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► **To cite this version:**

Ombéline Claux, Cyrille Santerre, Maryline Abert-Vian, David Touboul, Nadine Vallet, et al.. Alternative and sustainable solvents for green analytical chemistry. *Current opinion in green and sustainable chemistry*, 2021, 31, pp.100510. 10.1016/j.cogsc.2021.100510 . hal-03378099

HAL Id: hal-03378099

<https://hal.science/hal-03378099v1>

Submitted on 14 Oct 2021

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Alternative and Sustainable Solvents for Green Analytical Chemistry

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Abstract

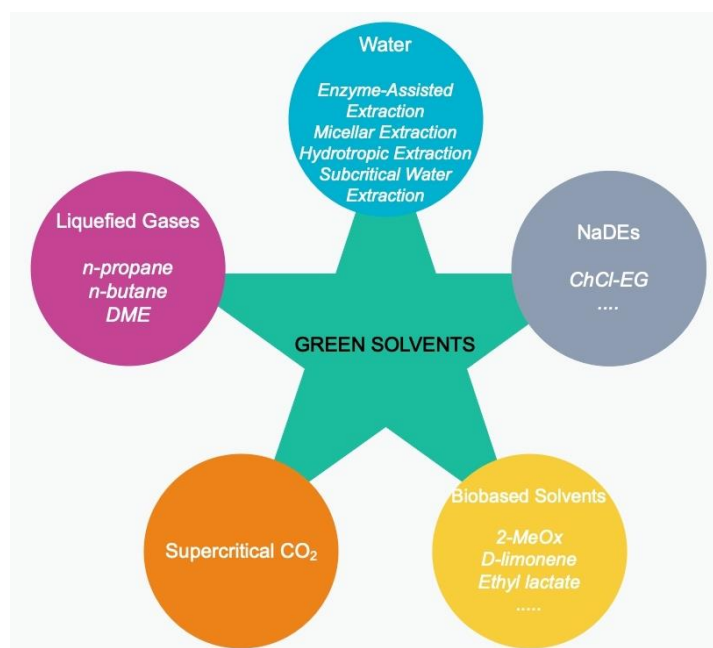
Analytical chemistry relies massively on solvents, which are generally petroleum-based and have hazardous effects. The ideal alternative solvents suitable for analysis should have high selectivity, solvency, low toxicity and low environmental impacts, be easily biodegradable and recyclable and obtained from renewable resources at a reasonable price. Obviously, finding the ideal solvent that meets all the aforementioned requirements is a big challenge. Therefore, the selection of the optimum solvent will always be a compromise depending on the extraction procedure, the analytical method, the matrix and the target molecules. In this current opinion we provide an instantaneous picture of current knowledge on alternative and sustainable solvents used in analytical laboratories either for sample preparation or analysis in terms of innovation and development of safe products and procedures.

Keywords

Alternative solvent, green extraction, green analysis, NADES, bio-based solvents, supercritical solvent, liquefied gases

28 Introduction

29 The greenest and most sustainable solvent that could be used in analytical chemistry is
 30 undoubtedly no solvent. However, both sample preparation and analytical methods require
 31 solvent, to have samples in liquid form and enable convenient separation of molecules of
 32 interest. Common solvents are principally volatile organic compounds (VOCs) obtained from
 33 non-renewable petrochemical resources and suspected to be harmful to both human health and
 34 the environment. Due to the new emphasis on environmental and safety protections and the
 35 development of green chemistry, finding alternative solvents to petroleum-derived solvents has
 36 become a major concern for analytical chemists. Therefore, sustainable alternatives are getting
 37 more and more numerous and the suitable solvent needs to be chosen wisely. This current
 38 opinion is aimed to give an instantaneous picture of current knowledge on alternative and
 39 sustainable solvents (Figure 1) used in analytical laboratories either for sample preparation or
 40 analysis.



