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► To cite this version:

Thibault Lefebvre, Emilie Destandau, Eric Lesellier. Selective extraction of bioactive compounds from plants using recent extraction techniques: A review. *Journal of Chromatography A*, 2021, 1635, pp.461770 -. 10.1016/j.chroma.2020.461770 . hal-03493488

HAL Id: hal-03493488

<https://hal.science/hal-03493488v1>

Submitted on 15 Dec 2022

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1 **Selective extraction of bioactive compounds from plants using recent**
2 **extraction techniques: A Review**

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9 Abstract

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

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

22 Technical advances have allowed the development of recent, and sometimes
23 green, extraction techniques, such as Microwave-Assisted Extraction (MAE),
24 Ultrasound-Assisted Extraction (UAE), Pressurized Liquid Extraction (PLE) and
25 Supercritical Fluid Extraction (SFE). This review focuses on the specificity of these
26 recent techniques and the influence of their physical parameters (i.e. pressure,
27 intensity, etc.). In addition to the solvent selection, which is of prime interest, the
28 physical parameters applied by the different techniques influence the extraction
29 results in different ways. Besides, SFE is a versatile and green technique suitable to
30 achieve selectivity for some compounds. Due to its properties, SC-CO₂ allows
31 tailoring conditions to improve the selectivity.

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37 1 Introduction

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

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

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

56 First, the nature of the solvent is investigated as the right choice of solvent can
57 by itself induce selectivity. In a second part, the review focuses on different
58 techniques and their respective parameters to examine their role in selective
59 extraction. Three extraction methods are described: Ultrasound-Assisted Extraction
60 (UAE), Microwave-Assisted Extraction (MAE) and Pressurized Liquid Extraction
61 (PLE). For example, the impact of frequency and power on selectivity is studied for
62 UAE, pressure for PLE and so on. In the last part, the use of supercritical carbon
63 dioxide (SC-CO₂) in Supercritical Fluid Extraction (SFE) is detailed. This fluid is well
64 known for its selectivity properties. For this reason, this extraction method will be
65 dealt with at greater length than the other three. Carbon dioxide modulation is studied
66 and other parameters such as the use of separators or extraction vessel geometry
67 are presented.

68 2 Extraction solvent

69 2.1 Solubility models

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

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

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

$$88 \quad \text{Log } K_{O/W} = \text{Log} \left(\frac{C_{\text{octanol}}}{C_{\text{water}}} \right)$$

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

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

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

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

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

154 Figure 4 shows the location of some natural products and extraction solvents
155 studied. First, and as discussed previously, depending on the calculation method, the
156 values obtained can differ dramatically. For instance, the location of rosmarinic acid
157 (RA) [18,21] can be close to ethanol or 1,3 butanediol when using the Stefanis
158 method [22] whereas it is close to glycerol carbonate when using the Just method
159 [23]. The differences between these calculation methods were recently discussed by
160 Mathieu [24], who reported the superiority of the Stefanis model for polar compounds,
161 as it takes into account local effects associated with conjugation.

162 Artemisin, a sesquiterpenoid known for its antimalarial activity, which is located
163 lower on the diagram (fig.4), displays a very high solubility in dichloromethane (DCM)
164 (1195 mg/mL), a rather high solubility in dimethylsulfoxide (DMSO) (103.7 mg/mL)
165 and a satisfactory one in ethyl acetate (39.4 mg/mL) [9]. However, the diagram

166 shows that the location of artemisin toward these three solvents is not fully in
167 accordance with the experimental solubility measurements. Similarly, the solubility of
168 kahweol and cafestol toward varied solvents has been studied [12]. The normalized
169 values range from 100% for the best extraction obtained in methyl-t-butylether
170 (MTBE), to 0% for ethyl acetate, reaching 88% for DCM and 1.3% for hexane.
171 Although these four solvents seem to be at equivalent distances from the two
172 diterpenes, the experimental solubility values are quite different. Another study was
173 done on the extraction of phenolic compounds (tyrosol, hydroxytyrosol) and
174 phytosterol (β -sitosterol) from olive oil. As expected, the addition of a hydroxyl group
175 to tyrosol improved the δh parameter of hydroxytyrosol, but despite these high δh
176 values, both were only slightly soluble in water [16]. When looking at the respective
177 solubility of these compounds towards green solvents such as ethanol, ethyl lactate,
178 ethyl acetate and limonene, the use of ethanol allows the selective extraction of
179 phenolic compounds, and the use of limonene the selective extraction of β -sitosterol.
180 The other two solvents, ethyl lactate and acetate, could be used for the simultaneous
181 extraction of interesting compounds [16]. The extraction recovery for fucoxanthin was
182 studied in four green solvents, ethanol, ethyl acetate, ethyl lactate and limonene [20].
183 The best recovery was obtained with ethyl acetate, and the worst with limonene,
184 despite its very close location to fucoxanthin on figure 4. The authors mentioned that
185 the Hansen parameters were related to solubility, but not to the extraction kinetics,
186 which depend on the matrices. Consequently, the use of Hansen parameters should
187 be restricted to initial evaluation for the solvent selection. Nevertheless, when looking
188 at the extraction selectivity between carotenoids and chlorophylls, the values were
189 0.52 for ethanol, 0.54 for ethyl lactate, 1.22 for ethyl acetate and 3.54 for limonene
190 (at 40°C), showing the satisfactory relationship between the Hansen parameter
191 location and this relative value.

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

199 2.2 Solvent selectivity

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

209 To illustrate the solvent effects, Santovo *et al.* [25] extracted antimicrobial
210 molecules from freeze-dried *Haematococcus pluvialis* microalgae using PLE. Hexane
211 and ethanol were used and compared. They confirmed that hexane (Log P = 2.6)
212 favors the extraction of alkanes (i.e. octane Log P = 3.4) and methyl esters (i.e.
213 Hexadecanoic acid ethyl ester Log P = 6.0) without carboxylic acids, while ethanol
214 (Log P = 0.0) extracts carboxylic acids (i.e. butanoic acid Log P = 0.9) without any
215 alkanes or methyl esters. Otero *et al.* [26] demonstrated that ethyl acetate is a better
216 solvent to extract fatty acids from freeze dried Galician Algae compared to less polar
217 (hexane) and more polar (ethanol, and ethanol/water) solvents using PLE. The fatty
218 acid content (expressed as mg per g of extract) was higher using ethyl acetate
219 (693.20 mg/g) than hexane (426.12 mg/g) or ethanol (554.42 mg/g). However, it
220 highlighted the fact that solubility is not a binary term (solutes are neither completely
221 soluble nor not soluble at all).

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

232 oxygenated functions (ketone, epoxy, hydroxyl). Saha *et al.* [28] studied different
233 solvent compositions (using acetone $\text{LogP} = -0.24$, hexane and ethanol) on the
234 extraction of lutein and β -carotene from orange carrot using PLE. Acetone mixtures
235 led to extracts with a lower content of both carotenoids. However, ethanol mixed with
236 hexane demonstrated a higher recovery of lutein and β -carotene. Macías-Sánchez *et al.*
237 *al.* [29] extracted the same pigments by UAE from *Dunaliella salina* micro-algae using
238 two other solvents, methanol and DMF ($\text{LogP} = -0.83$). The carotenoid/chlorophyll
239 ratio was measured. Between these two solvents, the ratios were respectively around
240 5 and 8, demonstrating a higher carotenoid selectivity with DMF, which is less polar
241 than methanol. This selectivity was also investigated by Sánchez-Camargo *et al.* [10]
242 on *Phaeodactylum tricornutum* diatom by PLE. Among varied solvents, some
243 considered as greener were tested such as d-limonene or ethyl lactate. They
244 demonstrated a higher carotenoid/chlorophyll ratio, showing higher selectivity. The
245 minimum ratio was obtained using ethanol (0.52) while the maximum was obtained
246 with d-limonene at (1.73).

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

264 In the last decades, new kinds of solvent have been developed. Ionic liquids (IL)
265 were some of the first. They were discovered at the end of the XIXth century, but
266 found application only from the 1970s on (first used as electrolytes in batteries). They
267 consist in blending two ionic compounds with opposite charges. This blend creates a
268 mixture with different physicochemical properties from those of the compounds used.
269 For example, this difference can be visibly seen by mixing two solids and obtaining a
270 liquid mixture. This kind of solvent has been used in plant extraction and shows
271 interesting selectivity. Liu *et al.* [34] studied the use of an ionic liquid
272 ($[\text{HO}_3\text{S}(\text{CH}_2)_4\text{mim}]\text{HSO}_4$) at different concentrations in water: from 0.2 to 1.6 M for
273 the extraction of phenolic acids from *Eucalyptus globulus* leaves by MAE. The ionic
274 solvent $[\text{HO}_3\text{S}(\text{CH}_2)_4\text{mim}]\text{HSO}_4$ at 1.0 M in water improved extraction by playing a
275 catalytic role in the formation of ellagic and gallic acids from hydrolysable tannins
276 such as tellimagrandin II. Selectivity was observed by changing the concentration of
277 the ionic solvent, inducing different catalysis mechanisms that resulted in different
278 ellagic and gallic acid compositions. Similar results were obtained by Sukor *et al.* [35]
279 who used BmimTf₂N for the extraction of gallic and tannic acids from oak galls during
280 UAE. Different concentrations from 0.05 to 0.20 M led to different acid contents.
281 Compared to other classical solvents, for example methanol, ionic liquids doubled the
282 extraction yield of these phenolic compounds. These studies confirm the interest in
283 these IL compared to more classical solvents such as methanol. This catalytic agent
284 allows the extraction of compounds that are not extractable with other selective
285 solvents.

286 Another family of solvents was developed historically from IL, Deep Eutectic
287 Solvents (DES). DES are more recent, as they appeared at the beginning of the
288 2000s. The principle is close to that of IL. However, the compounds are not ionic and
289 the interactions result from hydrogen bonding. To create a DES, one hydrogen-
290 bonding donor and one hydrogen-acceptor are required. This results in a eutectic
291 mixture with a lower melting point. Bubalo *et al.* [36] developed different DES for the
292 extraction of phenols from grape skin using MAE and UAE. Choline chloride was
293 used as hydrogen acceptor while different hydrogen donors were tested (i.e. glycerol,
294 oxalic acid, malic acid, sorbose). Results showed that the selectivity could be tailored
295 as a function of the different DES used. This was especially the case for the recovery
296 of p-coumaroylmonoglucosides (i.e. malvidin-3-O-(6-p-coumaroyl)glucoside) using a
297 choline chloride:glycerol 1:2 (molar ratio) mixture compared to other compounds such

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

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

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

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

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

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

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

364 miscibility between ethanol and water. Ethanol is then excluded from the upper part
365 of the mixture. For example, Guo *et al.* [45] used different salts ((NH₄)₂SO₄, KH₂PO₄,
366 CaCl₂, NaCl and sodium citrate) to extract lignans (schizandrin, schisantherin A and
367 deoxyschizandrin) from *Schisandra chinensis* (turcs.) Baill seeds by UAE. The ATPS
368 excluded ethanol in the upper part but also other water-free molecules, and in the
369 present case, lignans. Excluding lignans during the process enhanced extraction by
370 maintaining a maximum concentration gradient between plant and solvent, thereby
371 favoring their solubilization. Although yields were similar to classic ethanol extraction,
372 purities increased: the purity of the three target compounds doubled with UAE-ATPS
373 compared to classic UAE-ethanol extraction. This technique was also used by Cheng
374 *et al.* [46] to extract polysaccharides from *Gentiana scabra Bunge* by MAE. This two-
375 phase system allowed the selective recovery of polysaccharides in the upper part,
376 enhancing the purity, and hence the selectivity. Polysaccharides that are soluble in
377 ethanol (homopolysaccharides made of glucose for example) were better extracted in
378 the upper phase while those soluble in water (heteropolysaccharides made of
379 arabinose, galacturonic acid for example) remained in the bottom phase. This is a
380 selective way of extracting different groups of polysaccharides.

