from plants when modulating Sc-CO_2 properties.

4.1.3. Alkaloids and Cannabinoids

Cannabinoids and alkaloids are known for their pharmaceutical properties [115,116]. Pimentel *et al*. [117] extracted amides (piperovatine and pipercallosidine) from Piper piscatorum (*Trel Yunc*.). With pure CO_2, temperature (40 and 70°C at 40 MPa) had a different impact on these two compounds. While selectivity (expressed in g/100g of extract) increased for pipercallosidine at higher temperature (from 0.004 to 0.031 g/100g), the selectivity of piperovatine did not change significantly (from 0.26 to 0.30 g/100g). This can be explained by autoxidation which can occur for piperovatine at higher temperature, which balances selectivity changes. However, the biggest selectivity changes for these compounds were obtained with a polar modifier (especially ethanol at 10%). At 40°C, the selectivity obtained for pipercallosidine was 0.24 g/100g and for piperovatine it was 0.93. Selectivity was lower at 70°C but this can be explained by the extraction of other compounds due to an increase in solubility in the extraction solvent. Liu *et al*. [118] observed that the modifier can reduce selectivity. They studied the extraction of two alkaloids: evodiamine and rutaecarpine from *Evodia Rutaecarpa*. Different modifiers were tested (at 0.4 mL/min for 2 L/min gaseous CO_2): no modifier, pure methanol and methanol with water at 50, 30, and 5%. Water decreased the yield of evodiamine and rutaecarpine, but also their purity, whereas methanol increased their yield with a similar purity.

Gallo-Molina *et al*. [119] optimized the extraction of tetrahydrocannabinol (THC) from *Cannabis sativa* L. and observed different behaviors. They obtained the highest levels of THC using 2 wt% of modifier (ethanol) at the highest (34 MPa and 60°C) and lowest (15 MPa and 40°C) sets of pressure and temperature. This demonstrates that ethanol can significantly impact Sc-CO_2 behavior even when used in low amounts (2 wt%). Attard *et al*. [120] studied the influence of pressure and temperature for the extraction of waxes and cannabidiol (CBD) from hemp wastes. They observed that at low Sc-CO_2 densities (8 MPa, 35°C), selectivity was high for lipophilic compounds (alkanes and fatty acids) with a low extracted content for other molecular families. At higher density (i.e. 35 MPa and 50°C), other groups of compounds (such as CBD) were better extracted, reducing selectivity for the previous compounds.

4.1.4. Polyphenols

Polyphenols are also part of secondary metabolites and are considered as quite polar plant components. They are of interest due to their antioxidant properties [121].

Antunes-Ricardo *et al*. [122] worked on the extraction of isorhamnetin from *Opuntia ficus-india* L. A higher recovery of this compound was observed with high pressure and intermediate temperature (30 MPa and 50°C). At the highest temperature (65°C), isorhamnetin content decreased while global yield increased. As described previously, an increase in density increases yields, and thus can result in a decrease in selectivity. Another parameter can influence extraction selectivity: the flow rate. A maximum amount of isorhamnetin was obtained at the maximum flow rate (100 g/min) while the maximum global yield was obtained at an intermediate flow rate (80 g/min). When the Sc-CO_2 flow rate increases, it may reduce mass transfer resistance between compounds and extraction solvent, resulting in an improvement of the extraction kinetic. However, increasing the flow rate may prevent the solvent from entering sample pores, thereby decreasing the extraction of other compounds.

Conde *et al*. [123] extracted flavonoids from *Pinus pinaster* wood. They also observed that the extraction yield of polar compounds was higher at high pressure and temperature (25 MPa and 50°C). However, the use of 10 wt% ethanol as modifier also significantly improved the extraction of flavonoids against other compounds. Yilmaz *et al*. [124] confirmed the interest of using ethanol as modifier for the extraction of polar molecules. They investigated the influence of pressure, temperature and modifier percentage on the extraction of catechins (EGC, CT, ECT, EGCG and ECG). Setting the conditions at 30 MPa, 50°C and 20% of ethanol extracted a maximum of GA, EGC and EGCG, while 30 MPa, 30°C and the same modifier were optimal conditions for CT and ECT. The best conditions for ECG were 25 MPa, 30°C and 15% of modifier. These extractions highlight the fact that using high temperature (*i.e*. 50°C) may degrade compounds, resulting in a lower yield (*i.e*., 50°C with CT, ECT and ECG)

Nagavekar *et al*. [125] extracted oleoresin from Curcuma longa and Curcuma amada. They studied the influence of previously tested parameters: pressure, temperature and modifier percentage. They confirmed the need to use high pressure (35 MPa), high temperature (65°C) and polar modifier (ethanol) at 30 wt% in order to extract curcuminoids. These conditions improved both the yield and selectivity of

1011 these interesting polar compounds. Konar *et al*. [126] extracted caffeic acid
1012 derivatives (echinacoside, chlorogenic acid, cynarin and caftaric acid) from
1013 *Echinacea purpurea* aerial parts. They also observed similar results for these kinds
1014 of compounds with high pressure (30 MPa), high temperature (60°C) and modifier
1015 (10% ethanol). Gourguillon *et al*. [127] evaluated different extraction methods (MAE,
1016 PLE and SFE) to extract dicaffeoylquinic acids from a halophyte plant. They
1017 demonstrated the need to use a hydro-alcoholic modifier (EtOH:water 80/20 v/v) at
1018 different percentages (5 to 20%) in order to extract these compounds with SFE.
1019 Chromatographic analysis also showed the selectivity achieved with this polar
1020 modifier regarding polar compounds against less polar compounds. Polyphenols can
1021 also be extracted under their glycosylated forms. However, this requires the use of
1022 highly polar modifiers (i.e. a high percentage of water) which may be incompatible
1023 with supercritical CO_2.

1024 #### 4.1.5. Carbohydrates

1025 Carbohydrates are important molecules from plants, but no studies were found
1026 on their extraction using Sc-CO_2. This can be explained by the same reason stated at
1027 the end of the previous part. Montañez *et al*. [128–130] developed SFE methods on
1028 homemade and commercial carbohydrate samples. Different conditions such as
1029 temperature, pressure and modifier were compared for the extraction of carbohydrate
1030 compounds (lactose, lactulose, galactose, tagatose, etc.). Different alcohols from n-
1031 butanol to ethanol and different mixtures of ethanol and water were tested. Results
1032 highlighted the need for a high-polarity modifier, confirming the necessity to introduce
1033 water in the modifier. These studies confirmed that at high temperature (80°C) high
1034 pressure (30 MPa) and high co-solvent flow rate, the addition of 5% of water in
1035 ethanol selectively modified the carbohydrate extraction [130]. As expected, all the
1036 previous studies show the need to use both high-density Sc-CO_2 and polar modifier
1037 in order to extract polar metabolites.

1038 #### 4.1.6. Selectivity loss

1039 As described previously, Sc-CO_2 behavior can be modulated using different
1040 parameters, but these changes are not always selective towards the target
1041 compounds. This was the case in the study by Naziri *et al*. [131] who worked on the
1042 recovery of squalene from wine lees. As it contains only carbon and hydrogen atoms,
1043 squalene is one of the least polar compounds in plants. Thus high-density Sc-CO_2 is

required, implying high pressure. However, high density will increase the total yield but reduce squalene selectivity. As pointed out in the previous section, a modifier, also known as co-solvent, is often used to increase the extraction capacity of Sc-CO_2 by increasing its polarity. But in some cases, this “improvement” can lead to a decrease in selectivity. This was observed by Valente *et al*. [132]. They worked on the extraction of antioxidant molecules from *Botryosphaeria dothidea*. They observed that antioxidant capacity was reduced using 10 wt% modifier (ethanol) compared to pure Sc-CO_2. Even if a modifier helps to extract more polar compounds, it shows that these new compounds have a lower antioxidant capacity than the less polar ones obtained without a modifier. Pereira *et al*. [133] also showed a selectivity decrease using a modifier for the extraction of lignans from *Phyllanthus amarus Schum* and *Thonn*.

Modulating Sc-CO_2 properties through temperature, pressure and modifier represents an important key point to achieve extraction selectivity. In addition, selectivity can be obtained for a wide range of compounds, from non-polar (squalene)[85] to very polar (carbohydrates)[128-130]. However, certain technical parameters can also affect selectivity.

