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Applications of (natural) deep eutectic solvents in liquid phase microextraction: a review

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Abstract:	<p>Natural deep eutectic solvents (NADES) have gained significant attention as green solvents due to their unique properties, such as high solubility, low volatility, low toxicity, and tunability. Liquid phase microextraction (LPME) is a sample preparation technique that plays a crucial role in analytical chemistry, and the use of NADES as extraction solvents in LPME offers numerous benefits compared to traditional solvents. NADES can effectively extract bioactive compounds from natural sources without damaging their structure and activity. They can also serve as solvents and catalysts in organic reactions, enhancing the bioavailability of natural compounds. In addition, NADES can be utilized as mobile or stationary phases in chromatographic techniques for separating and analyzing natural compounds. The review highlights the efficiency of NADES in terms of extraction ability, analyte stabilization capacity, and detection compatibility. Moreover, the availability of their components, ease of preparation, low toxicity, cost-effectiveness, and biodegradability make NADES attractive for researchers in the field of analytical chemistry. The applications of NADES in LPME contribute to the principles of green analytical chemistry and green sample preparation by providing a sustainable and environmentally friendly approach to sample preparation. A comprehensive overview of the applications of NADES in liquid phase microextraction is provided, emphasizing their potential for advancing green practices in analytical chemistry.</p>



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Dear Editor,

Please find enclosed the revised manuscript "*Applications of (natural) deep eutectic solvents in liquid phase microextraction: a review*" submitted to the **Microchemical Journal** as a review article.

We are very grateful to the Editor and Reviewers for their suggestions. All were accepted and reported in the revised version.

Changes were highlighted in yellow in order to better evaluate the improvements following the suggestions.

We hope that in the present form the paper fulfil with Journal high quality.

The submitted manuscript matches the journal's scopes. We hope that our manuscript will receive favorable peer reviews and subsequent publication in your esteemed journal.

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Sincerely,

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Proposed Reviewers:

1. **Prof. Dr. Victoria Samanidou**; Aristotle University of Thessaloniki, Department of Chemistry, Laboratory of Analytical Chemistry, Greece; samanidu@chem.auth.gr
2. **Prof. Dr. Abuzar Kabir**; International Forensic Research Institute, Department of Chemistry and Biochemistry, Florida International University, Miami, USA, akabir@fiu.edu
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4. **Prof. Dr. Sibel A. Ozkan**; Ankara University, Faculty of Pharmacy, Ankara, Turkey; ozkan@pharmacy.ankara.edu.tr

Dear Prof. Justyna Plotka-Wasyłka;

(Editor, Microchemical Journal)

Thank you for the review of our manuscript (MICROC-D-23-05391R1) entitled “**Applications of (natural) deep eutectic solvents in liquid phase microextraction: a review**”. We have deeply considered the referees' comments and made the suggested changes to the best of our ability. These revisions are highlighted in the manuscript and are summarized below:

Comment	Response
Reviewer #1	
The authors made the requested changes. Therefore, I recommend that the article be accepted.	We are truly grateful to the Reviewer for the final evaluation and for considering this review publishable in the Journal
Reviewer #2	
	We are truly grateful to the Reviewer for the final evaluation and for considering this review publishable in the Journal
LPME again appears in the abstract without mentioning full form. Though it is given in the list of abbreviations, abstract is meant to be stand alone.	Liquid phase microextraction has been defined in the abstract at its first mention (Line 32).
Not convinced with the re-framed statements 227-31. "Besides" is not required here.	We have removed “Besides” from the re-framed statements as suggested (Line 230)
Reviewer # 3	
As stated in the first review, the main drawback of the MS is the citation of improper references and the lack of the appropriate ones, that is a sufficient argument to reject the submission (citation of the relevant references is an essential part of a review work). The entire text and tables are full of references to deep eutectic solvents (DES), not to natural deep eutectic solvents (NADES). [104, 120, 123, 124, 125, 126, 127, 129, 131, 132, 133, 134, 135, 136] An excellent review on the use of deep eutectic solvents (including some NADES) in liquid-phase microextraction was carried out by Santos et al in 2022 (Trends in analytical Chemistry, doi:10.1016/j.trac.2021.116478.), as the authors point out in line 108.	Although we agree with the reviewer that citing improper references and lacking the appropriate ones is a sufficient argument to reject a submission, we assure that this is not the case with our submission, also because the criticisms that were highlighted in the first submission were revised in R1 version following the Reviewer suggestions. In particular, in the first round of evaluation, Reviewer 3 had reported "The main drawback of the MS is the citation of improper references and the lack of the appropriate ones". This point has been extensively revised in the R1 version, as per the uploaded R1 files. He/She had made no mention of the fact that "The entire text and tables are full of references to deep eutectic solvents (DES), not to natural deep eutectic solvents (NADES). [104, 120, 123, 124, 125, 126, 127 , 129, 131, 132, 133, 134, 135, 136]. An excellent review on the use of deep eutectic solvents (including some NADES) in

liquid-phase microextraction was carried out by Santos et al in 2022 (Trends in analytical Chemistry, doi:10.1016/j.trac.2021.116478.), as the authors point out in line 108".