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

390 3 Selectivity in modern liquid extraction techniques

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

395 3.1 Ultrasound Assisted Extraction (UAE)

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

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

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

413 Ultrasound power, on the contrary, has shown a significant effect on selectivity.
414 Alvez-Filho *et al.* [48] focused on the extraction of chlorogenic acids from sweet
415 potato peels. Different power densities from 0 to 50 W/L (equivalent to 500 W in this
416 case) were applied during the extraction and revealed that some compound yields
417 such as 4,5-dicaffeoylquinic, 3-caffeoyl-4-feruloylquinic, and 3-caffeoylquinic acids
418 improved with intensity. These compounds result from hydrolysis reactions on other
419 molecules such as tricaffeoylquinic acid. This reaction is due to the formation of OH
420 radicals, caused by ultrasonic waves, which produce H₂O₂. Hydrogen peroxide and
421 hydroxyl radicals can induce a hydrolysis reaction. This article highlighted the fact
422 that ultrasound-assisted extraction can be used to extract or modify solutes by
423 adjusting the power, resulting in a selective process. Sousa *et al.* [49] observed
424 similar results in an earlier study on gallic acid formation from other polyphenols
425 extracted from *Phyllanthus amarus* using of different intensity range (99 to 301
426 W/cm³). They demonstrated that a higher gallic acid content was obtained with the
427 highest intensity during the longest extraction time tested (9 min). Hydrolysis

428 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
429 pieces, affecting the selectivity of the process. The same effect on polysaccharide
430 was studied by Zhu *et al.* [51] on pomegranate peel, varying the power from 100 to
431 200 W.
432

433 Differences can also be seen with different instruments. Jacotet-Navarro *et al.*
434 [52] compared three ultrasonic devices (bath, reactor and probe) by extracting
435 rosmarinic, carnosic and ursolic acid from rosemary leaves. Differences were
436 observed regarding the yield of these compounds and their purities. These
437 differences were due to the different ultrasonic power provided by each device.

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

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

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

470 3.2 Microwave Assisted Extraction (MAE)

471 Microwave-Assisted Extraction (MAE) uses microwave technology in order to
472 heat a solid and liquid mixture. Heating is induced by microwave irradiation absorbed
473 by molecules depending on their dielectric constant. Polar molecules with a high
474 dielectric constant (*i.e.* water with a dielectric constant of 78.5 at 25°C, ethanol with
475 24.3 at 25°C) are able to absorb this energy and re-emit it, resulting in heating the
476 system, whereas solvents with a low dielectric constant such as hexane (1.87 at
477 25°C) are insensitive to microwaves.

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

483 Power must be considered a key parameter in order to optimize extraction when
484 using MAE. Chen *et al.* [56] extracted trans-resveratrol from tree peony seed oil-
485 extracted residues. Changing the microwave irradiation power impacted the yield of
486 resveratrol: increasing the power from 120 to 385 W increased the yield (from 1.2
487 $\mu\text{mol/g}$ to 2.9 $\mu\text{mol/g}$) with a similar purity level (between 80 and 90%). This can be
488 due to increased diffusivity of the solvent, induced by the irradiation energy coming
489 from the plant matrix to the solvent [57]. However, from 385 to 700 W, the yield
490 decreased. Excessive irradiation can cause internal over-heating, leading to
491 carbonization and then other reactions such as isomerization and/or degradation of
492 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.

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

531 3.3 Pressurized Liquid Extraction (PLE)

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

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

558 However, because carotenoids are sensitive to high temperature, the yield increase
559 resulting from temperature was maybe hidden by a yield decrease due to
560 degradation, finally resulting in no change observed. Alvarez-Casas *et al.* [67]
561 observed similar degradation results on different polyphenols through the extraction
562 from white grape marc. Some compounds such as gallic acid and catechin were
563 negatively impacted by high temperature (above 100°C) while total phenolic and
564 flavonoid contents were increased, even at the highest temperature. Similar effects
565 were observed by Dobiáš *et al.* [68] for the extraction of esculetin, rutin, scopoletin, 7-
566 hydroxy-coumarin and quercetin from different plant samples. While compound yields
567 improved as a function of temperature, quercetin content decreased from 80° to
568 100°C.

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

579 Pressurized hot water extraction (PHWE) or subcritical water extraction (SWE),
580 which are considered as new “green” extraction techniques, are based on the
581 dramatic change in the dielectric constant of water at high temperature (figure 5
582 reproduced from [71]). High temperature favors the movement of water molecules
583 that reduces intermolecular hydrogen bonding, and induces a lower polarity.
584 Selectivity behavior of heated water was reported by Ko *et al.* [72] for the extraction
585 of flavonoids from different plant samples using SWE. The maximum extraction
586 temperature for quercetin was 170°C, while the extraction of quercitrin, which
587 contains more hydroxyl groups due to one glycoside substituent, was optimal at
588 110°C, indicating that it was more soluble when the polarity of water was higher (at
589 the moderately high temperature of 110°C). However, another study by Kumar *et al.*
590 [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), CO₂ 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-CO₂) interactions, *i.e.* on
640 solubility. Parameters such as pressure, temperature and modifier can change these
641 Sc-CO₂ 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-CO₂. For instance, adding an alcoholic modifier (such as ethanol) to
653 carbon dioxide increases the polarity of the extraction fluid.

654 4.1.1 Lipophilic compounds

655 Due to the low polarity of carbon dioxide, supercritical fluid extraction has been
656 widely applied to oils and more particularly lipids. Lipids are a large family with
657 different subcategories (for example glycerides, phospholipids, waxes...). Sc-CO₂
658 SFE has been involved in oil removal processes in order to replace the classical
659 process using n-hexane. Markom *et al.* [78] optimized process parameters to recover
660 crude palm oil. After varying temperature (40°C to 60°C) and pressure (11 to 20
661 MPa), they studied the extraction kinetics and monitored fatty acid (FA) chain lengths
662 (C12 to C20, saturated and unsaturated) in the glycerides extracted. For any
663 conditions and any related density, light fatty acids such as C12:0 and C14:0 were
664 extracted at the beginning of the process while heavier chains were extracted later.
665 The FA chain length was the most influential parameter for selectivity compared to
666 unsaturation number. It was then possible to collect lighter or heavier fractions of
667 glycerides based on their extraction kinetic differences. Moreover, using a slower
668 extraction kinetic and the right CO₂ density can induce a longer extraction process,
669 making it easier to collect separate fractions (with light or heavy compounds).

670 In the field of oils and fats, Free Fatty Acid (FFA) content is an important
671 property of oils. It can affect flavor perceived as a metallic taste. FFA come from a
672 lipolysis reaction directly in oil/fat samples. The content of FFA was studied by King
673 *et al.* [79] as a function of different pressures and temperatures. In conditions where
674 the Sc-CO₂ density was the lowest (40°C and 13.8 MPa), larger amounts of FFA
675 were extracted. Then, FFA content in the extracted oil decreased when the
676 temperature increased (up to 100°C). Pressure and temperature had a selective
677 impact on FFA content. To conclude, FFA can be considered as light lipids and thus,
678 require low-density Sc-CO₂ to be extracted. They are similar to short chain
679 glycerides.

680 Dos Santos Garcia *et al.* [80] worked on the extraction of *Mucuna* seed oil in
681 order to produce defatted meal. Their study also focused on the extraction of L-
682 DOPA (3,4-dihydroxyphenylalanine), an amino acid with antioxidant properties. The
683 aim was to obtain an alternative to other conservatives, such as butylated-hydroxy-
684 toluene (BHT), butylated-hydroxy-anisole (BHA), or tocopherols, which are usually
685 added to avoid oxidation. *Mucuna* seeds are known to be a high-yielding source of L-
686 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 CO₂ 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-CO₂, 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-CO₂ density and hence the solubility of
714 compounds. This indicates that pressure, temperature and modifier can all modify
715 Sc-CO₂ 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-CO₂. 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, α -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 α -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-CO₂ 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 Felföldi-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-CO₂ 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-CO₂ density, to be extracted.

745 de Melo *et al.* [88] studied the recovery of stigmasterol from water hyacinth
746 using Sc-CO₂. 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-CO₂ 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 *Spilanthus 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-CO₂ 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-CO₂ 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-CO₂ can also be used to selectively extract other metabolites
780 such as terpenes. These metabolites are composed of isoprene units (C₅H₈).
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-CO₂ at 8.5 MPa (and the same temperature) was used. This difference
800 may seem insignificant but it has a significant impact on Sc-CO₂ 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-CO₂ 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-CO₂ 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.

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

832 Allawzi *et al.* [97] optimized the extraction of Jordanian rosemary essential oil by
833 SFE. The paper also confirmed that a pressure increase (from 7.6 to 9 MPa at 35°C)
834 improved the extraction of monoterpenes (α -pinene and eucalyptol), while methyl
835 esters (i.e. palmitic acid methyl ester, hexadecenoic acid methyl ester) were
836 extracted only at 7.6 MPa. The selectivity between oxygenated terpenes and other
837 terpenes was investigated by Mira *et al.* [98]. They carried out SFE on orange peel
838 and showed that the ratios of oxygenated compounds (mainly linalool) over non-
839 oxygenated terpenes was high at the lowest pressure (8 MPa at 20°C) and then
840 decreased when the pressure increased (up to 15 MPa). Then, from a certain
841 pressure (i.e. 15 MPa at 20°C), it increased again but more slightly. It demonstrated
842 that the selectivity of oxygenated compounds over non-oxygenated ones was better
843 when using Sc-CO₂ at low density. The work by Van Opstaele *et al.* [99] confirmed
844 the same behavior. In order to develop hop aromas by SFE, the fraction responsible
845 for floral scent was more significant at low Sc-CO₂ density. One molecule responsible
846 for this floral scent is, among others, linalool. Jokic *et al.* [100] worked on *Salvia*
847 *officinalis* L. leaves and reported identical conclusions regarding oxygenated
848 monoterpenes.

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

851 monoterpenes and oxygenated monoterpenes ($S_{D/(M+OM)}$), the second with
852 sesquiterpenes and oxygenated sesquiterpenes ($S_{D/(S+OS)}$) and the third with
853 triterpenes, esters and waxes ($S_{D/(T+E+W)}$). These selectivities were plotted as a
854 function of pressure. Increasing the pressure had a different impact on terpenes. For
855 monoterpenes and oxygenated monoterpenes ($S_{D/(M+OM)}$), a pressure increase from 7
856 to 15 MPa decreased selectivity due to the higher solubility of monoterpenes in low-
857 density Sc-CO₂. Above 15 MPa, this selectivity increased slightly due to an increase
858 in diterpene solubility. In comparison with the other two selectivities (sesquiterpenes
859 $S_{D/(S+OS)}$ and triterpenes $S_{D/(T+E+W)}$), the increase in pressure increased both
860 selectivities, meaning that the solubility of diterpenes increased without increasing
861 that of other heavy compounds. This study confirmed the correlation between the
862 volatility of extracted compounds with Sc-CO₂ density: low-density Sc-CO₂ extracts
863 light terpenes better, while high-density CO₂ improves the recovery of heavier
864 compounds.

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

870 Klein *et al.* [103] worked on triterpenoid extraction from uvaia leaves (*Eugenia*
871 *pyriformis Cambess.*) and particularly on α/β -amyrin. They obtained the purest α/β -
872 amyrin extract using the lowest pressure tested (10 MPa) and the highest
873 temperature (60°C). Higher densities increased yield, but decreased purity. Oliveira
874 *et al.* [104] studied the extraction of *Piper divaricatum* essential oil, focusing on
875 another family of volatile compounds: phenylpropenes. After varying the pressure
876 and temperature parameters, they succeeded in selectively extracting high amounts
877 of eugenyl acetate and β -elemene with low amounts of eugenol and methyl eugenol
878 (at 35 °C and 10 MPa), showing again the selectivity of low density Sc-CO₂.