4.2Technical parameters

4.2.1Extraction modes

Beyond the complexity of Sc-CO_2, other parameters, related to the technology itself, can provide differences in selectivity. This is the case of the extraction modes: static or dynamic. The static mode can be limited by the lower diffusivity of compounds within plant cells reducing their migration into the extraction solvent, whereas the dynamic mode favors compound diffusion by maintaining at the optimum the concentration gradient between the plant and the solvent since the solvent is continuously renewed. Due to these different effects, the extraction of some solutes can be favored. Bermejo *et al*. [134] compared the two modes, using static and dynamic extraction with different modifiers (ethyl lactate, ethyl acetate and ethanol) on caffeine extraction from green tea. A slight change is that a modifier was introduced in the extraction cell with the plant, and then Sc-CO_2 was pumped. It showed that, depending on the modifier used, the static or dynamic mode showed a higher yield for caffeine. For example, with ethyl lactate, a higher concentration of caffeine in the extract (expressed in g of caffeine per g of extract) was obtained with

the dynamic mode (14.3% in static mode and 18.2% in dynamic mode). On the contrary, with ethyl acetate, the dynamic mode seemed to have a negative impact compared to the static mode for the same compound (8.1% in static mode *vs*. 5.5% in dynamic mode). This highlighted the fact that the extraction mode affects extraction yield differently depending on the solvent used. Massias *et al*. [135] confirmed the previous study by showing that some compounds such as flavonoids or phenolic acids could be affected by this mode. Using CO_2:EtOH:H_2O 75:22:3 %mol as solvent, phloridzine was better extracted in static mode while chlorogenic acid was better extracted in dynamic mode. However, no explanations were found to correlate these modes to the kind of compounds affected.

4.2.2. Sequential extraction

Supercritical fluid extraction systems allow the use of successive extraction conditions. It is possible to start extracting the sample at a certain temperature, pressure and percentage of modifier, then use other parameters for a second step, change from static to dynamic mode and so on. Vardanega *et al*. [136] carried out a two-step method in order to extract different terpenes from annatto seeds. They carried out a first extraction step using low density fluid (60°C and 10 MPa) in order to extract lighter molecules (*i.e*. geranylgeraniol) and a second step at higher density (40°C and 20 MPa) to extract heavier compounds (i.e. tocotrienols). Bogdanovic *et al*. [137] developed a 4-step method in order to extract different compounds from Lemon balm (*Melissa officinalis L., Lamiaceae*) at different temperature and pressure settings (respectively 10 MPa/40°C, 30 MPa/25°C, 30 MPa/40°C and 30 MPa/100°C). The contents of the extracts for different families (monoteprenes, sesquiterpenes, diterpenes, fatty acids, methyl esters and alkanes) were evaluated by monitoring the content in specific molecules (*i.e*. geranial for monoterpenes, palmitic acid for fatty acids …). The results demonstrated that some compounds such as monoterpenes and sesquiterpenes were mostly extracted during the first and second steps, while other compounds such as alkanes and methyl esters were extracted during the third and last steps. A similar process was developed by Vigano *et al*. [138] with a 3-step extraction (60°C/17 MPa, 50°C/17 MPa and 60°C/26 MPa) in order to extract respectively tocols (*i.e*. γ-tocopherols, γ/δ-tocotrienols), fatty acids (*i.e*. oleic and linoleic acids) and carotenoids (evaluated with total carotenoid content).

It is also possible to carry out sequential extraction with a modifier. Sökkmen *et al*. [5] extracted caffeine and catechin separately (from green tea) in a 2-step process using respectively pure Sc-CO_2 (25 MPa and 60°C) and Sc-CO_2 modified with ethanol (same pressure and temperature, with 0.5 mL/min of ethanol in 10g/min CO_2 flow). A similar study was carried out by Domingues *et al*., [139] in order to extract fatty acids, long-chain aliphatic alcohols and triterpenoids from *Eucalyptus globulus* bark. Likewise, Serra *et al*. [140], demonstrated that a first step using pure Sc-CO_2 (25 MPa and 50°C) was helpful to recover anthocyanin compounds in the second step with modified Sc-CO_2 (with 10 wt% ethanol). This can be explained by the fact that the first step removed lipophilic and non-polar compounds, which makes anthocyanins more available during the second extraction step. Finally, it is possible to go beyond modified Sc-CO_2 and to use only modifier as the extraction solvent. Bitencourt *et al*. [141] carried out a 4-step extraction starting from a pure Sc-CO_2 step (50°C, 30 MPa), adding modifier (30% wt% ethanol) in the second step, using only modifier (ethanol) in the third step, and finishing with a mixture of ethanol and water. During the first step, unidentified non-polar compounds were extracted. The second step extracted β-ecdysone and less polar saponins. The third, pure ethanol step extracted β-ecdysone with more and less polar saponins. Finally, hydro-alcoholic extraction showed more polar saponins. This extraction process can selectively extract different saponins based on their polarity. However, using only ethanol or hydro alcoholic solution during extraction is moving away from the realm of supercritical fluid extraction.

4.2.3. Extractor geometry

Another technical aspect that can affect selectivity is the geometry of the extraction vessel. Zabot *et al*. [142] worked on two different extractor geometries which led to two different effects. The first one was on temperature diffusion. Different shapes of the vessel may cause different temperature profiles. As we saw previously, temperature changes Sc-CO_2 behavior, which may in turn change solubility. The second change is due to carbon dioxide velocity changes. This change can impact the extraction kinetic, and then result in a faster extraction process. In other words, an equivalent extraction time would require less solvent in a more efficient extractor. The same authors applied these changes to rosemary extraction [143]. Results confirmed that different components from volatile (monoterpenes) to non-volatile

(terpernoic acids …) compound families can be extracted differently depending on the extractor geometry.

4.3.4. Separators

The separator, which is located after the extraction cell, controls precipitation using the appropriate pressure and temperature. The controlled release of pressure can selectively precipitate particular compounds over others. Vasquez *et al*. [144] used this feature in order to purify squalene from vegetable oil. High pressure was needed to extract this compound. However, it has been shown previously [131] that high pressure was unable to improve selectivity towards squalene extraction. Varying the collector pressure from high to low (23 to 15 MPa) made compounds precipitate according to their thermodynamic properties. Thus, it was possible to improve the purity of this compound using separators. A similar study was carried out by Reverchon *et al*. [145]. Likewise, Baldino *et al*. [146,147] used these separators in order to separate cuticular waxes from other active compounds using different pressure settings (25 and 20 MPa). They also used the same process but with a low temperature (-7°C) in the collector, in order to remove paraffinic compounds from *Artemisia annua L.* extract. Rovetto *et al*. [148] used a 3-separator system in order to extract different fractions of *Cannabis sativa L*. extract. Three conditions were used: 13 MPa/ 55°C; 9 MPa / 55°C; 6 MPa / 35°C. The results demonstrated that cannabinoids were mainly collected in the first separator (with cuticular waxes).

As previously presented, Schukla *et al*. [149] extracted volatile and non-volatile compounds using high-pressure Sc-CO_2. Then two separators were used in order to separate these two families. The first separator was set at 17.5 MPa and the second one at 4 MPa. These pressures resulted in the separation of non-volatile compounds in the first separator and then the collection of volatile compounds in the second one. Cavero *et al*. [150] carried out a similar study in order to selectively precipitate antioxidant compounds in a first separator with Sc-CO_2 at high density (10 MPa and 40°C), and recover volatile compounds (essential oil) in a second separator at a lower density (2 MPa and 20°C). In the same vein, Fornari *et al*. [151] separated volatile (*i.e*. thymol) from less and non-volatile compounds (*i.e*. carnosic acid) using two separators (at 10 MPa and 1 atm). Separation using separators can be more selective when pressures are closer. Costa *et al*. [152] carried out the extraction of volatile compounds from *Thymus lotocephalus* using separators at 18 MPa and 12

MPa. The first separator extract was composed of sesquiterpenes such as globulol (a caryophylene oxide), while the second separator extract was composed of lighter compounds such as linalool or 1,8-cineole. Fuentes-Gandara *et al*. [153] carried out extraction using pure Sc-CO_2 and modified CO_2 with different percentages of ethanol and water (50% modifier with pure ethanol, 50/50 ethanol/water, and pure water) in order to extract allelopathic compounds from *Helianthus annuus L.* leaves. The extracts were then fractionated using three collectors at different pressure and temperature settings (20 MPa/45°C; 9 MPa/40°C; 1 atm/30°C). This combination of conditions allowed the selective recovery of different bioactive compounds. For example, using CO_2:water 50/50 extraction conditions allowed the collection of the free chlorophyll fraction in the third collector. This fraction was also rich in bioactive compounds.

