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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

Introduction

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

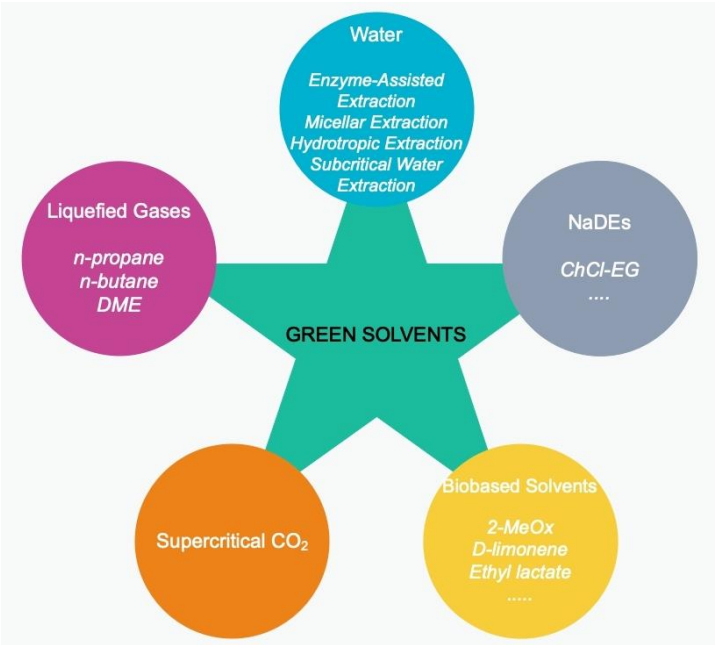

Figure 1. Alternative and sustainable solvents

Alternative solvents for sample preparation

Overview of alternative solvents for sample preparation

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

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

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

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

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

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

Supercritical fluids (SFs) are substances at conditions of temperature and pressure above their critical point. Under these conditions, the fluid phase possesses characteristics between those of gas and liquid phases. The main advantage of a SF is that its density (and hence its solvating power) can be tuned by changing its pressure and/or temperature, permitting selective extraction of target analytes. On top of that, SFs exhibit almost no surface tension making them able to penetrate microporous materials and leave almost no solvent residue in the final extract. Carbon dioxide (CO_2) is the most commonly used SF thanks to its moderate critical temperature and pressure, *i.e.* 31°C and 74 bar. Moreover, this fluid is inert, inexpensive, non-flammable, environmentally sustainable odorless and tasteless. A lot of studies report the use of supercritical CO_2 for the extraction of various analytes such as essential oils, carotenoids or vegetable oils [18].

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 molar ratio 1:1	*Gingko biloba* leaves *Panax ginseng* leaves	Phenolic acids Saponins	40°C, 1 h, SLR 1:20 (*w/v*)	HPTLC	[7]
ChCl-EG molar ratio 1:4, 10%w water	Orange peels	Polyphenols	60°C, 100 min, SLR 1:10 (*w/v*)	HPLC-UV	[8]
ChCl-Gly molar ratio 1:1	*Byrsonima intermedia* 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	*Litsea cubeba* kernels	Oil	Reflux, BP, 3 h, SLR 1:20 (*w/v*)	GC-FID, GC-MS, HPLC-UV	[14]
Liquefied gases					
n-butane	Flaxseed	Oil	54°C, 0.5 MPa, 1 h, SLR 1:20 (*w/v*)	GC-FID	[16]
n-propane	Cashew nuts	Oil	60°C, 8 MPa, 1 h, 6%w EtOH	GC-FID, GC-MS, HPLC-MS	[15]
DME	*Chaetoceros gracilis* *Pleurochrysis carterae*	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]