41

42

Figure 1. Alternative and sustainable solvents

43 Alternative solvents for sample preparation

44 *Overview of alternative solvents for sample preparation*

45 The common belief is generally that water is the greenest and safest solvent, partly because it
 46 is the most abundant molecule on the Earth's surface. Water also presents the advantages of
 47 having a low economical cost, being environmentally harmless and non-toxic. The simplest and
 48 most conventional way to perform extraction using water as a solvent is maceration [1]. The

49 procedure can be optimized regarding soaking time, temperature and the repetition of several
50 extraction steps to exhaust the matrix. The properties of water can be slightly modified by using
51 specific additives. For example, the addition of enzymes can greatly improve the selectivity or
52 the efficiency of the extraction [2]. A wide range of enzymes are available with specific
53 properties, mode of action and operational conditions. Micellar and hydrotropic extractions also
54 rely on water and an additional compound, respectively a surfactant and a hydrotrope. Those
55 amphiphilic molecules can improve the solubility of hydrophobic compounds in the aqueous
56 media by respectively forming micelles and aggregates [3,4]. The main difference between the
57 two techniques is that micellar extraction resembles a two-liquid-phase extraction method
58 (above a temperature called “cloud point” micelles become instable and two phases are formed)
59 while hydrotropic extraction only involves a continuous liquid phase. Subcritical water
60 extraction (SWE) can be used to extract non-polar compounds with water as well. SWE takes
61 place at temperatures between the boiling and critical points of water, *i.e.* 100°C at 1 bar and
62 374.1°C at 221 bar, at pressures high enough to keep water in the liquid state. The polarity of
63 subcritical water is measured by the value of its dielectric constant ϵ , which decreases as
64 temperature increases. Therefore, by tuning water temperature at high pressure, its polarity can
65 be modulated to become similar to those of organic solvents in order to target specific molecules
66 of interest [5].

67 Natural Deep Eutectic Solvents (NADESs) are mixtures of natural solids (common primary
68 metabolites such as sugars, organic acids, amino acids, alcohols and choline chloride [6–8])
69 that have melting points far below those of any of their individual components. This specificity
70 is mainly due to the generation of intermolecular hydrogen bonds between hydrogen bond
71 acceptors and hydrogen bond donors. NADESs are environmentally friendly and readily
72 biodegradable as they are considered the third solvent in living cells [9]. This feature explains
73 their high solubilizing capacity for natural products. The large number of combinations that can
74 be made, their simple preparation and low cost are also major advantages that are encouraging
75 research on their extraction applications.

76 The term “bio-based solvents” gathers a lot of biomolecules that can be sorted into three
77 categories based on the agro-sector they are produced from: cereal/sugar, oleo-proteaginous
78 and wood. Bio-solvents obtained from cereal or sugar sources are mainly obtained by
79 fermentation of sweet juices and valorization of lignocellulose residues derived from cereal
80 production wastes. In this category we can find for example ethanol [10], ethyl acetate [11],
81 esters of lactic acid [12], derivatives of succinic acid, or furfural and its derivatives such as 2-

82 methyl-tetrahydrofuran also known as 2-methyloxolane (2-MeOx) [13] or cyclopentyl methyl
83 ether (CPME) [14]. The oleo-proteaginous bio-based solvents are produced from oilseeds
84 (sunflower, soybean, rapeseed). It is typically the case of fatty acid esters and glycerol
85 derivatives. The wood sector offers the possibility to produce terpene hydrocarbons such as d-
86 limonene, p-cymene or α - and β -pinene from conifers or fruit peels. Overall, a wide range of
87 bio-based solvents are currently available and each one has its own specificities and properties.
88 The selection of a particular solvent makes it possible to target specific molecules to extract
89 and analyze such as polyphenols, carotenoids, aromas or lipids.

90 Liquefied gases are gases that can be liquefied under their own vapor pressure inside a
91 pressurized container and under moderate pressure (1 to 100 bar). They offer the advantages
92 of dissolving natural substances at relatively low temperatures avoiding deterioration of
93 sensitive components and being easy to remove from the extracts due to their volatility. More
94 and more studies report the use of liquefied gases as green solvents for extraction such as *n*-
95 propane [15], *n*-butane [16] and dimethyl ether (DME) [17].