Supercritical fluid extraction provides high selectivity due to the numerous parameters that can affect it. This high selectivity may come from pure Sc-CO_2 density differences, from the addition of various modifiers, and also from technical parameters (vessel geometry, separators), or even from the kind of plant (terrestrial plant, algae…). A large range of compounds can be addressed by this selectivity, from volatile terpenes to non-polar waxes and polar carbohydrates. This last part of the review has described the different possible approaches providing selectivity, in relation to the extraction objective. However, the same parameters can also lead to a decrease in selectivity.

5 Conclusion

This review has surveyed the key points that need to be considered in order to modify selectivity during the extraction of bioactive compounds from plants. In particular, it has highlighted the importance of the chemical nature of the solvent, and of the physicochemical properties of the different techniques: wave modulation using UAE, microwave irradiation power using MAE, pressure with PLE and finally pressure, temperature and modifier addition for supercritical extraction using carbon dioxide.

The aim of this review was to provide an overview of the different possibilities as a function of technique and molecular family. For techniques using liquid solvents (MAE, UAE and PLE), it highlighted the strong impact of the extraction solvent in

improving selectivity. Moreover, physical parameters can be more suitable for some compounds and matrix couples. For example, microwaves favor the extraction of polar compounds in fresh plants thanks to their dipole moment.

SFE is a major technique for selective extraction. Due to Sc-CO_2 behavior, it is possible to modulate its density with pressure and temperature and thus to favor or disfavor the extraction of ta compounds. Low density (with pressure below 15 MPa and temperature below 40°C) will help recover volatile compounds (*i.e.* monoterpenes, …) while higher densities (with pressures above 25 MPa and temperatures below 40°C) will extract non-volatile and non-polar compounds (*i.e.* tocopherols, non-saponifiable lipids) more efficiently. For more polar compounds (*i.e.* phenols), the introduction of a polar solvent as modifier improves their yields. Other parameters can affect selectivity such as vessel geometry, separators, and so on.

Considering all these different effects, it is also possible to develop new systems by coupling many parameters that was described before. This represents a good perspective for selective extraction.

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Figure and table captions.

Figure 1: Metabolite families and solvents organized as a function of log P and formulas of different metabolites.

Figure 2: Hansen solubility parameters of solvent (in blue: classical solvents, in green: green solvents, in purple: carbon dioxide)

Figure 3: Hansen solubility parameters of different metabolites and their formulas

Figure 4: Hansen solubility parameters (HSP) of different compounds (in yellow: different rosmarinic acid (RA) HSPs, in green: green solvents, in brown: organic solvents, in blue: polar natural products, in blue: mid and non-polar natural products)

Figure 5: Water dielectric constant variation as a function of temperature

Figure 6: Classical Supercritical Fluid Extractor (SFE) scheme highlighting selectivity key points (green)

Table S1. Table of names, log P and formulas of lipids cited in the review (part 1)

Table S2. Table of names, log P and formulas of lipids cited in the review (part 2)

Table S3. Table of names, log P and formulas of terpenes cited in the review (part 1)

Table S4. Table of names, log P and formulas of terpenes cited in the review (part 2)

Table S5. Table of names, log P and formulas of terpenes cited in the review (part 3)

Table S6. Table of names, log P and formulas of coumarins cited in the review

Table S7. Table of names, log P and formulas of pigments cited in the review

Table S8. Table of names, log P and formulas of cannabinoids and alkaloids cited in the review

Table S9. Table of names, log P and formulas of polyphenols cited in the review (part 1)

Table S10. Table of names, log P and formulas of polyphenols cited in the review (part 2)

Table S11. Table of names, log P and formulas of polyphenols cited in the review (part 3)

Table S12. Table of names, log P and formulas of polyphenols cited in the review (part 4)

Table S13. Table of names, log P and formulas of polyphenols cited in the review (part 5)

Table S14. Table of names, log P and formulas of carbohydrates and polysaccharides cited in the review

Table S15. Table of names, log P and formulas of other molecules cited in the review

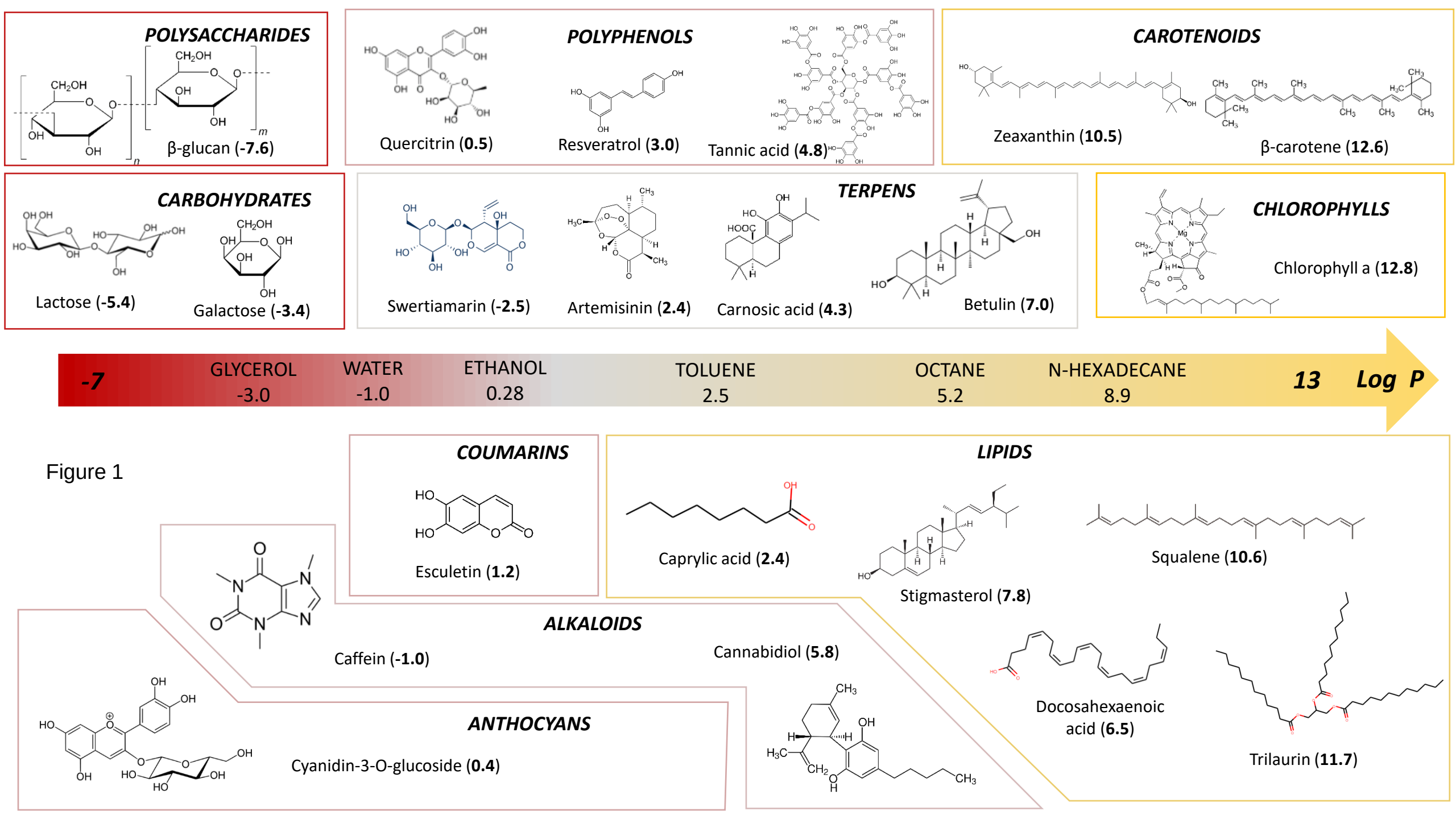

POLYSACCHARIDES
β-glucan (-7.6)
POLYPHENOLS
Quercitrin (0.5)
Resveratrol (3.0)
Tannic acid (4.8)
CAROTENOIDS
Zeaxanthin (10.5)
β-carotene (12.6)
CARBOHYDRATES
Lactose (-5.4)
Galactose (-3.4)
TERPENS
Swertiamarin (-2.5)
Artemisinin (2.4)
Carnosic acid (4.3)
Betulin (7.0)
CHLOROPHYLLS
Chlorophyll a (12.8)
-7
GLYCEROL -3.0
WATER -1.0
ETHANOL 0.28
TOLUENE 2.5
OCTANE 5.2
N-HEXADECANE 8.9
13
Log P
COUMARINS
Esculetin (1.2)
LIPIDS
Caprylic acid (2.4)
Stigmasterol (7.8)
Squalene (10.6)
Docosahexaenoic acid (6.5)
Trilaurin (11.7)
ALKALOIDS
Caffein (-1.0)
Cannabidiol (5.8)
ANTHOCYANS
Cyanidin-3-O-glucoside (0.4)