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

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

886 Like lipid extraction, SFE is suitable for terpene extraction, from volatile
887 monoterpenes to non-volatile triterpenes. Low-density Sc-CO₂ favors the selectivity
888 of volatile compounds, whatever their polarity.

889 4.1.2 Pigments

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

898 Carotenoids are divided into two families: carotenes and xanthophylls. The
899 latter group is differentiated by the presence of oxygen atoms, increasing the
900 compound polarity, which may cause them to interact differently with Sc-CO₂. Filho *et al.*
901 [107] studied the impact of pressure (10 to 40 MPa) and temperature (40 and
902 60°C) of pure Sc-CO₂ on different compounds from the carotene and xanthophyll
903 families. It was shown that oxygen-containing molecules were not, or only weakly,
904 extracted at any setoff pressure and temperature. However, one xanthophyll
905 behaved differently: rubixanthin. This can be explained by the fact that it contains
906 only one hydroxyl group against two for other xanthophylls (*i.e.* cryptoxanthin).
907 Regarding the behavior of carotenes, higher pressure and/or temperature values
908 increased carotene yields. Gomez-Prieto *et al.* [108] confirmed this behavior using
909 *Mentha spicata* L.. In addition, they suggested a sequential extraction of β-carotene
910 and lutein, using first Sc-CO₂ at 40°C and 11.3 MPa for carotene, and then
911 increasing the temperature to 60°C to extract lutein. Contrary to what Filho *et al.*
912 [107] observed, lutein was affected by temperature compared to the other
913 xanthophylls they studied. Chronopoulou *et al.* [109] selectively extracted
914 menaquinon-7 from other carotenoids at low Sc-CO₂ density (10 MPa and 40°C)
915 using *Tetrademus Obliquus* microalgae. Gomez-Prieto *et al.* [110] extracted trans-
916 lycopene from tomato. At 40°C, changing the density of Sc-CO₂ through pressure

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

922 Wrona *et al.* [111] studied the impact of pressure and temperature on lipids,
923 phenolic and chlorophyll content by carrying out SFE on *Solidago gigantean Ait.*
924 They confirmed that lipidic and phenolic contents increased when pressure increased
925 (up to 80 MPa). But contents decreased when the temperature increased (up to
926 70°C). However, chlorophyll content was improved using high pressure and
927 temperature. Because pressure had a positive impact on every yield, temperature
928 appeared to be a good factor for the selective extraction of chlorophyll pigments over
929 lipids and phenolic compounds.

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

944 Even if SFE using carbon dioxide is an extraction technique of interest for non-
945 polar molecules, it is also possible to selectively extract polar metabolites from plants
946 when modulating Sc-CO₂ properties.

947 4.1.3. Alkaloids and Cannabinoids

948 Cannabinoids and alkaloids are known for their pharmaceutical properties
949 [115,116]. Pimentel *et al.* [117] extracted amides (piperovatine and pipercollosidine)
950 from *Piper piscatorum* (*Trel Yunc.*). With pure CO₂, temperature (40 and 70°C at 40
951 MPa) had a different impact on these two compounds. While selectivity (expressed in
952 g/100g of extract) increased for pipercollosidine at higher temperature (from 0.004 to
953 0.031 g/100g), the selectivity of piperovatine did not change significantly (from 0.26
954 to 0.30 g/100g). This can be explained by autoxidation which can occur for
955 piperovatine at higher temperature, which balances selectivity changes. However, the
956 biggest selectivity changes for these compounds were obtained with a polar modifier
957 (especially ethanol at 10%). At 40°C, the selectivity obtained for pipercollosidine was
958 0.24 g/100g and for piperovatine it was 0.93. Selectivity was lower at 70°C but this
959 can be explained by the extraction of other compounds due to an increase in
960 solubility in the extraction solvent. Liu *et al.* [118] observed that the modifier can
961 reduce selectivity. They studied the extraction of two alkaloids: evodiamine and
962 rutaecarpine from *Evodia Rutaecarpa*. Different modifiers were tested (at 0.4 mL/min
963 for 2 L/min gaseous CO₂): no modifier, pure methanol and methanol with water at 50,
964 30, and 5%. Water decreased the yield of evodiamine and rutaecarpine, but also
965 their purity, whereas methanol increased their yield with a similar purity.

966 Gallo-Molina *et al.* [119] optimized the extraction of tetrahydrocannabinol (THC)
967 from *Cannabis sativa* L. and observed different behaviors. They obtained the highest
968 levels of THC using 2 wt% of modifier (ethanol) at the highest (34 MPa and 60°C)
969 and lowest (15 MPa and 40°C) sets of pressure and temperature. This demonstrates
970 that ethanol can significantly impact Sc-CO₂ behavior even when used in low
971 amounts (2 wt%). Attard *et al.* [120] studied the influence of pressure and
972 temperature for the extraction of waxes and cannabidiol (CBD) from hemp wastes.
973 They observed that at low Sc-CO₂ densities (8 MPa, 35°C), selectivity was high for
974 lipophilic compounds (alkanes and fatty acids) with a low extracted content for other
975 molecular families. At higher density (i.e. 35 MPa and 50°C), other groups of
976 compounds (such as CBD) were better extracted, reducing selectivity for the previous
977 compounds.

978 4.1.4. Polyphenols

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

981 Antunes-Ricardo *et al.* [122] worked on the extraction of isorhamnetin from
982 *Opuntia ficus-india* L. A higher recovery of this compound was observed with high
983 pressure and intermediate temperature (30 MPa and 50°C). At the highest
984 temperature (65°C), isorhamnetin content decreased while global yield increased. As
985 described previously, an increase in density increases yields, and thus can result in a
986 decrease in selectivity. Another parameter can influence extraction selectivity: the
987 flow rate. A maximum amount of isorhamnetin was obtained at the maximum flow
988 rate (100 g/min) while the maximum global yield was obtained at an intermediate flow
989 rate (80 g/min). When the Sc-CO₂ flow rate increases, it may reduce mass transfer
990 resistance between compounds and extraction solvent, resulting in an improvement
991 of the extraction kinetic. However, increasing the flow rate may prevent the solvent
992 from entering sample pores, thereby decreasing the extraction of other compounds.

993 Conde *et al.* [123] extracted flavonoids from *Pinus pinaster* wood. They also
994 observed that the extraction yield of polar compounds was higher at high pressure
995 and temperature (25 MPa and 50°C). However, the use of 10 wt% ethanol as
996 modifier also significantly improved the extraction of flavonoids against other
997 compounds. Yilmaz *et al.* [124] confirmed the interest of using ethanol as modifier for
998 the extraction of polar molecules. They investigated the influence of pressure,
999 temperature and modifier percentage on the extraction of catechins (EGC, CT, ECT,
1000 EGCG and ECG). Setting the conditions at 30 MPa, 50°C and 20% of ethanol
1001 extracted a maximum of GA, EGC and EGCG, while 30 MPa, 30°C and the same
1002 modifier were optimal conditions for CT and ECT. The best conditions for ECG were
1003 25 MPa, 30°C and 15% of modifier. These extractions highlight the fact that using
1004 high temperature (*i.e.* 50°C) may degrade compounds, resulting in a lower yield (*i.e.*,
1005 50°C with CT, ECT and ECG)

1006 Nagavekar *et al.* [125] extracted oleoresin from *Curcuma longa* and *Curcuma*
1007 *amada*. They studied the influence of previously tested parameters: pressure,
1008 temperature and modifier percentage. They confirmed the need to use high pressure
1009 (35 MPa), high temperature (65°C) and polar modifier (ethanol) at 30 wt% in order to
1010 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 CO₂.

1024 4.1.5. Carbohydrates

1025 Carbohydrates are important molecules from plants, but no studies were found
1026 on their extraction using Sc-CO₂. 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-CO₂ and polar modifier
1037 in order to extract polar metabolites.

1038 4.1.6. Selectivity loss

1039 As described previously, Sc-CO₂ 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-CO₂ is

1044 required, implying high pressure. However, high density will increase the total yield
1045 but reduce squalene selectivity. As pointed out in the previous section, a modifier,
1046 also known as co-solvent, is often used to increase the extraction capacity of Sc-CO₂
1047 by increasing its polarity. But in some cases, this “improvement” can lead to a
1048 decrease in selectivity. This was observed by Valente *et al.* [132]. They worked on
1049 the extraction of antioxidant molecules from *Botryosphaeria dothidea*. They observed
1050 that antioxidant capacity was reduced using 10 wt% modifier (ethanol) compared to
1051 pure Sc-CO₂. Even if a modifier helps to extract more polar compounds, it shows that
1052 these new compounds have a lower antioxidant capacity than the less polar ones
1053 obtained without a modifier. Pereira *et al.* [133] also showed a selectivity decrease
1054 using a modifier for the extraction of lignans from *Phyllanthus amarus Schum* and
1055 *Thonn*.

1056 Modulating Sc-CO₂ properties through temperature, pressure and modifier
1057 represents an important key point to achieve extraction selectivity. In addition,
1058 selectivity can be obtained for a wide range of compounds, from non-polar
1059 (squalene)[85] to very polar (carbohydrates)[128-130]. However, certain technical
1060 parameters can also affect selectivity.

1061 4.2 Technical parameters

1062 4.2.1 Extraction modes

1063 Beyond the complexity of Sc-CO₂, other parameters, related to the technology
1064 itself, can provide differences in selectivity. This is the case of the extraction modes:
1065 static or dynamic. The static mode can be limited by the lower diffusivity of
1066 compounds within plant cells reducing their migration into the extraction solvent,
1067 whereas the dynamic mode favors compound diffusion by maintaining at the optimum
1068 the concentration gradient between the plant and the solvent since the solvent is
1069 continuously renewed. Due to these different effects, the extraction of some solutes
1070 can be favored. Bermejo *et al.* [134] compared the two modes, using static and
1071 dynamic extraction with different modifiers (ethyl lactate, ethyl acetate and ethanol)
1072 on caffeine extraction from green tea. A slight change is that a modifier was
1073 introduced in the extraction cell with the plant, and then Sc-CO₂ was pumped. It
1074 showed that, depending on the modifier used, the static or dynamic mode showed a
1075 higher yield for caffeine. For example, with ethyl lactate, a higher concentration of
1076 caffeine in the extract (expressed in g of caffeine per g of extract) was obtained with

1077 the dynamic mode (14.3% in static mode and 18.2% in dynamic mode). On the
1078 contrary, with ethyl acetate, the dynamic mode seemed to have a negative impact
1079 compared to the static mode for the same compound (8.1% in static mode vs. 5.5%
1080 in dynamic mode). This highlighted the fact that the extraction mode affects
1081 extraction yield differently depending on the solvent used. Massias *et al.* [135]
1082 confirmed the previous study by showing that some compounds such as flavonoids
1083 or phenolic acids could be affected by this mode. Using CO₂:EtOH:H₂O 75:22:3
1084 %mol as solvent, phloridzine was better extracted in static mode while chlorogenic
1085 acid was better extracted in dynamic mode. However, no explanations were found to
1086 correlate these modes to the kind of compounds affected.