96 Supercritical fluids (SFs) are substances at conditions of temperature and pressure above their
97 critical point. Under these conditions, the fluid phase possesses characteristics between those
98 of gas and liquid phases. The main advantage of a SF is that its density (and hence its solvating
99 power) can be tuned by changing its pressure and/or temperature, permitting selective
100 extraction of target analytes. On top of that, SFs exhibit almost no surface tension making them
101 able to penetrate microporous materials and leave almost no solvent residue in the final extract.
102 Carbon dioxide (CO₂) is the most commonly used SF thanks to its moderate critical temperature
103 and pressure, *i.e.* 31°C and 74 bar. Moreover, this fluid is inert, inexpensive, non-flammable,
104 environmentally sustainable odorless and tasteless. A lot of studies report the use of
105 supercritical CO₂ for the extraction of various analytes such as essential oils, carotenoids or
106 vegetable oils [18].

107 Table 1. Examples of application of alternative solvents for sample preparation^a

Technique	Matrix	Analytes	Conditions	Analysis	Reference
Water					
Conventional maceration	Apple pomace	Polyphenols	100°C, 1 h, pH 2.5, SLR 1:5 (w/v), repeated 4 times	UHPLC-DAD, UHPLC-MS	[1]
Enzyme-assisted extraction	Tomato waste	Lycopene	40°C, 5 h, ESR 0.2 (v/w)	HPLC-DAD	[2]
Surfactant-assisted extraction	Orange peel	Pectin	7 min, 400 W, pH 1.2, LSR 21.5 (v/w), 8 g/L surfactant	FTIR	[3]
Hydrotrope extraction	Rosemary leaves	Carnosic acid	RT, 24 h, pH 2, SLR 1:10 (w/v), 30%w amphiphile solution	HPLC-UV	[4]
Subcritical water extraction	Defatted orange peels	Flavanones	150°C, 10 MPa, 10 mL/min	HPLC-UV	[5]
NADESS					
ChCl-MA ratio 1:1	<i>Ginkgo biloba</i> leaves <i>Panax ginseng</i> leaves	Phenolic acids Saponins	40°C, 1 h, SLR 1:20 (w/v)	HPTLC	[7]
ChCl-EG ratio 1:4, 10%w water	Orange peels	Polyphenols	60°C, 100 min, SLR 1:10 (w/v)	HPLC-UV	[8]
ChCl-Gly ratio 1:1	<i>Byrsonima intermedia</i> leaves	Polyphenols	45°C, 25 min, SLR 1:15 (w/v)	HPLC-DAD, UHPLC-MS	[6]
Bio-based solvents					
EtOH	Bilberry	Polyphenols	UAE, 24 kHz, 30 min, SLR 1:10 (w/v)	HPTLC	[10]
Ethyl acetate	Blackcurrant pomace	Polyphenols	Maceration, RT, SLR 1:100 (w/v), repeated 3 times	HPLC-DAD	[11]
Ethyl lactate	Turmeric	Curcuminoids	Maceration, RT, 30 min, SLR 1:1000 (w/v)	HPLC-DAD	[12]
2-MeOx	Lentisk fruits	Oil	Soxhlet, 45-60°C, 8 h, SLR 1:4 (w/v)	HPTLC, GC-FID	[13]
CPME	<i>Litsea cubeba</i> kernels	Oil	Reflux, BP, 3 h, SLR 1:20 (w/v)	GC-FID, GC-MS, HPLC-UV	[14]
Liquefied gases					
<i>n</i> -butane	Flaxseed	Oil	54°C, 0.5 MPa, 1 h, SLR 1:20 (w/v)	GC-FID	[16]
<i>n</i> -propane	Cashew nuts	Oil	60°C, 8 MPa, 1 h, 6%w EtOH	GC-FID, GC-MS, HPLC-MS	[15]
DME	<i>Chaetoceros gracilis</i> <i>Pleurochrysis carterae</i>	Lipids	25°C, 0.59 MPa, 45 min	GC-MS	[17]
Supercritical fluid extraction					
CO ₂	Apple seeds	Oil Phenolic compounds	40°C, 24 MPa, 140 min, flow rate 1 L/h	GC-FID, HPLC-MS	[18]