Figure 1

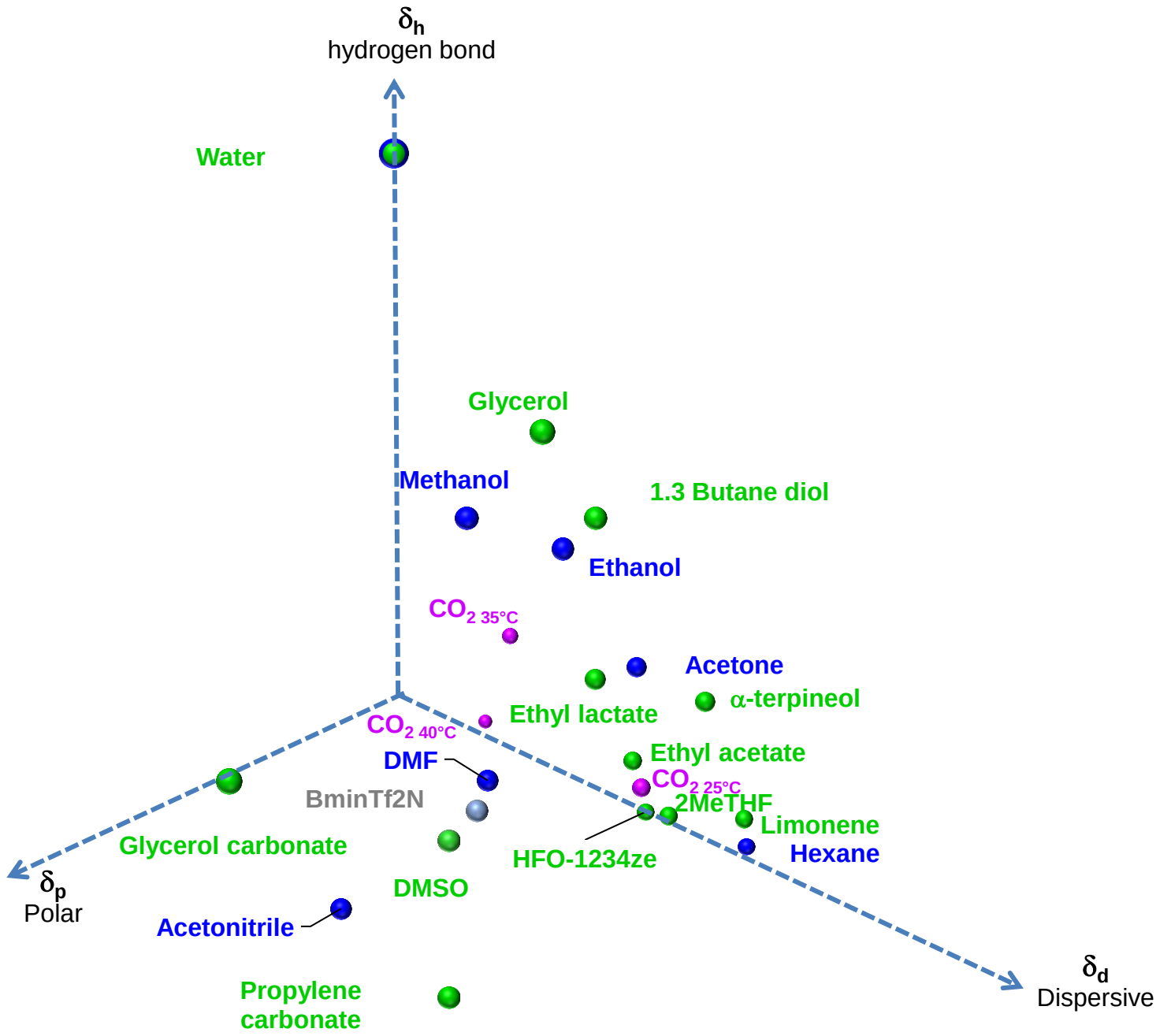

δ_h
hydrogen bond
Water
Glycerol
Methanol
1.3 Butane diol
Ethanol
$CO_{2\ 35°C}$
Acetone
α-terpineol
Ethyl lactate
$CO_{2\ 40°C}$
DMF
Ethyl acetate
$CO_{2\ 25°C}$
BminTf2N
2MeTHF
Limonene
Hexane
Glycerol carbonate
HFO-1234ze
DMSO
δ_p
Polar
Acetonitrile
Propylene carbonate
δ_d
Dispersive

Figure 2

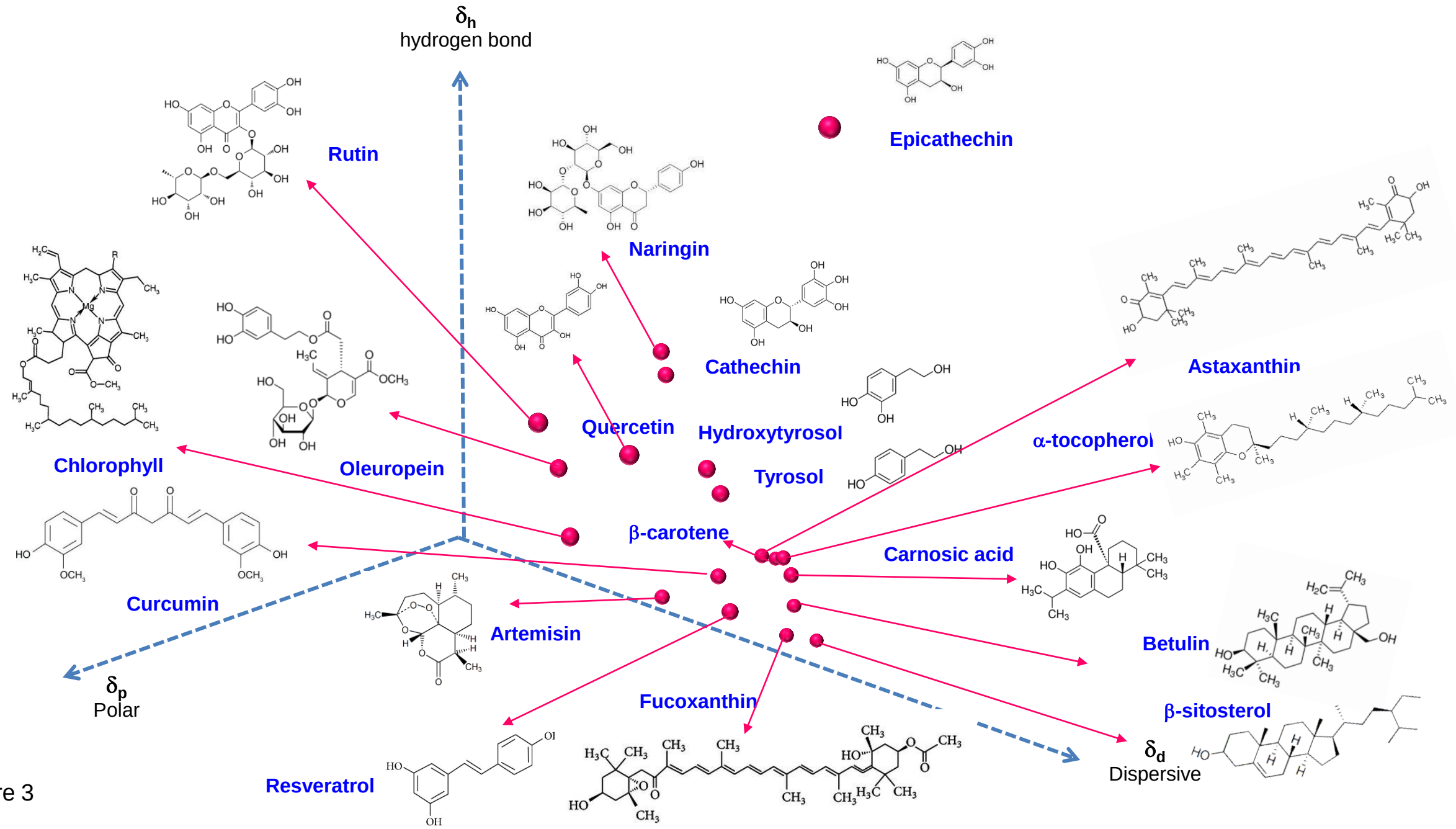

δ_h
hydrogen bond
Rutin
Naringin
Epicathechin
Cathechin
Quercetin
Hydroxytyrosol
Tyrosol
Oleuropein
Chlorophyll
Astaxanthin
α-tocopherol
β-carotene
Carnosic acid
Curcumin
Artemisin
Betulin
Fucoxanthin
β-sitosterol
Resveratrol
δ_p
Polar
δ_d
Dispersive