1087 4.2.2. Sequential extraction

1088 Supercritical fluid extraction systems allow the use of successive extraction
1089 conditions. It is possible to start extracting the sample at a certain temperature,
1090 pressure and percentage of modifier, then use other parameters for a second step,
1091 change from static to dynamic mode and so on. Vardanega *et al.* [136] carried out a
1092 two-step method in order to extract different terpenes from annatto seeds. They
1093 carried out a first extraction step using low density fluid (60°C and 10 MPa) in order
1094 to extract lighter molecules (*i.e.* geranylgeraniol) and a second step at higher density
1095 (40°C and 20 MPa) to extract heavier compounds (*i.e.* tocotrienols). Bogdanovic *et al.*
1096 [137] developed a 4-step method in order to extract different compounds from
1097 Lemon balm (*Melissa officinalis L., Lamiaceae*) at different temperature and pressure
1098 settings (respectively 10 MPa/40°C, 30 MPa/25°C, 30 MPa/40°C and 30
1099 MPa/100°C). The contents of the extracts for different families (monoterpenes,
1100 sesquiterpenes, diterpenes, fatty acids, methyl esters and alkanes) were evaluated
1101 by monitoring the content in specific molecules (*i.e.* geraniol for monoterpenes,
1102 palmitic acid for fatty acids ...). The results demonstrated that some compounds such
1103 as monoterpenes and sesquiterpenes were mostly extracted during the first and
1104 second steps, while other compounds such as alkanes and methyl esters were
1105 extracted during the third and last steps. A similar process was developed by Viganò
1106 *et al.* [138] with a 3-step extraction (60°C/17 MPa, 50°C/17 MPa and 60°C/26 MPa)
1107 in order to extract respectively tocopherols (*i.e.* γ -tocopherols, γ/δ -tocotrienols), fatty acids
1108 (*i.e.* oleic and linoleic acids) and carotenoids (evaluated with total carotenoid
1109 content).

1110 It is also possible to carry out sequential extraction with a modifier. Sökkmen *et*
1111 *al.* [5] extracted caffeine and catechin separately (from green tea) in a 2-step process
1112 using respectively pure Sc-CO₂ (25 MPa and 60°C) and Sc-CO₂ modified with
1113 ethanol (same pressure and temperature, with 0.5 mL/min of ethanol in 10g/min CO₂
1114 flow). A similar study was carried out by Domingues *et al.*, [139] in order to extract
1115 fatty acids, long-chain aliphatic alcohols and triterpenoids from *Eucalyptus globulus*
1116 bark. Likewise, Serra *et al.* [140], demonstrated that a first step using pure Sc-CO₂
1117 (25 MPa and 50°C) was helpful to recover anthocyanin compounds in the second
1118 step with modified Sc-CO₂ (with 10 wt% ethanol). This can be explained by the fact
1119 that the first step removed lipophilic and non-polar compounds, which makes
1120 anthocyanins more available during the second extraction step. Finally, it is possible
1121 to go beyond modified Sc-CO₂ and to use only modifier as the extraction solvent.
1122 Bitencourt *et al.* [141] carried out a 4-step extraction starting from a pure Sc-CO₂ step
1123 (50°C, 30 MPa), adding modifier (30% wt% ethanol) in the second step, using only
1124 modifier (ethanol) in the third step, and finishing with a mixture of ethanol and water.
1125 During the first step, unidentified non-polar compounds were extracted. The second
1126 step extracted β-ecdysone and less polar saponins. The third, pure ethanol step
1127 extracted β-ecdysone with more and less polar saponins. Finally, hydro-alcoholic
1128 extraction showed more polar saponins. This extraction process can selectively
1129 extract different saponins based on their polarity. However, using only ethanol or
1130 hydro alcoholic solution during extraction is moving away from the realm of
1131 supercritical fluid extraction.

1132 4.2.3. Extractor geometry

1133 Another technical aspect that can affect selectivity is the geometry of the
1134 extraction vessel. Zobot *et al.* [142] worked on two different extractor geometries
1135 which led to two different effects. The first one was on temperature diffusion. Different
1136 shapes of the vessel may cause different temperature profiles. As we saw previously,
1137 temperature changes Sc-CO₂ behavior, which may in turn change solubility. The
1138 second change is due to carbon dioxide velocity changes. This change can impact
1139 the extraction kinetic, and then result in a faster extraction process. In other words,
1140 an equivalent extraction time would require less solvent in a more efficient extractor.
1141 The same authors applied these changes to rosemary extraction [143]. Results
1142 confirmed that different components from volatile (monoterpenes) to non-volatile

1143 (terpernoic acids ...) compound families can be extracted differently depending on
1144 the extractor geometry.

1145 4.3.4. Separators

1146 The separator, which is located after the extraction cell, controls precipitation
1147 using the appropriate pressure and temperature. The controlled release of pressure
1148 can selectively precipitate particular compounds over others. Vasquez *et al.* [144]
1149 used this feature in order to purify squalene from vegetable oil. High pressure was
1150 needed to extract this compound. However, it has been shown previously [131] that
1151 high pressure was unable to improve selectivity towards squalene extraction. Varying
1152 the collector pressure from high to low (23 to 15 MPa) made compounds precipitate
1153 according to their thermodynamic properties. Thus, it was possible to improve the
1154 purity of this compound using separators. A similar study was carried out by
1155 Reverchon *et al.* [145]. Likewise, Baldino *et al.* [146,147] used these separators in
1156 order to separate cuticular waxes from other active compounds using different
1157 pressure settings (25 and 20 MPa). They also used the same process but with a low
1158 temperature (-7°C) in the collector, in order to remove paraffinic compounds from
1159 *Artemisia annua L.* extract. Rovetto *et al.* [148] used a 3-separator system in order to
1160 extract different fractions of *Cannabis sativa L.* extract. Three conditions were used:
1161 13 MPa/ 55°C; 9 MPa / 55°C; 6 MPa / 35°C. The results demonstrated that
1162 cannabinoids were mainly collected in the first separator (with cuticular waxes).

1163 As previously presented, Schukla *et al.* [149] extracted volatile and non-volatile
1164 compounds using high-pressure Sc-CO₂. Then two separators were used in order to
1165 separate these two families. The first separator was set at 17.5 MPa and the second
1166 one at 4 MPa. These pressures resulted in the separation of non-volatile compounds
1167 in the first separator and then the collection of volatile compounds in the second one.
1168 Cavero *et al.* [150] carried out a similar study in order to selectively precipitate
1169 antioxidant compounds in a first separator with Sc-CO₂ at high density (10 MPa and
1170 40°C), and recover volatile compounds (essential oil) in a second separator at a
1171 lower density (2 MPa and 20°C). In the same vein, Fornari *et al.* [151] separated
1172 volatile (*i.e.* thymol) from less and non-volatile compounds (*i.e.* carnosic acid) using
1173 two separators (at 10 MPa and 1 atm). Separation using separators can be more
1174 selective when pressures are closer. Costa *et al.* [152] carried out the extraction of
1175 volatile compounds from *Thymus lotocephalus* using separators at 18 MPa and 12

1176 MPa. The first separator extract was composed of sesquiterpenes such as globulol (a
1177 caryophyllene oxide), while the second separator extract was composed of lighter
1178 compounds such as linalool or 1,8-cineole. Fuentes-Gandara *et al.* [153] carried out
1179 extraction using pure Sc-CO₂ and modified CO₂ with different percentages of ethanol
1180 and water (50% modifier with pure ethanol, 50/50 ethanol/water, and pure water) in
1181 order to extract allelopathic compounds from *Helianthus annuus L.* leaves. The
1182 extracts were then fractionated using three collectors at different pressure and
1183 temperature settings (20 MPa/45°C; 9 MPa/40°C; 1 atm/30°C). This combination of
1184 conditions allowed the selective recovery of different bioactive compounds. For
1185 example, using CO₂:water 50/50 extraction conditions allowed the collection of the
1186 free chlorophyll fraction in the third collector. This fraction was also rich in bioactive
1187 compounds.

1188 Supercritical fluid extraction provides high selectivity due to the numerous
1189 parameters that can affect it. This high selectivity may come from pure Sc-CO₂
1190 density differences, from the addition of various modifiers, and also from technical
1191 parameters (vessel geometry, separators), or even from the kind of plant (terrestrial
1192 plant, algae...). A large range of compounds can be addressed by this selectivity,
1193 from volatile terpenes to non-polar waxes and polar carbohydrates. This last part of
1194 the review has described the different possible approaches providing selectivity, in
1195 relation to the extraction objective. However, the same parameters can also lead to a
1196 decrease in selectivity.

1197 5 Conclusion

1198 This review has surveyed the key points that need to be considered in order to
1199 modify selectivity during the extraction of bioactive compounds from plants. In
1200 particular, it has highlighted the importance of the chemical nature of the solvent, and
1201 of the physicochemical properties of the different techniques: wave modulation using
1202 UAE, microwave irradiation power using MAE, pressure with PLE and finally
1203 pressure, temperature and modifier addition for supercritical extraction using carbon
1204 dioxide.

1205 The aim of this review was to provide an overview of the different possibilities
1206 as a function of technique and molecular family. For techniques using liquid solvents
1207 (MAE, UAE and PLE), it highlighted the strong impact of the extraction solvent in

1208 improving selectivity. Moreover, physical parameters can be more suitable for some
1209 compounds and matrix couples. For example, microwaves favor the extraction of
1210 polar compounds in fresh plants thanks to their dipole moment.

1211 SFE is a major technique for selective extraction. Due to Sc-CO₂ behavior, it is
1212 possible to modulate its density with pressure and temperature and thus to favor or
1213 disfavor the extraction of ta compounds. Low density (with pressure below 15 MPa
1214 and temperature below 40°C) will help recover volatile compounds (*i.e.*
1215 monoterpenes, ...) while higher densities (with pressures above 25 MPa and
1216 temperatures below 40°C) will extract non-volatile and non-polar compounds (*i.e.*
1217 tocopherols, non-saponifiable lipids) more efficiently. For more polar compounds (*i.e.*
1218 phenols), the introduction of a polar solvent as modifier improves their yields. Other
1219 parameters can affect selectivity such as vessel geometry, separators, and so on.

1220 Considering all these different effects, it is also possible to develop new
1221 systems by coupling many parameters that was described before. This represents a
1222 good perspective for selective extraction.

1223 Acknowledgements

1224 This work was supported by the Centre-Val de Loire region, which provided the
1225 funding of the “Khloros” APR-IR (2017).

1226

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- 1865
- 1866

1867 **Figure and table captions.**

1868 Figure 1: Metabolite families and solvents organized as a function of log P and
1869 formulas of different metabolites.