108 ^aChCl, choline chloride; MA, malic acid; EG, ethylene glycol; Gly, glycerol; MeOH, methanol; EtOH, ethanol; DMC, dimethyl
109 carbonate; 2-MeOx, 2-methyloxolane; CPME, cyclopentyl methyl ether; DME, dimethyl ether; SLR, solid:liquid ratio; LSR,
110 liquid:solid ratio; ESR, enzyme:substrate ratio; RT, room temperature; BP, boiling point; PLE, pressurized liquid extraction;
111 UAE, ultrasound-assisted extraction; UHPLC, ultra-high-performance liquid chromatography; HPLC, high-performance liquid
112 chromatography; FTIR, Fourier transform infrared spectroscopy; HPTLC, high-performance thin layer chromatography; GC,
113 gas chromatography; DAD, diode array detector; UV, ultra-violet detector; MS, mass spectrometer

114 *Success story*

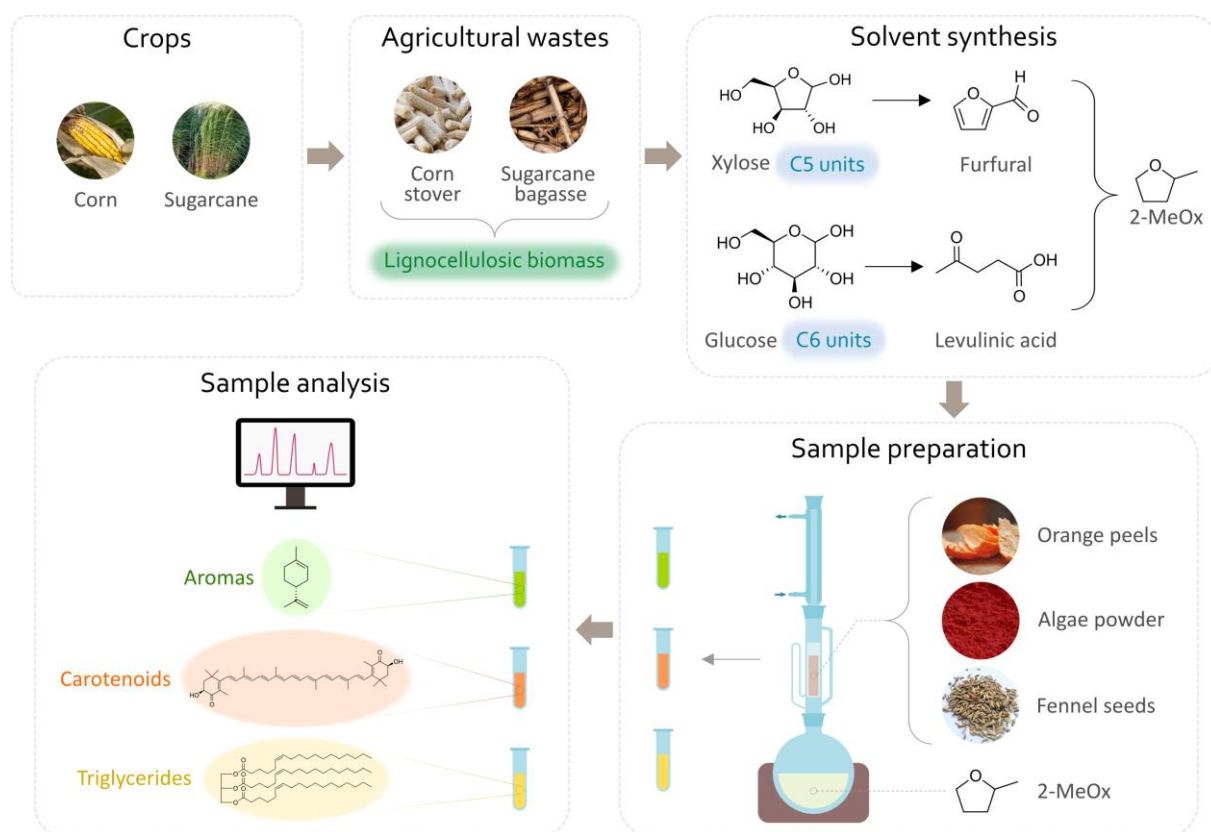
115 2-methyloxolane (2-MeOx), also known as 2-methyltetrahydrofuran, is a cyclic ether issued
116 from carbohydrates obtained from lignocellulosic biomass. 2-MeOx is produced at industrial
117 scale from agricultural wastes as corn stover or sugarcane bagasse. Its production involves three
118 steps: (i) a harsh acidic treatment of the material for deconstructing lignocellulose and release
119 pentose and hexose sugar units; (ii) a biorefining process for the conversion of C5 and C6 sugar
120 units into furfural and levulinic acid respectively; (iii) several hydrogenation reactions from
121 furfural and levulinic acid to finally obtained 2-MeOx [19].