Figure 3

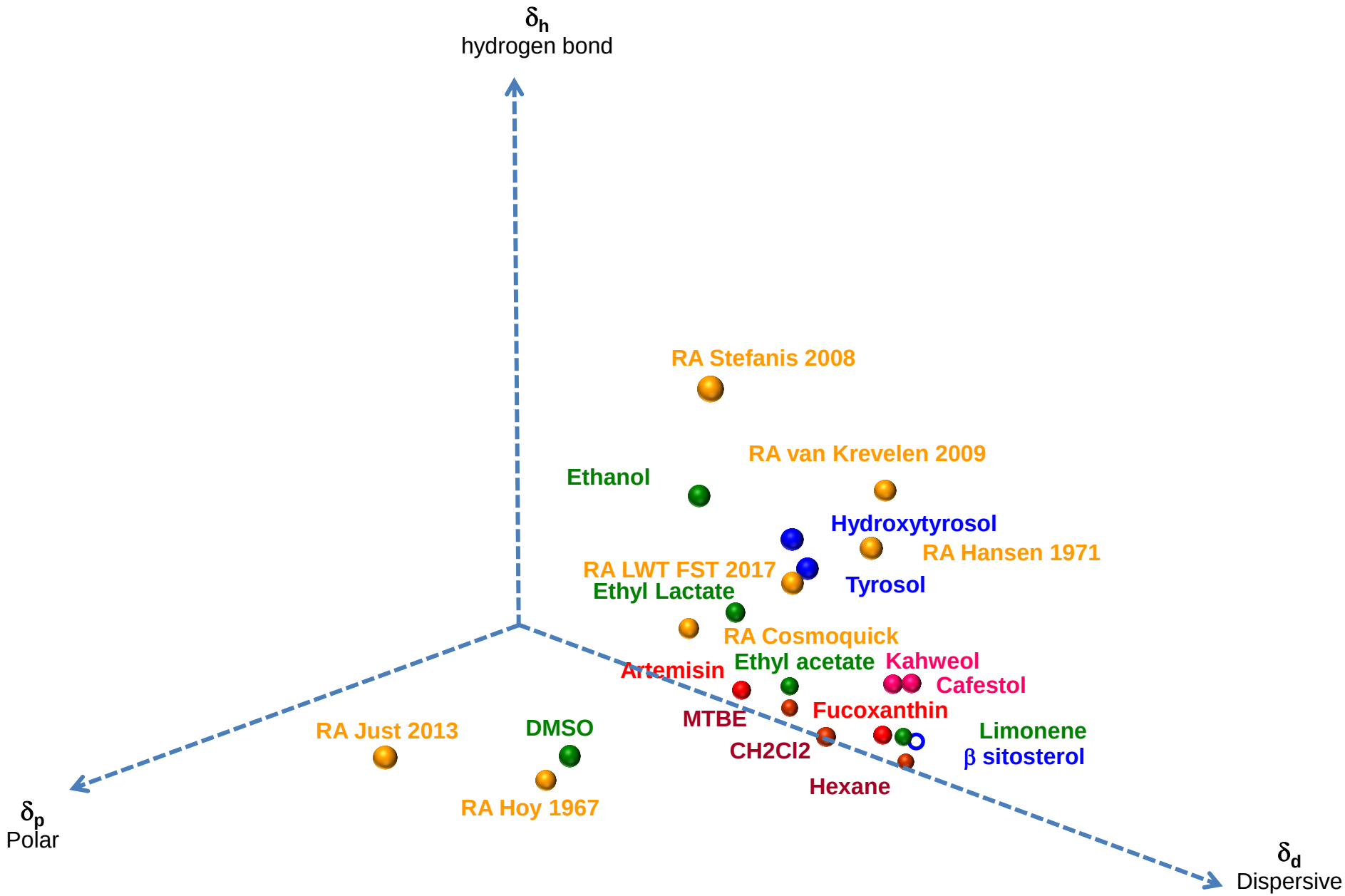

δh
hydrogen bond
RA Stefanis 2008
RA van Krevelen 2009
Ethanol
Hydroxytyrosol
RA Hansen 1971
RA LWT FST 2017
Tyrosol
Ethyl Lactate
RA Cosmoquick
Artemisin
Ethyl acetate
Kahweol
Cafestol
Fucoxanthin
MTBE
Limonene
β sitosterol
CH2Cl2
Hexane
RA Just 2013
DMSO
RA Hoy 1967
δp
Polar
δd
Dispersive

Figure 4

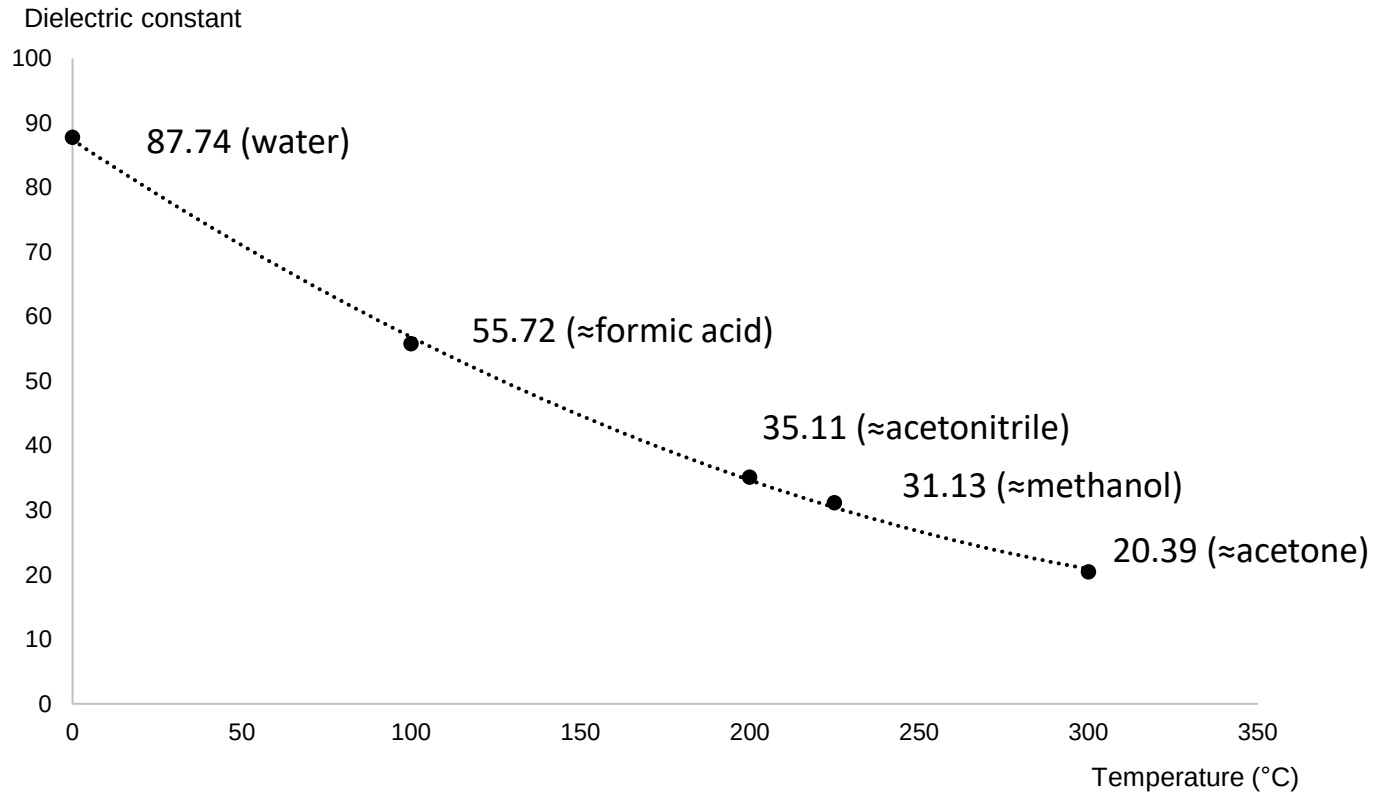

Dielectric constant
100
90
80
70
60
50
40
30
20
10
0
87.74 (water)
55.72 (≈formic acid)
35.11 (≈acetonitrile)
31.13 (≈methanol)
20.39 (≈acetone)
0
50
100
150
200
250
300
350
Temperature (°C)