1870 Figure 2: Hansen solubility parameters of solvent (in blue: classical solvents, in
1871 green: green solvents, in purple: carbon dioxide)

1872 Figure 3: Hansen solubility parameters of different metabolites and their
1873 formulas

1874 Figure 4: Hansen solubility parameters (HSP) of different compounds (in yellow:
1875 different rosmarinic acid (RA) HSPs, in green: green solvents, in brown: organic
1876 solvents, in blue: polar natural products, in blue: mid and non-polar natural products)

1877 Figure 5: Water dielectric constant variation as a function of temperature

1878 Figure 6: Classical Supercritical Fluid Extractor (SFE) scheme highlighting
1879 selectivity key points (green)

1880

1881 Table S1. Table of names, log P and formulas of lipids cited in the review (part
1882 1)

1883 Table S2. Table of names, log P and formulas of lipids cited in the review (part
1884 2)

1885 Table S3. Table of names, log P and formulas of terpenes cited in the review
1886 (part 1)

1887 Table S4. Table of names, log P and formulas of terpenes cited in the review
1888 (part 2)

1889 Table S5. Table of names, log P and formulas of terpenes cited in the review
1890 (part 3)

1891 Table S6. Table of names, log P and formulas of coumarins cited in the review

1892 Table S7. Table of names, log P and formulas of pigments cited in the review

1893 Table S8. Table of names, log P and formulas of cannabinoids and alkaloids
1894 cited in the review

1895 Table S9. Table of names, log P and formulas of polyphenols cited in the review
1896 (part 1)

1897 Table S10. Table of names, log P and formulas of polyphenols cited in the
1898 review (part 2)

1899 Table S11. Table of names, log P and formulas of polyphenols cited in the
1900 review (part 3)

1901 Table S12. Table of names, log P and formulas of polyphenols cited in the
1902 review (part 4)

1903 Table S13. Table of names, log P and formulas of polyphenols cited in the
1904 review (part 5)

1905 Table S14. Table of names, log P and formulas of carbohydrates and
1906 polysaccharides cited in the review

1907 Table S15. Table of names, log P and formulas of other molecules cited in the
1908 review

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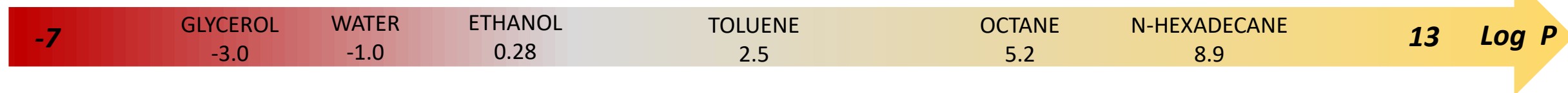
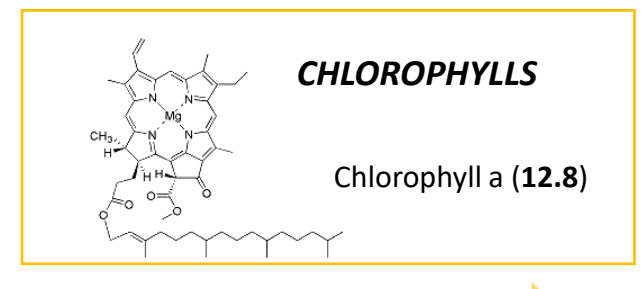
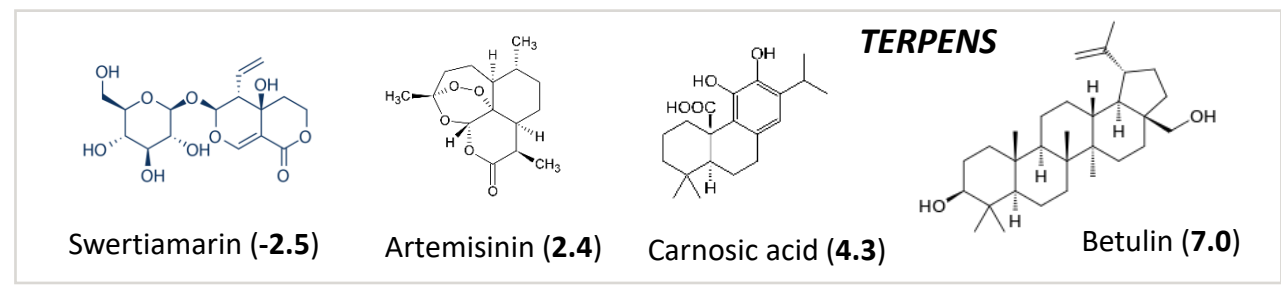
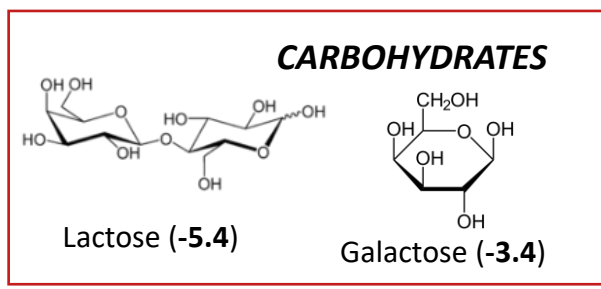
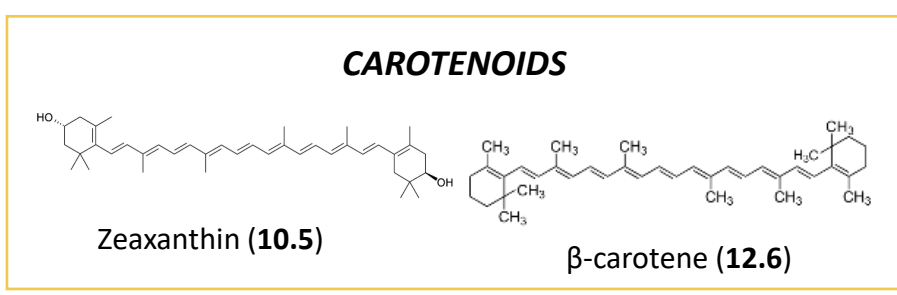
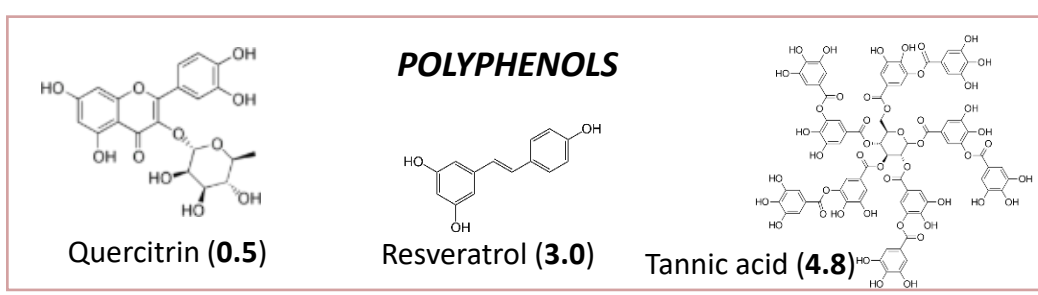
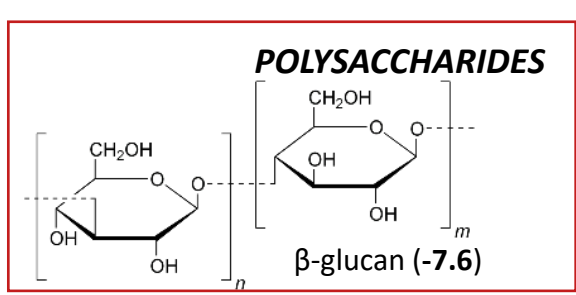
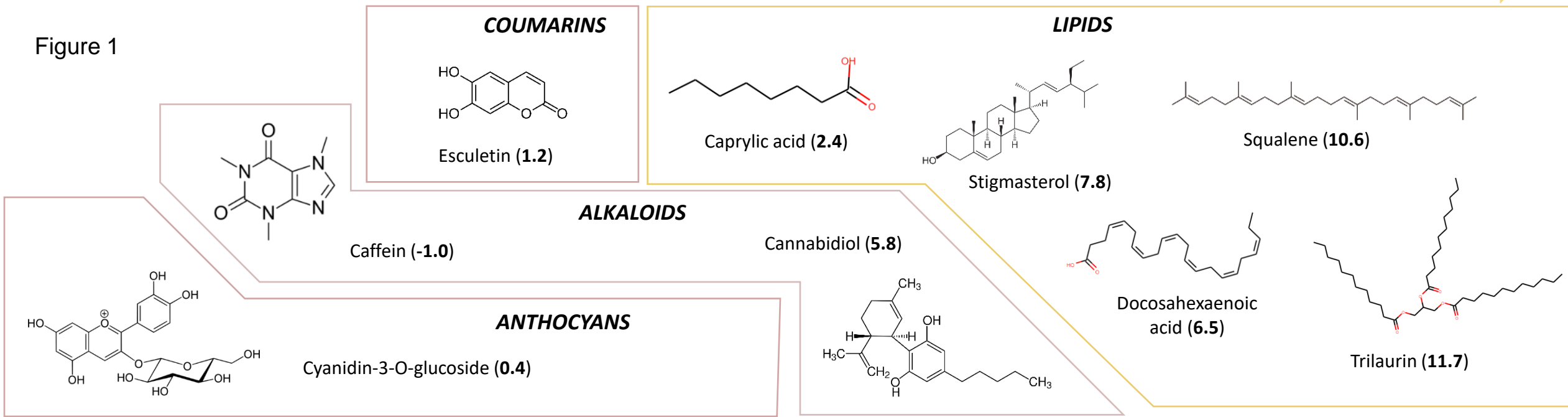