122 Recently, the potential of 2-MeOx to extract aromas from different matrices was investigated.
123 In 2019, Ozturk *et al.* used 2-MeOx among other bio-based solvents to perform the extraction
124 of limonene from orange peel residues and compared the results to those obtained with hexane
125 [20]. At optimum conditions, it was found that 2-MeOx outperformed hexane by increasing
126 limonene extraction yield by 40%. The following year, its ability to extract volatile compounds
127 from hop cones was also demonstrated [21]. This time again the aroma yield obtained with 2-
128 MeOx (20.2%) was higher than what was obtained with *n*-hexane (17.9%) and both extracts
129 had similar compositions and olfactory profiles.

130 2-MeOx appears to be an efficient bio-based solution for preparation of color samples as well,
131 particularly in the case of carotenoids. Its efficiency was lately evaluated to recover astaxanthin
132 from *Haematococcus pluvialis* cultures [22]. 2-MeOx enabled more than 80% of carotenoid
133 recovery in only 30 min and was hence one of the most effective bio-based solvent tested in
134 this study.

135 More and more studies report the efficiency of 2-MeOx for lipid extraction, either from plant
136 seeds, fruits, microalgae, microorganisms, or even animals such as larvae. As illustrations, the
137 studies of Bettaieb Rebey *et al.* on fennel and anise oils [23], and Ravi *et al.* on black soldier
138 fly larvae lipids [24] can be cited. Briefly, the papers describe that 2-MeOx enables a higher
139 crude oil yield than the benchmark *n*-hexane and that the extracts have similar fatty acid
140 profiles. 2-MeOx also provides extracts with higher phospholipids and total phenolic contents
141 than the conventional ones.

142 Overall, the results of recent studies on the possible use of 2-MeOx for extraction purposes
143 indicate that this bio-based solvent is suitable for eco-extraction of different analytes. Therefore,
144 it could replace hazardous petrochemical solvents as *n*-hexane, chloroform, dichloromethane
145 etc. in sample preparation stages for analysis of aromas, colors or lipids.