Figure 5

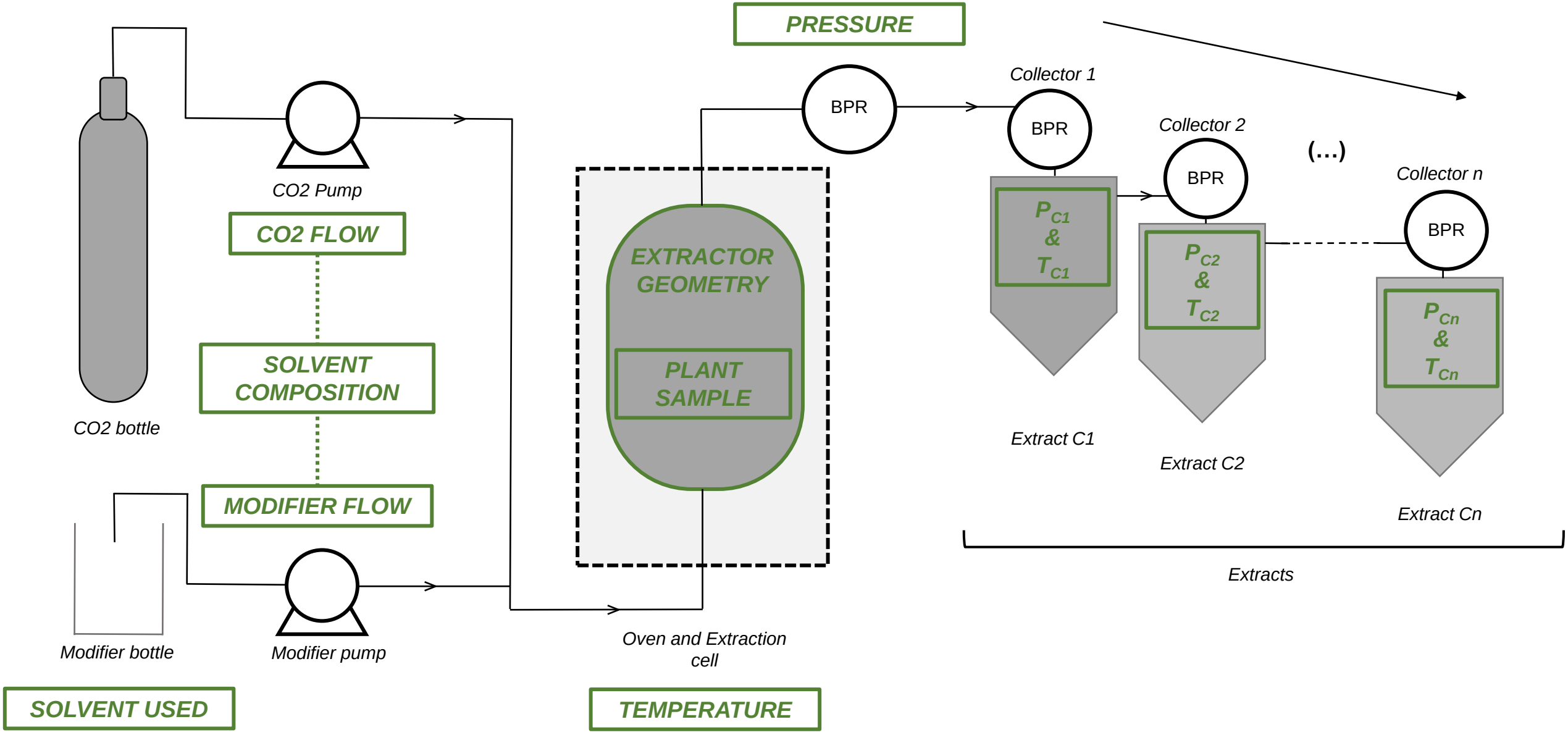

PRESSURE
BPR
Collector 1
BPR
Collector 2
BPR
(...)
Collector n
BPR
CO2 Pump
CO2 FLOW
CO2 bottle
SOLVENT COMPOSITION
MODIFIER FLOW
EXTRACTOR GEOMETRY
PLANT SAMPLE
P_{C1} & T_{C1}
P_{C2} & T_{C2}
P_{Cn} & T_{Cn}
Extract C1
Extract C2
Extract Cn
Extracts
Modifier bottle
Modifier pump
Oven and Extraction cell
SOLVENT USED
TEMPERATURE

Figure 6

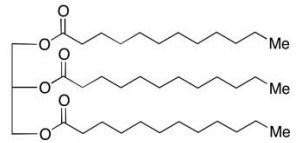
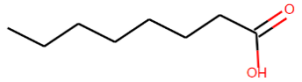
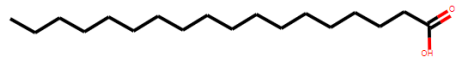
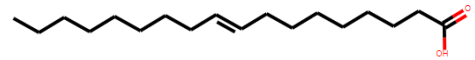
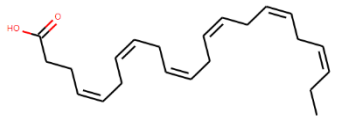
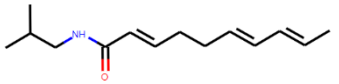
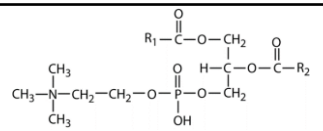
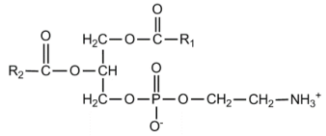
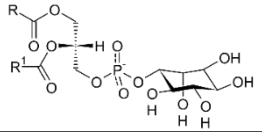
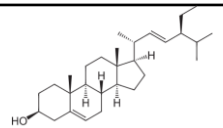
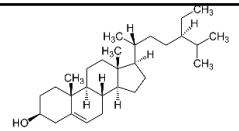
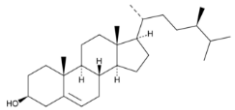
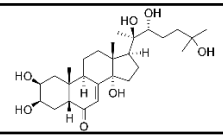
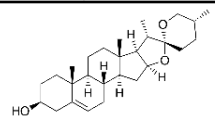
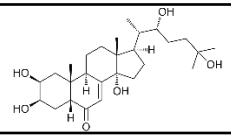
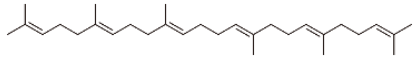
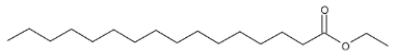
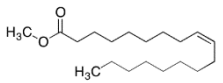
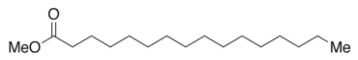
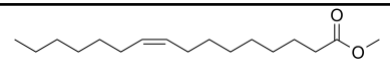
LIPIDS			
FAMILY	**COMPOUNDS**	**LogP**	**FORMULAS**
Glycerides (mainly triglycerides)	Trilaurin (C12:0)	11.7	
Free Fatty acids	FFA C8:0	2.4	
	FFA C18:0	6.3	
	FFA C18:1 Octodecenoic acid	6.1	
	DHA C22:6	6.5	
	Spilanthol	3.2	
Phospholipids	Phosphatidylcholine (i.e. C16:0 and C18:1)	11.2	
	Phosphatidyl-ethanolamine (i.e. C15:0 and C20:0)	11.7	
	a-phosphatidylinositol (i.e. C20:0 and C20:4)	9.9	