Figure 1



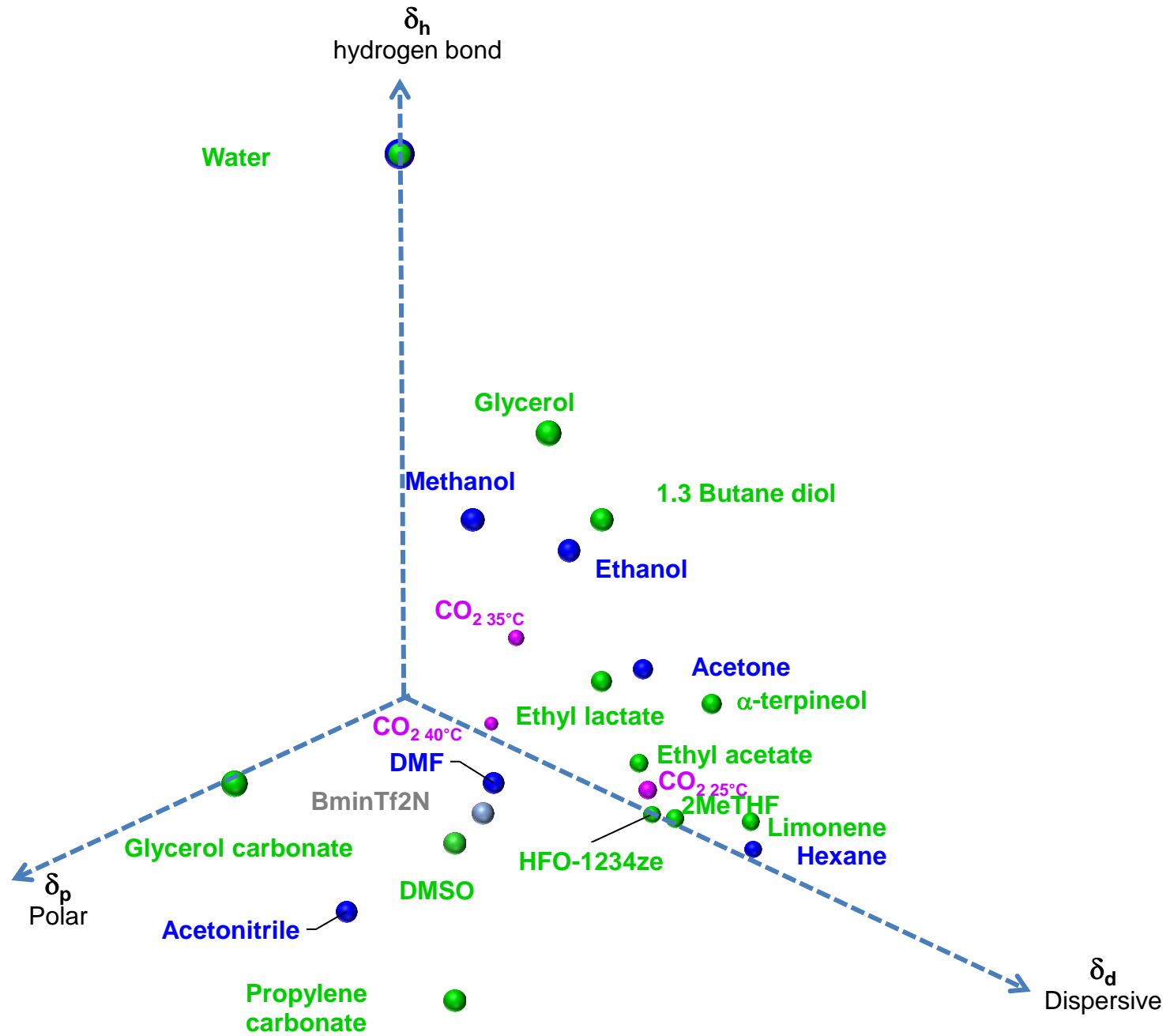


Figure 2

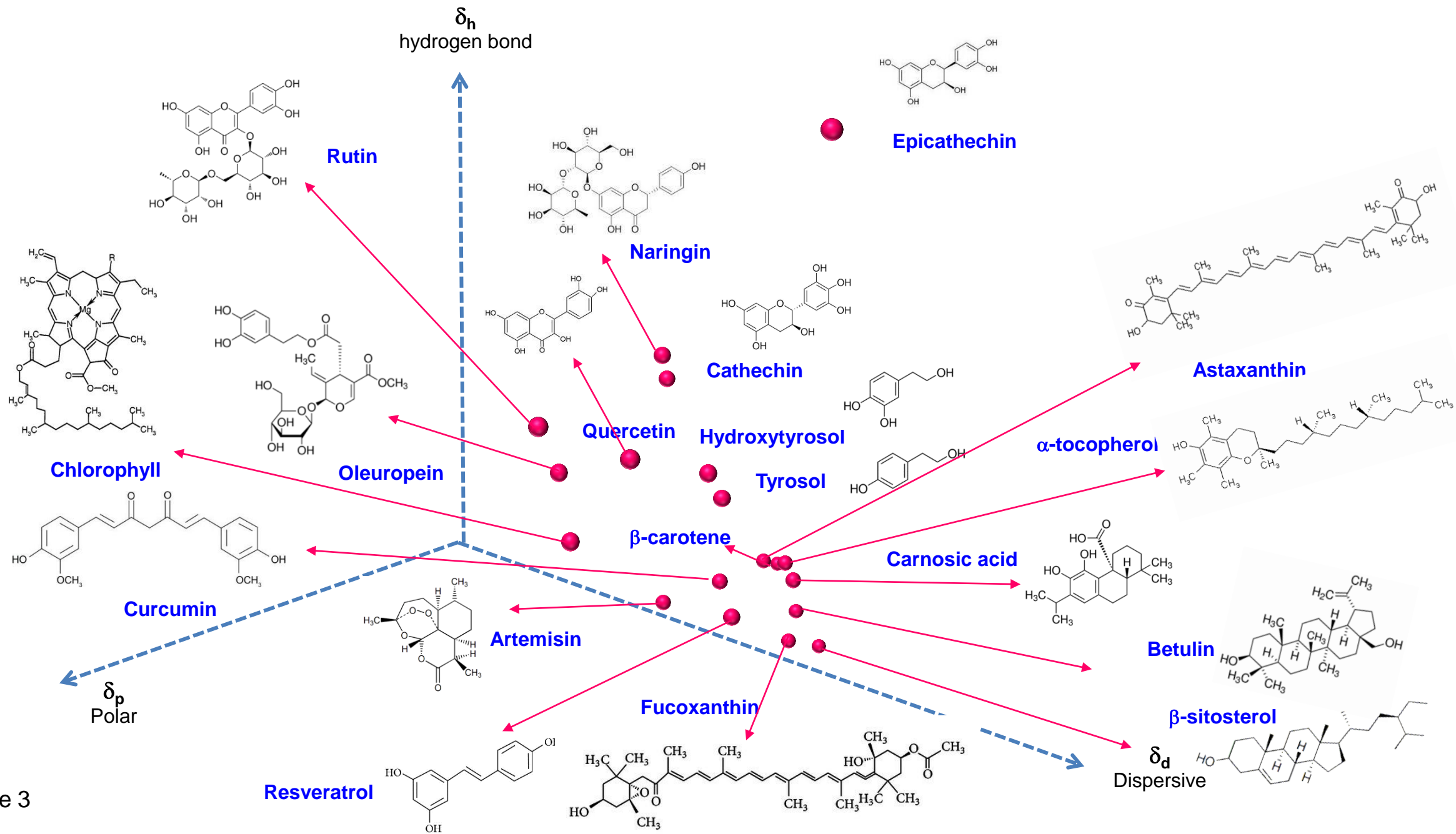


Figure 3

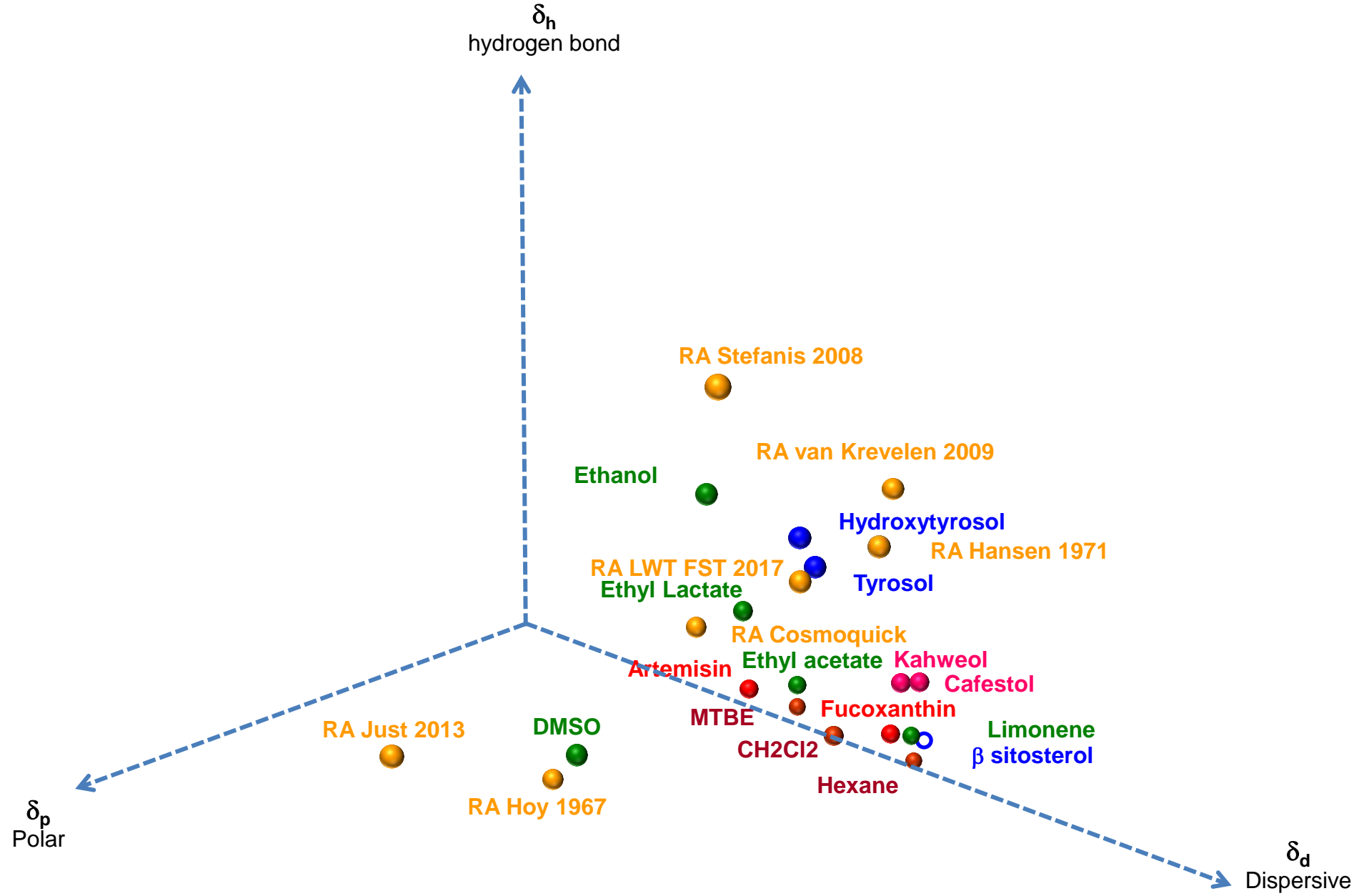


Figure 4

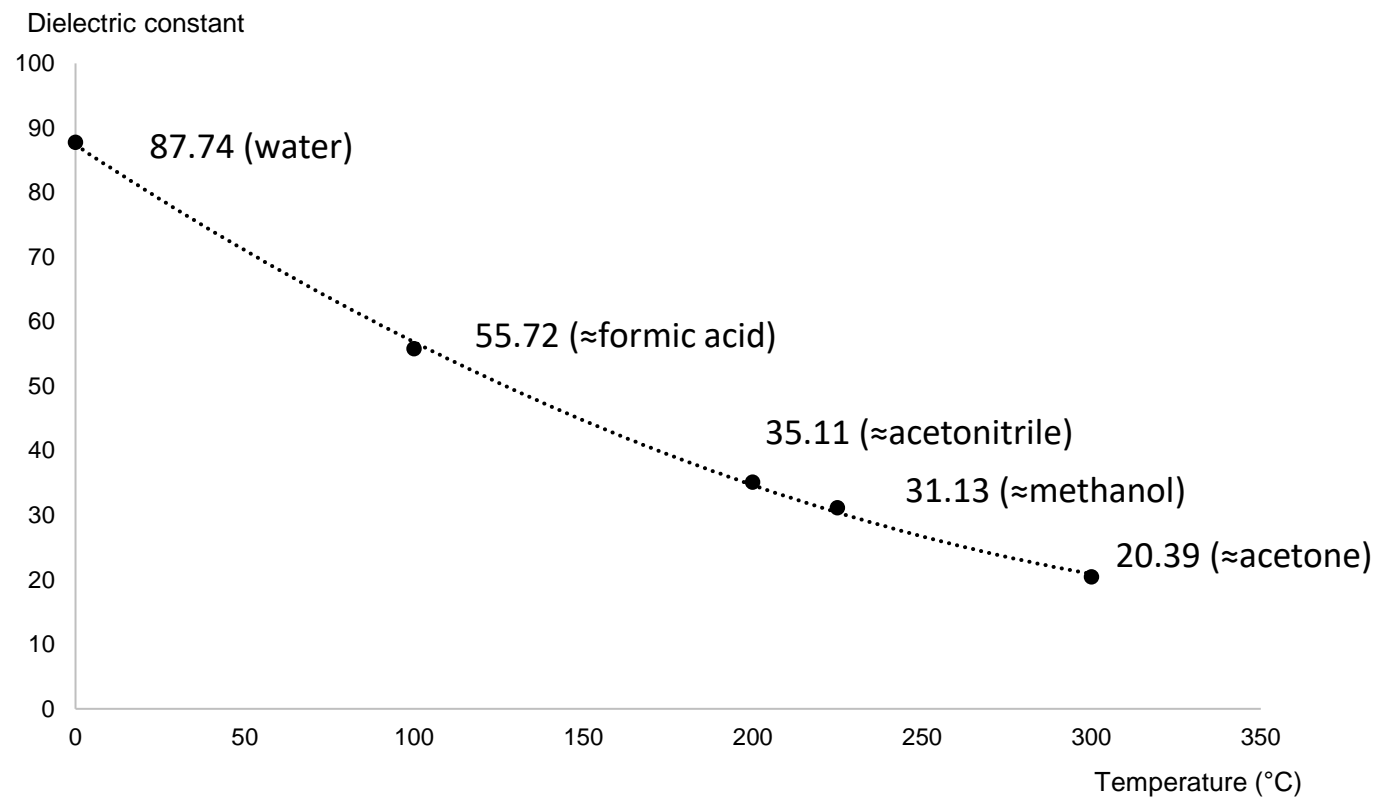


Figure 5

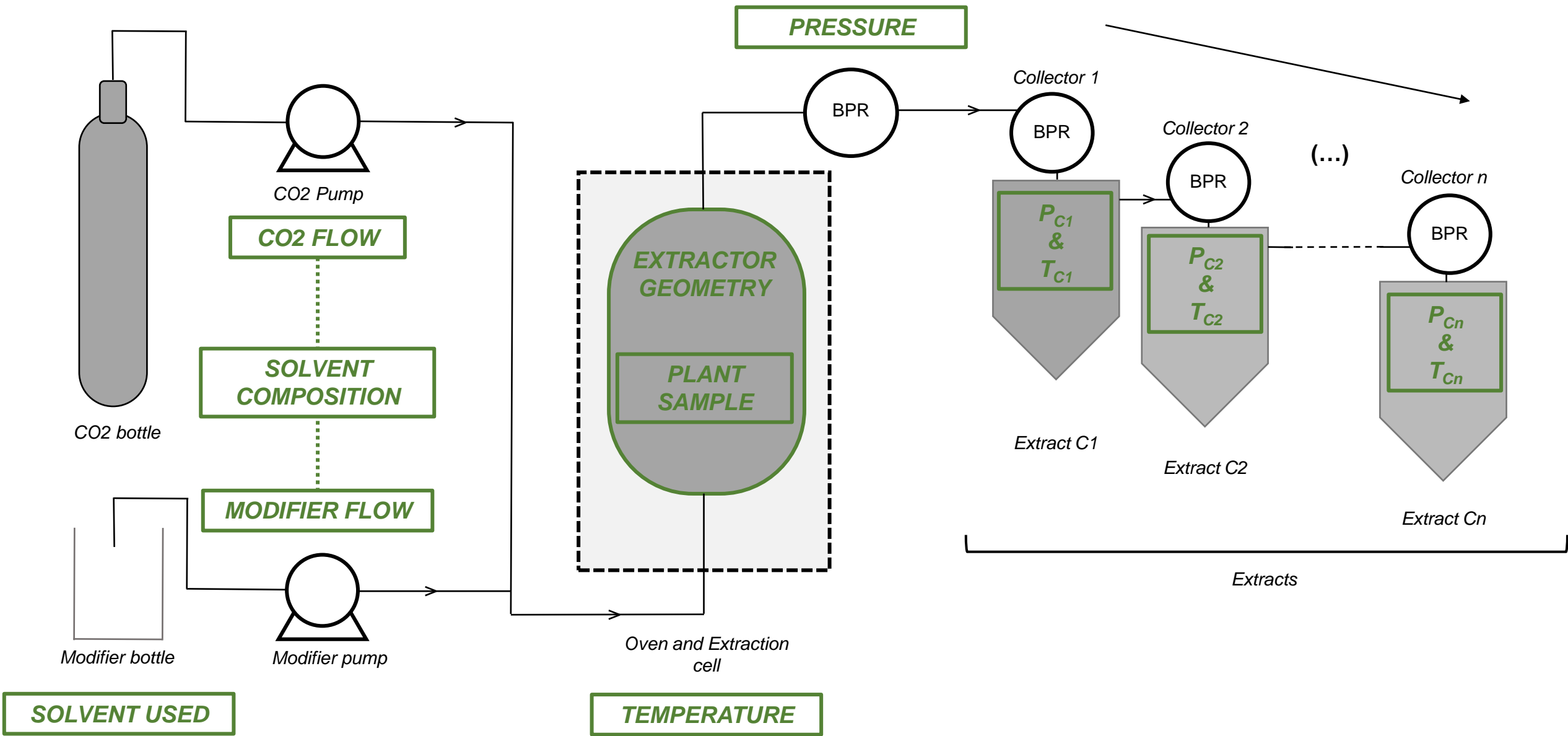


Figure 6

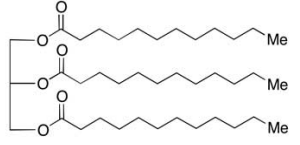
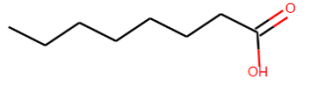
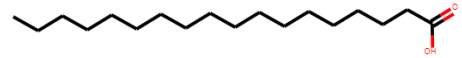
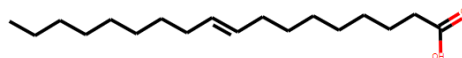
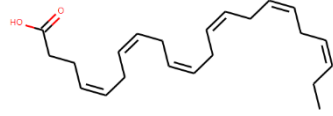
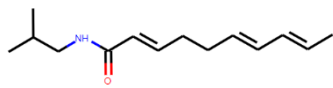
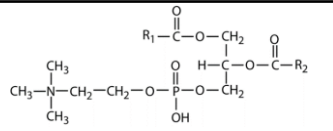
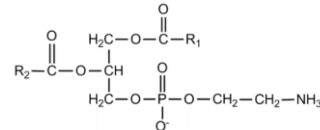
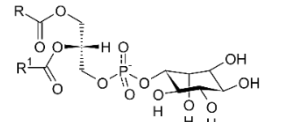
LIPIDS			
FAMILY	COMPOUNDS	LogP	FORMULAS
<i>Glycerides (mainly triglycerides)</i>	Trilaurin (C12:0)	11.7	
<i>Free Fatty acids</i>	FFA C8:0	2.4	
	FFA C18:0	6.3	
	FFA C18:1 Octadecenoic acid	6.1	
	DHA C22:6	6.5	
	Spilanthol	3.2	
<i>Phospholipids</i>	Phosphatidylcholine (i.e. C16:0 and C18:1)	11.2	
	Phosphatidylethanolamine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

Table S1

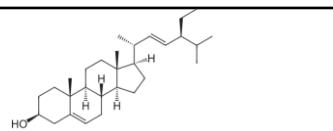
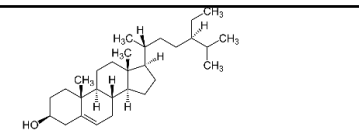
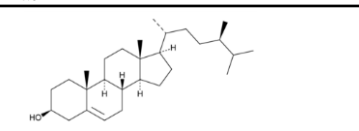
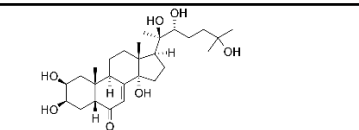
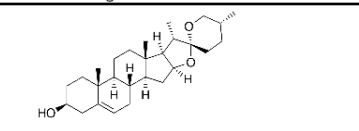
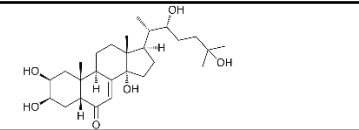
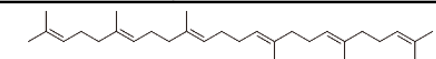
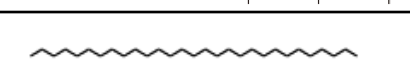
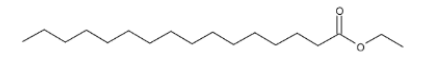
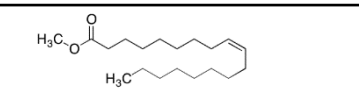
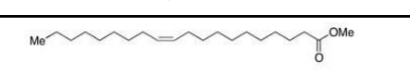
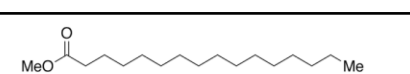
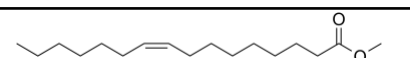
LIPIDS			
FAMILY	COMPOUNDS	LogP	FORMULAS
<i>Non-saponifiable (waxes, steroids, alcanes)</i>	Stigmasterol	7.8	
	β -sitosterol	8.0	
	Methylcholesterol	7.6	
	20-hydroxyecdysone	1.9	
	Diosgenin	5.7	
	β -ecdysone	2.7	
	Squalene	10.6	
	Nonacosane	11.6	
<i>Fatty esters</i>	Ethyl palmitate	6.0	
	Methyl oleate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

Table S2

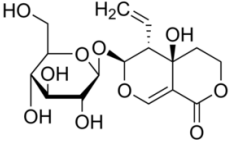
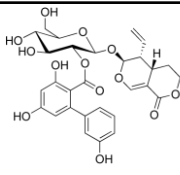
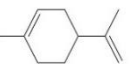