146

147 Figure 2. 2-MeOx as a bio-based alternative solvent for sample preparation in analytical
 148 chemistry

149 **Alternative solvents for analysis**

150 *Overview of alternative solvents for analysis*

151 The most widely used chromatography technique in the literature is currently reverse phase
 152 chromatography (RPLC) using C18 columns and binary water/acetonitrile mixtures.
 153 Acetonitrile is a toxic solvent obtained as a by-product of the production of acrylonitrile, the
 154 manufacture and use of which has a high environmental cost. One of the simplest alternatives
 155 is the use of alcohol, particularly ethanol, as a substitute for acetonitrile. Dogan *et al.* [25]
 156 demonstrated in 2020 the separation of pharmaceutical compounds such as famotidine,
 157 paracetamol and thiocolchicoside with water + phosphate buffer / ethanol gradients with similar
 158 sensitivity than methods based on water/acetonitrile mixtures. Another option is to eliminate
 159 the use of acetonitrile by drastically modifying the chromatographic conditions while keeping
 160 C18 stationary phase. For example, Ali *et al.* [26] proposed the separation of terephthalic acid
 161 (TPA) contaminants (mono-, di-, and tri-carboxylic aromatic acids) by saturating the stationary
 162 phase with Tween 20 (polyoxyethylene(20)sorbitan monolaurate) and eluting the compounds
 163 under isocratic conditions with a mobile phase composed of acidified water (pH 2) by a
 164 sulphuric acid solution. Finally, the water can also be employed as a subcritical fluid. The

165 dielectric constant of water together with the surface tension and viscosity are decreasing when
166 increasing temperature from 25°C to 250°C, meaning that subcritical water at 250°C has lower
167 polarity than pure methanol or acetonitrile. Therefore, Doctor and Yang [27] described the use
168 of subcritical water with phosphate buffer at pH between 3.4 and 3.85 for the separation and
169 analysis of aspirin and metformin HCl on C18 column.

170 It is also possible to eliminate the use of water and acetonitrile in micellar liquid
171 chromatography to achieve chromatographic analysis still on C18 column. Ramezani and
172 Absalan [28] published in 2019 the monitoring of melanin concentration in milk by micellar
173 liquid chromatography using a mobile phase containing a mixture of sodium dodecyl sulphate
174 (SDS) and a mixture of choline chloride-ethylene glycol-based natural deep eutectic solvent
175 (NADES), butanol, and glacial acetic acid. NADESs were firstly introduced by Choi *et al.*
176 (2011) [29] as a third class of liquids, unlike water and lipid phase, existing in living cells, and
177 playing a crucial role as an alternative medium for biosynthesis, transport and storage of
178 compounds with intermediate polarity. Due to their liquid stability within a wide temperature
179 range, very low volatility, chemical and thermal stability, non-flammability, and nontoxic
180 constituents, NADESs are considered as green solvents. The same methodology was then used
181 for the efficient analysis of four crucial cardiovascular drugs, optimizing in both cases the
182 composition of the mobile phase using chemometric tools [30]. Thus, Raj [31] carried out a
183 screening of NADESs as alternative solvents in thin layer chromatography (TLC) in 2020. The
184 most successful mobile phase, which enabled separation of all the tested alkaloids, was the
185 equimolar mixture of menthol and phenol with a 35% addition of methanol, avoiding the
186 classical use of acetone, chloroform or diethyl ether.

187 Beyond the elimination of acetonitrile or even water as a chromatographic solvent,
188 enantioselective or normal phase liquid chromatography (NPLC) are based on non-polar and/or
189 chlorinated organic solvents from petrochemistry for elution. The most popular approach in the
190 literature to overcome these solvents, in particular alkanes such as hexane, is the use of CO₂ as
191 a supercritical fluid. Finally, agro-solvents such as limonene or 2-methyloxolane also play an
192 important role in the substitution of apolar or intermediate polarity solvents in chromatography
193 even if their report in the literature is still scarce [32].