Table S1

Table S2

LIPIDS			
FAMILY	**COMPOUNDS**	**LogP**	**FORMULAS**
Non-saponifiable (waxes. steroids. alcanes)	Stigmasterol	7.8	
	β-sitosterol	8.0	
	Methylcholesterol	7.6	
	20-hydroxyecdysone	1.9	
	Diosgenin	5.7	
	β-ecdysone	2.7	
	Squalene	10.6	
	Nonacosane	11.6	
Fatty esters	Ethyl palmitate	6.0	
	Methyl oleate	6.2	
	Ethyl eicosenoate	7.4	
	Methyl palmitate	5.6	
	Methyl palmitoleate	5.4	

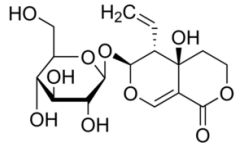
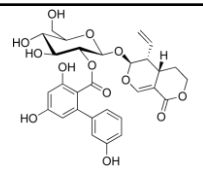
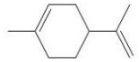
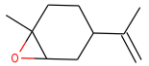
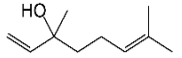
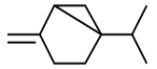
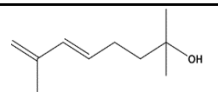
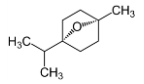
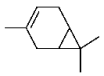
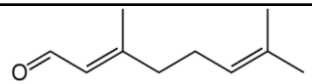
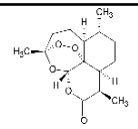
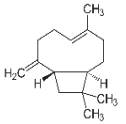
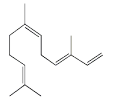
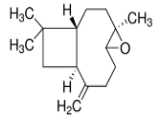
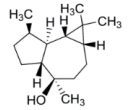
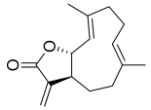
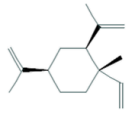
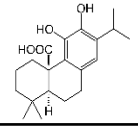
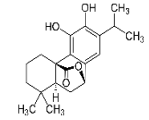
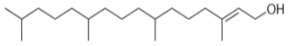
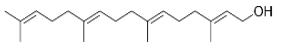
TERPENES			
FAMILY	**COMPOUNDS**	**LogP**	**FORMULAS**
Monoterpenoids	Swertiamarin	-2.5	
	Amarogentin	1.1	
Monoterpenes	Limonene	3.3	
	Limonene oxide	2.5	
	Linalool	2.7	
	Sabinene	3.0	
	Ocimenol	2.7	
	1.8-Cineole (also known as eucalyptol)	2.7	
	δ-3-carene	3.0	
	α-pinene	3.0	
	Geranial (also known as citral)	2.9	

Table S3

Table S4

TERPENES			
FAMILY	**COMPOUNDS**	**LogP**	**FORMULAS**
Sesquiterpenes	Artemisinin	2.4	
	α-caryophyllene	4.7	
	α-farnesene	5.2	
	Caryophylene oxide	3.9	
	Globulol	3.5	
	Germacranolides (i.e. costunolide)	3,6	
	β-elemene	4.7	
Diterpenes	Carnosic acid	4.3	
	Carnosol	4.3	
	Phytol	6.4	
	Geranylgeraniol	6.1	

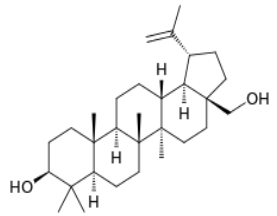
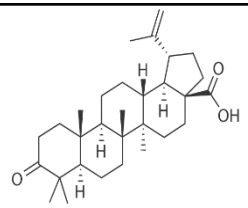
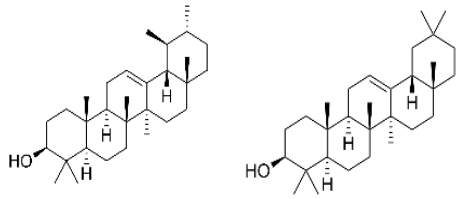
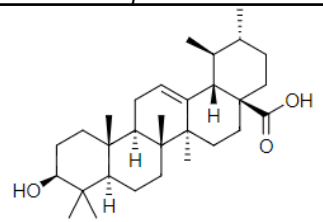
TERPENES			
FAMILY	**COMPOUNDS**	**LogP**	**FORMULAS**
Triterpenes	Betulin	7.0	
	Betulonic acid	7.3	
	α/β-amyrin	8.0/7.0	 *Alpha* *Beta*
	Ursolic acid	7.1	

Table S5

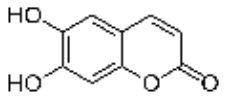
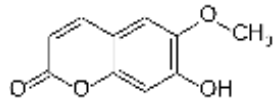
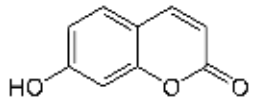
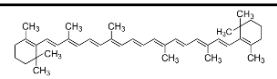
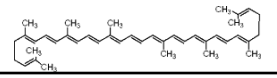
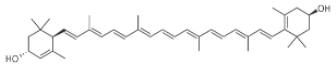
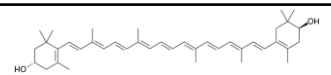
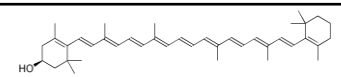
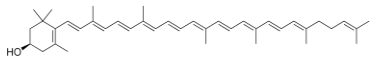
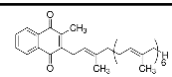
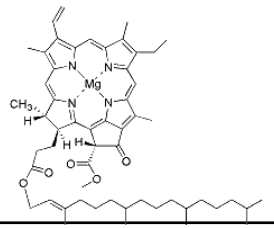
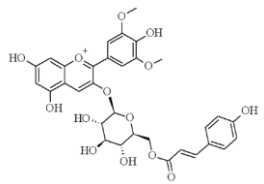
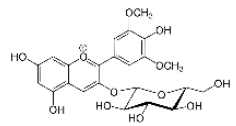
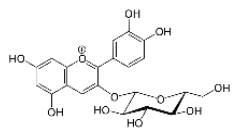
COUMARINS		
COMPOUNDS	**LogP**	**FORMULAS**
Esculetin	1.2	
Scopoletin	1.5	
7-hydroxy coumarine	1.5	

Table S6

Table S7

PIGMENTS			
FAMILY	**COMPOUNDS**	**LogP**	**FORMULAS**
Carotenoids	β-carotene	12.6	
	Lycopene	12.9	
	Lutein	10.4	
	Zeaxanthin	10.5	
	Cryptoxanthin	11.6	
	Rubixanthin	11.7	
	Menaquinon-7	8.9	
Chlorophylls	Chlorophyll a	12.8	
Anthocyanins	Malvidin-3-O-(6-p-coumaroyl)glucoside	2.7	
	Malvidin-3-O-glucosides	0.7	
	Cyanidin-3-O-glucoside	0.4	

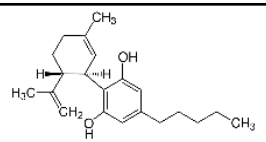
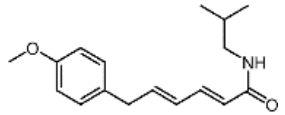
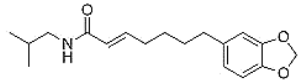
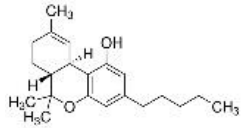
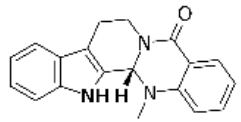
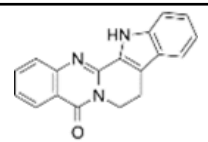
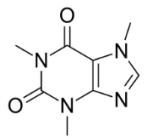
CANNABIDNOIDS AND ALKALOIDS		
COMPOUNDS	**LogP**	**FORMULAS**
Cannabidiol (CBD)	5.8	
Piperovatine	3.1	
Pipercallosidine	3.5	
Tetrahydrocannabinol	5.7	
Evodiamine	3.3	
Rutaecarpine	3.1	
Caffein	-1.0	