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

Success story

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

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

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

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

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

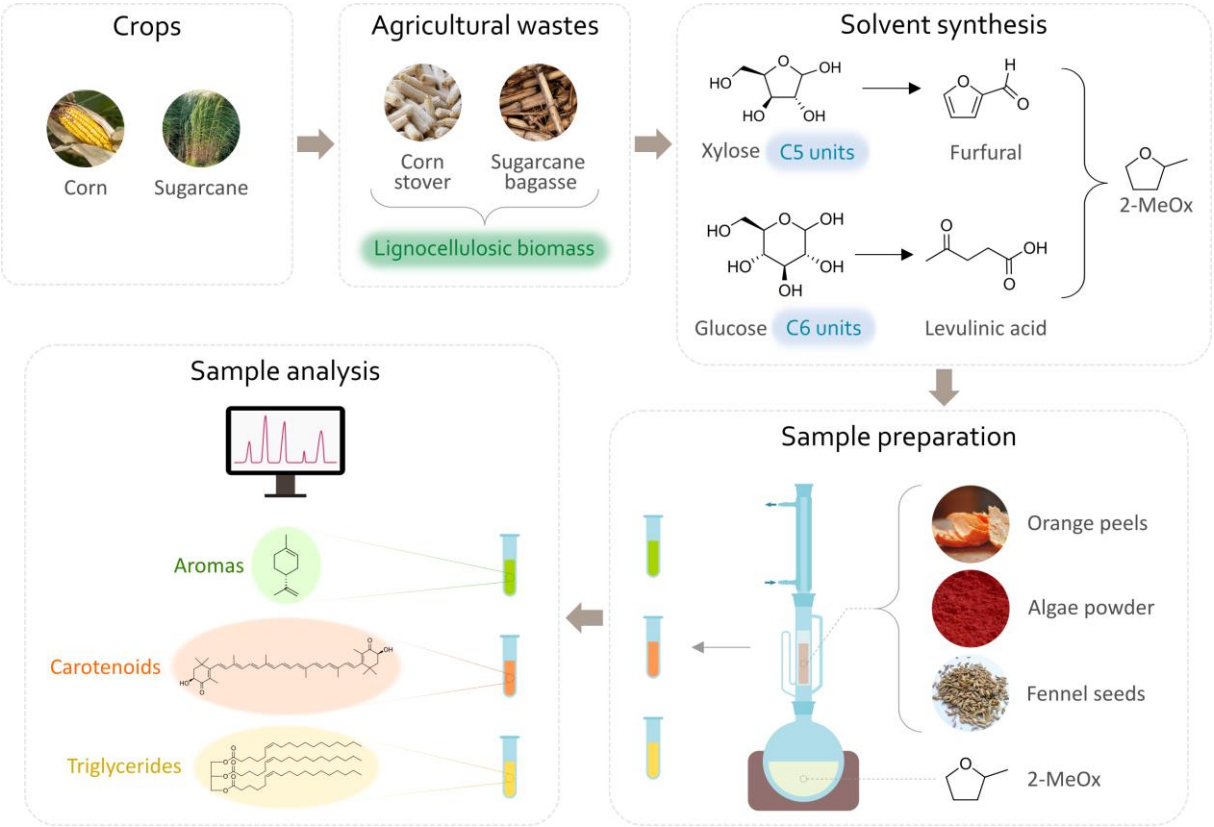

Figure 2. 2-MeOx as a bio-based alternative solvent for sample preparation in analytical chemistry

Alternative solvents for analysis

Overview of alternative solvents for analysis

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

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

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

Beyond the elimination of acetonitrile or even water as a chromatographic solvent, enantioselective or normal phase liquid chromatography (NPLC) are based on non-polar and/or chlorinated organic solvents from petrochemistry for elution. The most popular approach in the literature to overcome these solvents, in particular alkanes such as hexane, is the use of CO_2 as a supercritical fluid. Finally, agro-solvents such as limonene or 2-methyloxolane also play an important role in the substitution of apolar or intermediate polarity solvents in chromatography even if their report in the literature is still scarce [32].

Success story

Supercritical CO_2 has a low viscosity with liquid-like densities and high solubilizing power. Thus, the low viscosity and high diffusion allow separations and extractions 3 to 10 times faster than in liquid chromatography with equivalent particle size, moreover reducing health and environmental risks, and costs over long term. Supercritical CO_2 is miscible with alcohols, in particular ethanol, allowing a green approach in analytical and preparative chromatography. In the latter case, the purified samples are finally solubilized in alcohol, which requires little energy to evaporate, while the CO_2 can be recycled up to 98% per cycle. Supercritical Fluid Chromatography (SFC) is particularly suitable for the analysis of lipids, soluble in organic solvents and in the initial chromatographic conditions. In particular, the work of the groups of T. Bamba [33], M. Holcapeck [34] or D. Touboul [35] have demonstrated the capacity of SFC to efficiently separate complex lipid mixtures (phospholipids, sphingolipids, glycolipids ...) by subclasses with analytical retention times of about fifteen minutes, compared to about 45 minutes for classical NPLC methods using ternary mixtures of organic solvents (acetone, hexane, ethyl acetate ...). Chollet *et al.* [35] illustrated this approach by the analysis of *Nannochloropsis* extracts, considered as a promising alga for green industries due to its ability to accumulate polyunsaturated fatty acids at a high level. These methods can be quantitative within the limit of availability of pure standards for each lipid subclass. Beyond apolar analytes, Ventura [36] has established that SFC is also efficient for the separation of crude therapeutic peptides and peptide libraries when combining supercritical CO_2 elution with methanol and additives such as trifluoroacetic acid and ammonia. In the field of large-scale compound purification, supercritical CO_2 can be used as an eluent in flash chromatography [37], while the use of liquid CO_2 in centrifugal tubes to conduct TLC has been established [38].

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]
					[34]
					[35]
				Peptides	[36]
Liquid CO_2	Non polar	No	Flash chromatography	Fatty acid (sorbic acid), benzoic acid (4-hydroxybenzoic acid), Vitamin (niacinamide), Pharmaceutical drugs (antipyrine, ketoprofen, ibuprofen), Nitrogen compounds (N-Benzylbenzamide, 4-dimethylamino pyridine), Alkaloids (noscapin, caffeine)	[37]
			TLC	PAH (chamazulene)	[38]

[a]ChCl, choline chloride; EG, ethylene glycol; 2-MeOx, 2-methyloxolane; HPLC, high-performance liquid chromatography; SBWC, subcritical water chromatography; TLC, thin-layer chromatography; SFC, supercritical fluid chromatography; TPA, terephtalic acid; MGDG, monogalactosyldiacylglycerol; DGDG digalactosyldiacylglycerol; PAH, polycyclic aromatic hydrocarbon.

Future trends

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

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