It almost seems that "a little at a time" wants to take time (or prevent this work from being published), especially considering that NADES are a particular category of DES (AS WRITTEN BY THE SAME REVIEWER IN THIS EVALUATION) and often the boundary between the 2 "classes" is very thin. In this case, we would like to highlight that the mentioned references refer to the preparation of DES from:

1- ChCl: phenol [104, 120, 123-127, 129, 133, 134, 136]

2- ChCl:p-cresol [131]

3- ChCl: Maltose [132]

The materials used for the preparation are natural. Therefore, DES in such cases can be classified as NADES. Herein, we provide references as proof for considering ChCl, phenol, and maltose as natural compounds available in nature:

ChCl

10.1016/j.lwt.2023.114595
10.1021/acssuschemeng.2c01976
10.3390/molecules25071619

Phenol

10.1177/074823378700300407
<https://etheses.whiterose.ac.uk/29929/1/Zeolite%20Catalysts%20for%20Water%20Treatment%20Catalytic%20Wet%20Peroxide%20Oxidation%20of%28CWPO%29%20of%20Phenol.pdf>
10.1080/03067319.2020.1738412
10.1177/07482337870030040

p-Cresol

10.1007/978-3-319-26932-0_48
10.1046/j.0269-283x.2001.00297.x

Maltose

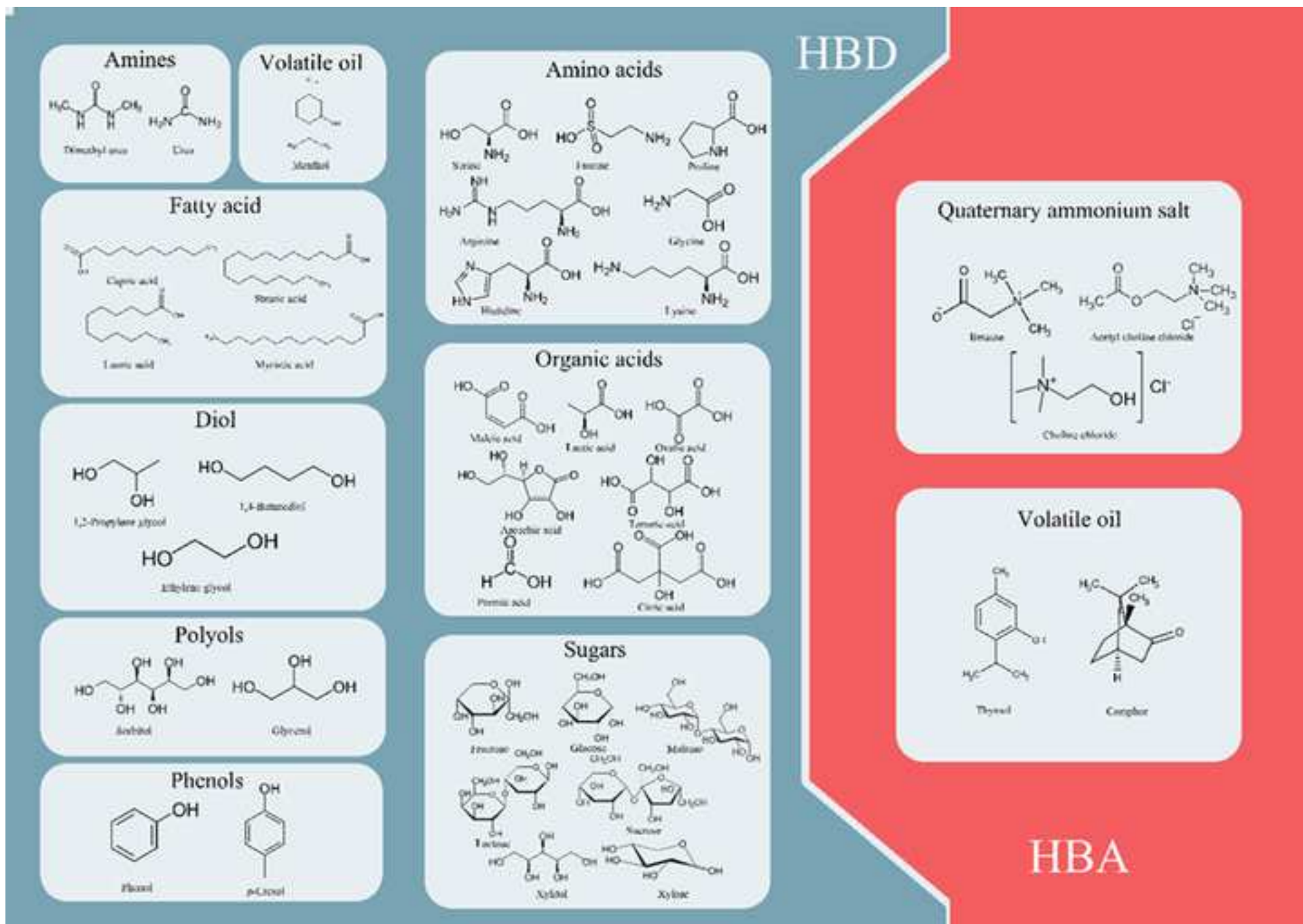
	<p>10.1016/j.seppur.2023.123271 10.25083/rbl/26.5/2936.2941 10.1111/tpj.15246</p> <p>In light of what has just been reported, and the extremely positive evaluations of the other 3 Reviewers (two specified the acceptance for publication and the third asked for 2 minimal revisions of the text), we do not understand why this Reviewer (net of further corrections and clarifications) remains in a clearly opposite position.</p> <p>However, once again we want to satisfy the Reviewer's requests and in light of what has highlighted and to avoid confusion, we believe that by changing the title of the review to "Applications of (natural) deep eutectic solvents in liquid phase microextraction: a review" (where the term "natural" is placed in brackets to indicate this subtle subdivision) may be a good compromise that satisfies the Reviewer.</p>
Reviewer # 4	
Accept	We are truly grateful to the Reviewer for the final evaluation and for considering this review publishable in the Journal