Table S8

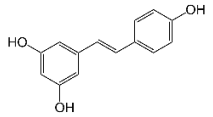
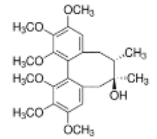
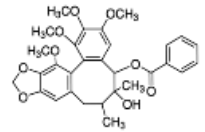
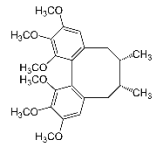
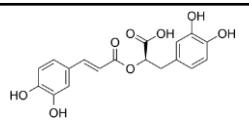
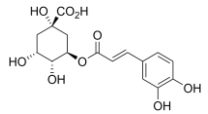
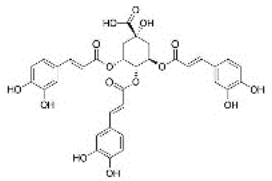
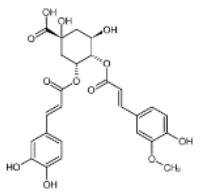
POLYPHENOLS			
FAMILY	**COMPOUNDS**	**LogP**	**FORMULAS**
Stilbenes	Resveratrol	3.0	
Lignans	Schizandrin	3.9	
	Schisantherin a	5.0	
	Deoxyschizandrin	4.8	
Phenols	Rosmarinic acid	1.8	
	Chlorogenic acid (3-caffeoylquinic acid)	-0.6	
	Tricaffeoylquinic acid	2.7	
	4.5-dicaffeoylquinic acid	1.0	

Table S9

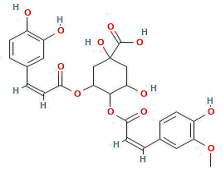
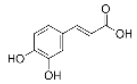
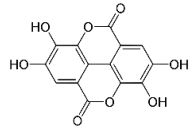
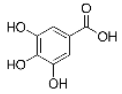
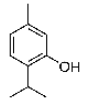
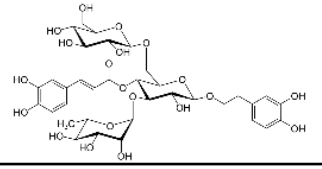
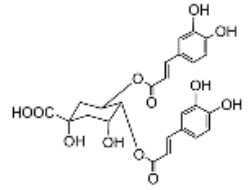
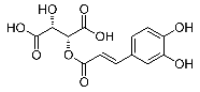
POLYPHENOLS			
FAMILY	**COMPOUNDS**	**LogP**	**FORMULAS**
Phenols	3-caffeoyl-4-feruloylquinic acid	1.3	
	Caffeic acid	1.2	
	Ellagic acid	1.3	
	Gallic acid	0.5	
	Thymol	2.8	
	Echinacoside	-3.2	
	Cynarine	1.0	
	Caftaric acid	-0.4	

Table S10

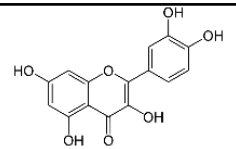
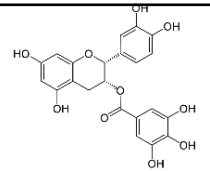
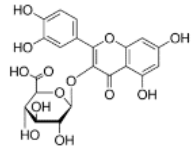
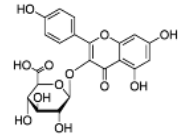
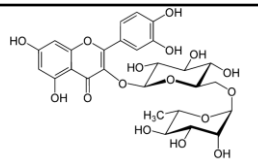
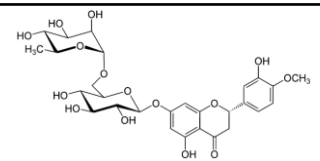
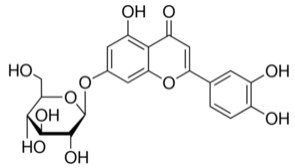
POLYPHENOLS			
FAMILY	**COMPOUNDS**	**LogP**	**FORMULAS**
Flavonoids	Quercetin	2.0	
	Quercitrin	0.5	
	Quercetin-3-O-β-D-glucuronide	-0.4	
	Kaempferol-3-O-β-D-glucuronide	-0.2	
	Rutin	-1.7	
	Hesperidin	-1.2	
	Luteolin-7-O-glucoside	-0.2	

Table S11

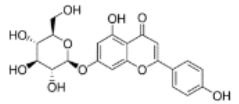
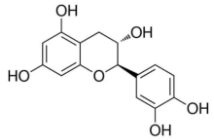
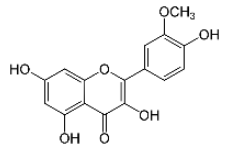
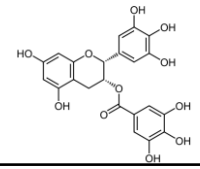
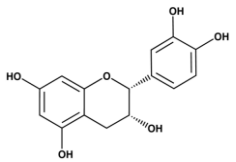
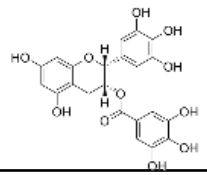
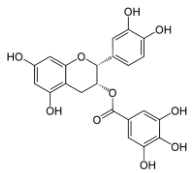
POLYPHENOLS			
FAMILY	**COMPOUNDS**	**LogP**	**FORMULAS**
Flavonoids	Apigenin-7-O-glucoside	0.0	
	Catechin (CT)	1.5	
	Isorhamnetin	2.3	
	Epigallocatechin (EGC)	1.3	
	Epicatechin (ECT)	1.5	
	Epigallocatechin gallate (EGCG)	2.2	
	Epicatechin gallate (ECG)	2.5	

Table S12

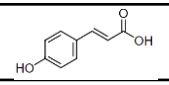
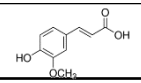
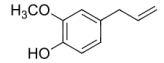
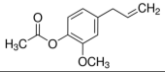
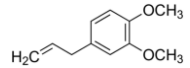
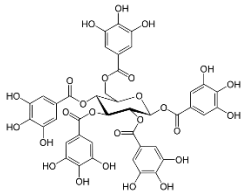
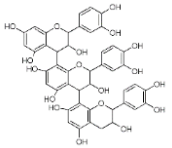
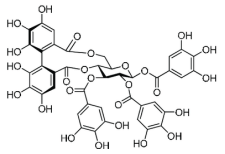
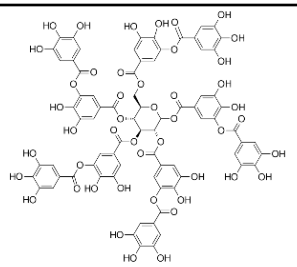
POLYPHENOLS			
FAMILY	**COMPOUNDS**	**LogP**	**FORMULAS**
Phenylpropenes	P-coumaric acid	1.5	
	Trans-ferulic acid	1.5	
	Eugenol	2.1	
	Eugenyl acetate	2.3	
	Methyl eugenol	2.4	
Tannins	Hydrolysable tannins (i.e. 1.2.3.4.6-Pentagalloyl glucose)	1.7	
	Condensed tannins (i.e. Procyanidin C1)	4.4	
	Tellimagrandin 2	1.7	
	Tannic acid	4.8	

Table S13

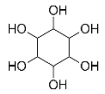
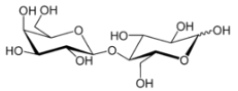
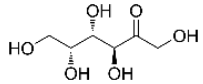
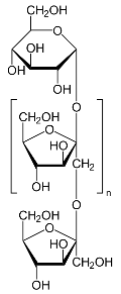
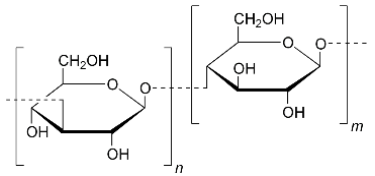
CARBOHYDRATES		
COMPOUNDS	**LogP**	**FORMULAS**
Inositols	-3.8	
Lactose	-5.4	
Galactose	-3.4	
Tagatose	-3.4	
POLYSACCHARIDES		
Inulin (i.e. n=35)	-83.7	
β-glucan (i.e. n=1 et m=2)	-7.6	

Table S14

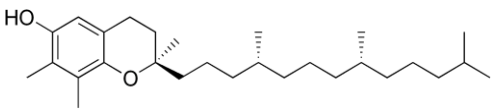
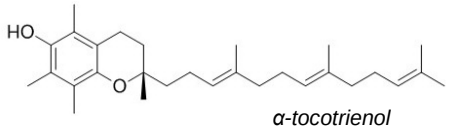
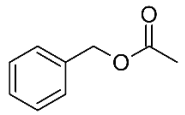
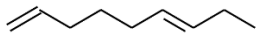
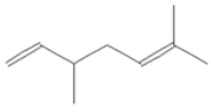
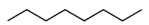
OTHERS		
COMPOUNDS	**LogP**	**FORMULAS**
γ-tocopherols	8.5	
γ/α-Tocotrienol	8.3/8.6	 *α-tocotrienol*
Benzyl acetate	1.7	
3.9-dodecadien	3.3	
Bicyclo[10.1.0]tridec-1-ene	4.1	
3.6-Dimethyl-1.5-heptadiene	3.2	
Octane	3.4	

Table S15