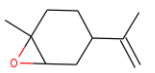
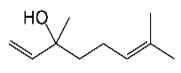
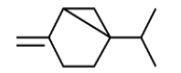
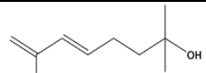
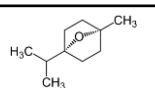
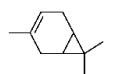
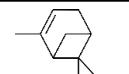
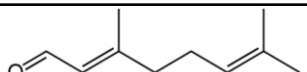
TERPENES			
FAMILY	COMPOUNDS	LogP	FORMULAS
<i>Monoterpenoids</i>	Swertiamarin	-2.5	
	Amarogentin	1.1	
<i>Monoterpenes</i>	Limonene	3.3	
	Limonene oxide	2.5	
	Linalool	2.7	
	Sabinene	3.0	
	Ocimenol	2.7	
	1.8-Cineole (also known as eucalyptol)	2.7	
	δ-3-carene	3.0	
	α-pinene	3.0	
	Geranial (also known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

Table S3

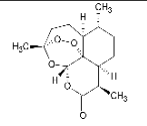
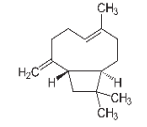
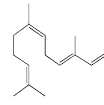
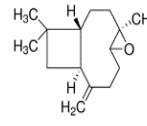
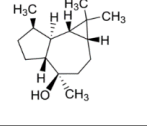
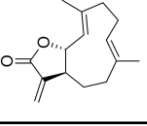
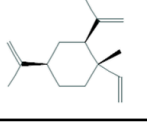
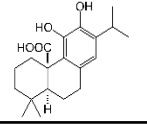
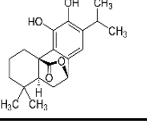
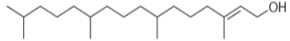
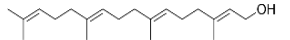
TERPENES			
FAMILY	COMPOUNDS	LogP	FORMULAS
<i>Sesquiterpenes</i>	Artemisinin	2.4	
	α -caryophyllene	4.7	
	α -farnesene	5.2	
	Caryophyllene oxide	3.9	
	Globulol	3.5	
	Germacranolides (i.e. costunolide)	3,6	
	β -elemene	4.7	
<i>Diterpenes</i>	Carnosic acid	4.3	
	Carnosol	4.3	
	Phytol	6.4	
	Geranylgeraniol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

Table S4

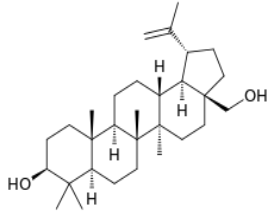
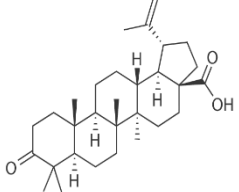
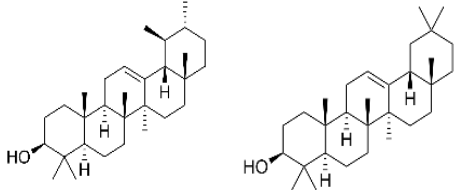
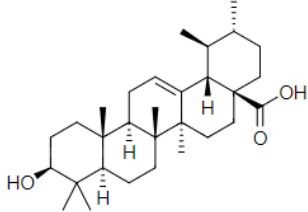
TERPENES			
FAMILY	COMPOUNDS	LogP	FORMULAS
<i>Triterpenes</i>	Betulin	7.0	
	Betulonic acid	7.3	
	α/β -amyrin	8.0/7.0	 <i>Alpha</i> <i>Beta</i>
	Ursolic acid	7.1	

Table S5

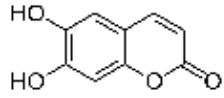
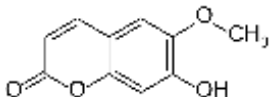
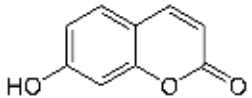
COUMARINS		
COMPOUNDS	LogP	FORMULAS
Esculetin	1.2	
Scopoletin	1.5	
7-hydroxy coumarine	1.5	