194 ***Success story***

195 Supercritical CO₂ has a low viscosity with liquid-like densities and high solubilizing power.
196 Thus, the low viscosity and high diffusion allow separations and extractions 3 to 10 times faster
197 than in liquid chromatography with equivalent particle size, moreover reducing health and
198 environmental risks, and costs over long term. Supercritical CO₂ is miscible with alcohols, in
199 particular ethanol, allowing a green approach in analytical and preparative chromatography. In
200 the latter case, the purified samples are finally solubilized in alcohol, which requires little
201 energy to evaporate, while the CO₂ can be recycled up to 98% per cycle. Supercritical Fluid
202 Chromatography (SFC) is particularly suitable for the analysis of lipids, soluble in organic
203 solvents and in the initial chromatographic conditions. In particular, the work of the groups of
204 T. Bamba [33], M. Holcapeck [34] or D. Touboul [35] have demonstrated the capacity of SFC
205 to efficiently separate complex lipid mixtures (phospholipids, sphingolipids, glycolipids ...) by
206 subclasses with analytical retention times of about fifteen minutes, compared to about 45
207 minutes for classical NPLC methods using ternary mixtures of organic solvents (acetone,
208 hexane, ethyl acetate ...). Chollet *et al.* [35] illustrated this approach by the analysis of
209 *Nannochloropsis* extracts, considered as a promising alga for green industries due to its ability
210 to accumulate polyunsaturated fatty acids at a high level. These methods can be quantitative
211 within the limit of availability of pure standards for each lipid subclass. Beyond apolar analytes,
212 Ventura [36] has established that SFC is also efficient for the separation of crude therapeutic
213 peptides and peptide libraries when combining supercritical CO₂ elution with methanol and
214 additives such as trifluoroacetic acid and ammonia. In the field of large-scale compound
215 purification, supercritical CO₂ can be used as an eluent in flash chromatography [37], while the
216 use of liquid CO₂ in centrifugal tubes to conduct TLC has been established [38].

217 Table 2. Example of applications of alternative solvents for analysis^a

Solvent	Polarity	Proton donor	Technology	Target	Reference
Ethanol					
Ethanol/water	Polar	Yes	HPLC	Pharmaceutical drugs (famotidine, paracetamol, thiocolchicoside), Alkaloid (caffeine)	[25]
Water					
Liquid water	Polar	Yes	Micellar and sub-micellar liquid chromatography	TPA contaminants (mono-, di-, and tricarboxylic aromatic acids)	[26]
Subcritical water	Polar	Yes	SBWC	Pharmaceutical drugs (aspirin, metformin)	[27]
Eutectic solvents					
ChCl and EG	Polar	Yes	Modified micellar chromatography	Nitrogen aromatic compound (melamine)	[28]
				Pharmaceutical drugs (aspirin, atorvastatin, metformin, metoprolol)	[29]
Phenolics and terpenes	Polar and non polar	/	TLC	Alkaloids (sanguinarine, coptisine, chelerythrine, chelidonine, berberine)	[31]
Agro-solvents					
Limonene	Non polar	No	HPLC	Lipids (cholesteryl ester, phospholipids)	[32]
2-MeOx	Mid polar	No			
Carbon dioxide					
Supercritical CO ₂	Non polar	No	SFC	Lipids (fatty acids, phospholipids, MGDG, DGDG)	[33]
				Peptides	[34]
				Fatty acid (sorbic acid), benzoic acid (4-hydroxybenzoic acid), Vitamin (niacinamide), Pharmaceutical drugs (antipyrene, ketoprofen, ibuprofen), Nitrogen compounds (N-Benzylbenzamide, 4-dimethylamino pyridine), Alkaloids (noscipin, caffeine)	[35]
Liquid CO ₂	Non polar	No	Flash chromatography		[36]
			TLC	PAH (chamazulene)	[37]
					[38]

218 ^aChCl, choline chloride; EG, ethylene glycol; 2-MeOx, 2-methyloxolane; HPLC, high-performance liquid chromatography;
 219 SBWC, subcritical water chromatography; TLC, thin-layer chromatography; SFC, supercritical fluid chromatography; TPA,
 220 terephthalic acid; MGDG, monogalactosyldiacylglycerol; DGDG digalactosyldiacylglycerol; PAH, polycyclic aromatic
 221 hydrocarbon.

222 Future trends

223 The selection of the ideal solvent for analytical chemistry is a compromise between the
 224 efficiency of extraction procedure, the analytical method, the matrix specificities and the target
 225 molecules. Sustainable alternatives to common petrochemical and hazardous solvents for
 226 sample preparation and analysis have been discussed in this review. Two recent success stories,
 227 2-MeOx, for sample preparation, and supercritical carbon dioxide, for analytical separation
 228 have been particularly emphasized. However, the panorama depicted in this paper reminds us
 229 that in front of the complexity of target molecules in natural products, there is no universal
 230 solvent for analytical chemistry.

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