Table S6

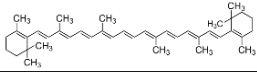
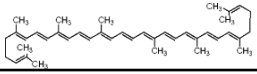
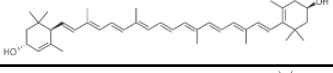
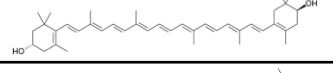
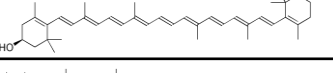
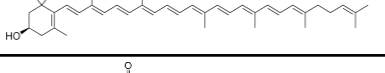
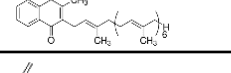
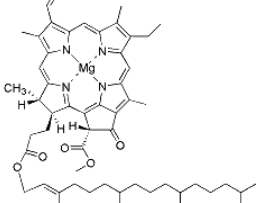
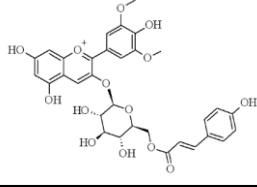
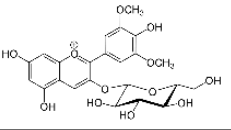
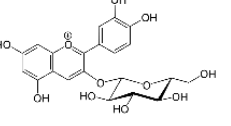
PIGMENTS			
FAMILY	COMPOUNDS	LogP	FORMULAS
<i>Carotenoids</i>	β -carotene	12.6	
	Lycopene	12.9	
	Lutein	10.4	
	Zeaxanthin	10.5	
	Cryptoxanthin	11.6	
	Rubixanthin	11.7	
	Menaquinon-7	8.9	
<i>Chlorophylls</i>	Chlorophyll a	12.8	
<i>Anthocyanins</i>	Malvidin-3-O-(6-p-coumaroyl)glucoside	2.7	
	Malvidin-3-O-glucosides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

Table S7

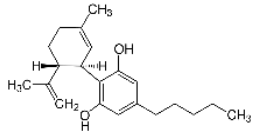
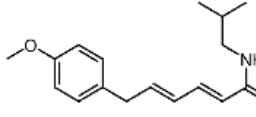
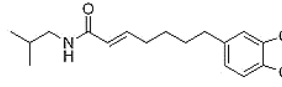
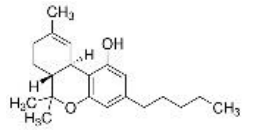
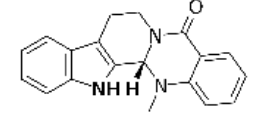
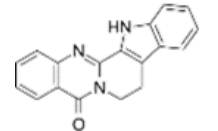
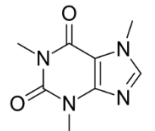
CANNABIDNOIDS AND ALKALOIDS		
COMPOUNDS	LogP	FORMULAS
Cannabidiol (CBD)	5.8	
Piperovatine	3.1	
Pipercollosidine	3.5	
Tetrahydrocannabinol	5.7	
Evodiamine	3.3	
Rutaecarpine	3.1	
Caffein	-1.0	

Table S8

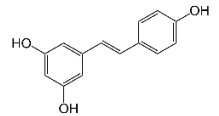
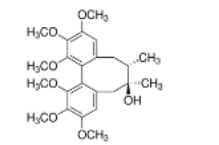
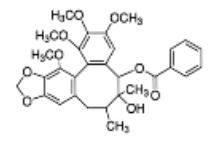
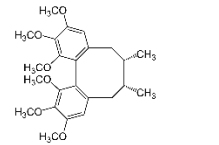
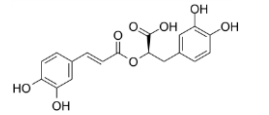
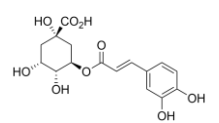
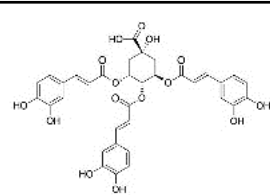
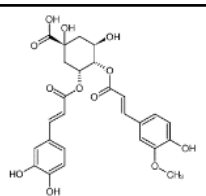
POLYPHENOLS			
FAMILY	COMPOUNDS	LogP	FORMULAS
<i>Stilbenes</i>	Resveratrol	3.0	
<i>Lignans</i>	Schizandrin	3.9	
	Schisantherin a	5.0	
	Deoxyschizandrin	4.8	
<i>Phenols</i>	Rosmarinic acid	1.8	
	Chlorogenic acid (3-caffeoylquinic acid)	-0.6	
	Tricaffeoylquinic acid	2.7	
	4,5-dicaffeoylquinic acid	1.0	

Table S9

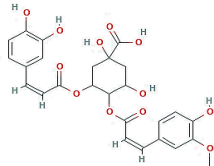
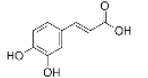
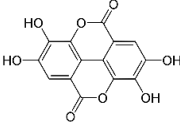
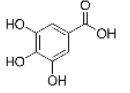
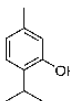
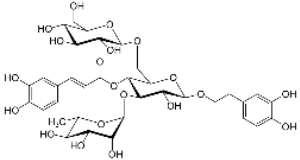
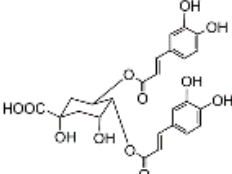
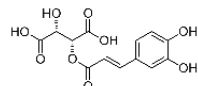
POLYPHENOLS			
FAMILY	COMPOUNDS	LogP	FORMULAS
<i>Phenols</i>	3-caffeoyl-4-feruloylquinic acid	1.3	
	Caffeic acid	1.2	
	Ellagic acid	1.3	
	Gallic acid	0.5	
	Thymol	2.8	
	Echinacoside	-3.2	
	Cynarine	1.0	
	Caftaric acid	-0.4	

Table S10

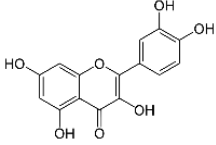
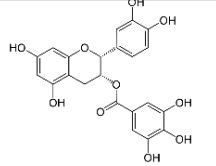
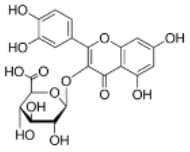
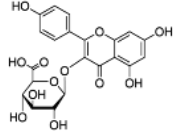
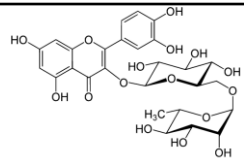
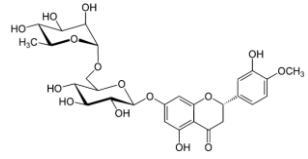
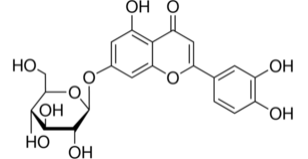
POLYPHENOLS			
FAMILY	COMPOUNDS	LogP	FORMULAS
<i>Flavonoids</i>	Quercetin	2.0	
	Quercitrin	0.5	
	Quercetin-3-O-β-D-glucuronide	-0.4	
	Kaempferol-3-O-β-D-glucuronide	-0.2	
	Rutin	-1.7	
	Hesperidin	-1.2	
	Luteolin-7-O-glucoside	-0.2	

Table S11

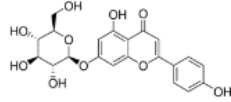
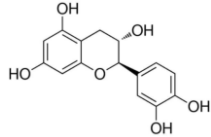
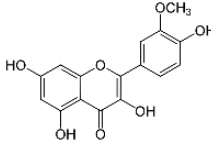
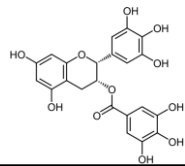
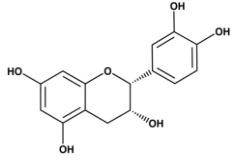
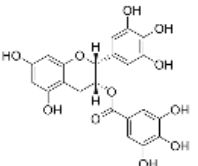
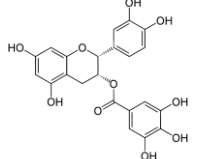
POLYPHENOLS			
FAMILY	COMPOUNDS	LogP	FORMULAS
<i>Flavonoids</i>	Apigenin-7-O-glucoside	0.0	
	Catechin (CT)	1.5	
	Isorhamnetin	2.3	
	Epigallocatechin (EGC)	1.3	
	Epicatechin (ECT)	1.5	
	Epigallocatechin gallate (EGCG)	2.2	
	Epicatechin gallate (ECG)	2.5	

Table S12

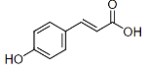
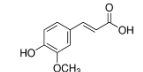
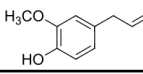
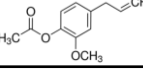
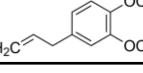
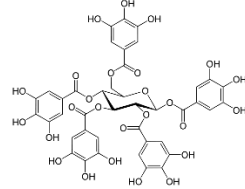
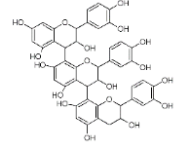
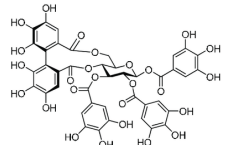
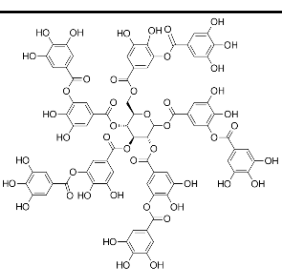
POLYPHENOLS			
FAMILY	COMPOUNDS	LogP	FORMULAS
<i>Phenylpropenes</i>	P-coumaric acid	1.5	
	Trans-ferulic acid	1.5	
	Eugenol	2.1	
	Eugenyl acetate	2.3	
	Methyl eugenol	2.4	
<i>Tannins</i>	Hydrolysable tannins (i.e. 1.2.3.4.6-Pentagalloyl glucose)	1.7	
	Condensed tannins (i.e. Procyanidin C1)	4.4	
	Tellimagrandin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

Table S13

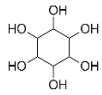
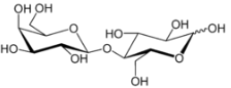
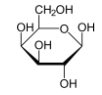
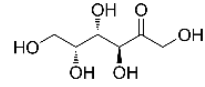
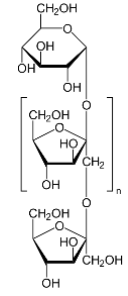
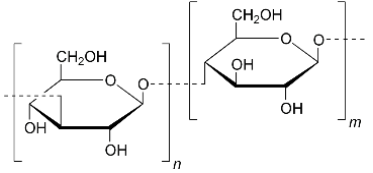
CARBOHYDRATES		
COMPOUNDS	LogP	FORMULAS
Inositols	-3.8	
Lactose	-5.4	
Galactose	-3.4	
Tagatose	-3.4	
POLYSACCHARIDES		
Inulin (i.e. n=35)	-83.7	
β -glucan (i.e. n=1 et m=2)	-7.6	

Table S14

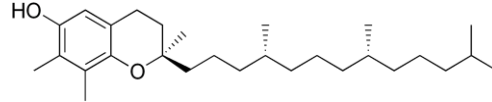
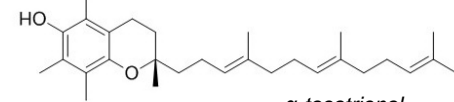
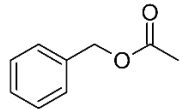
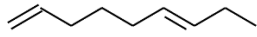
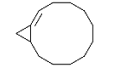
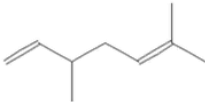
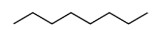
OTHERS		
COMPOUNDS	LogP	FORMULAS
γ -tocopherols	8.5	
γ/α -Tocotrienol	8.3/8.6	 <i>α-tocotrienol</i>
Benzyl acetate	1.7	
3.9-dodecadien	3.3	
Bicyclo[10.1.0]tridec-1-ene	4.1	
3.6-Dimethyl-1.5-heptadiene	3.2	
Octane	3.4	

Table S15