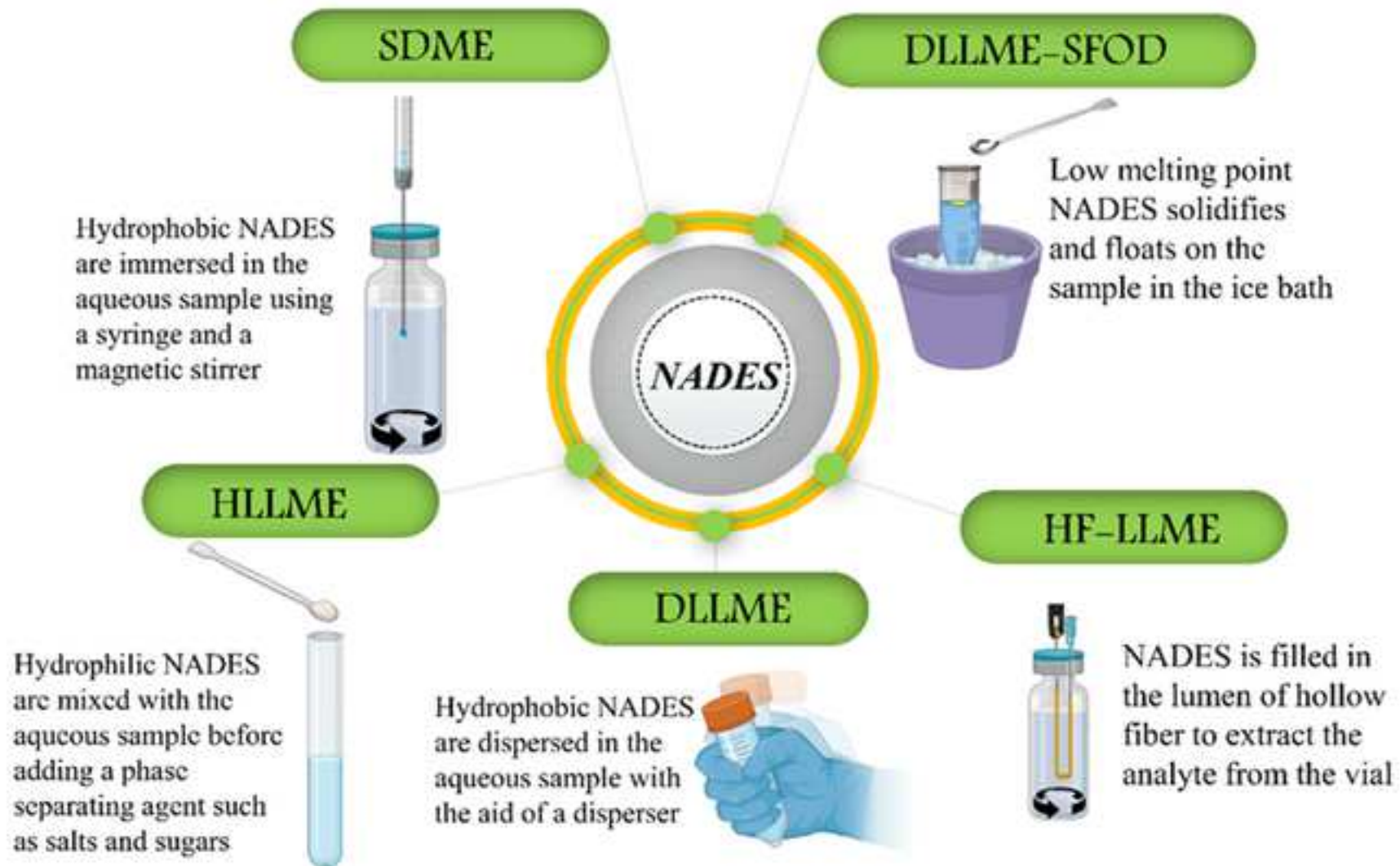
We hope the changes that have been made were appropriate and the manuscript can now be accepted for publication. Please address all correspondence to the author indicated below.

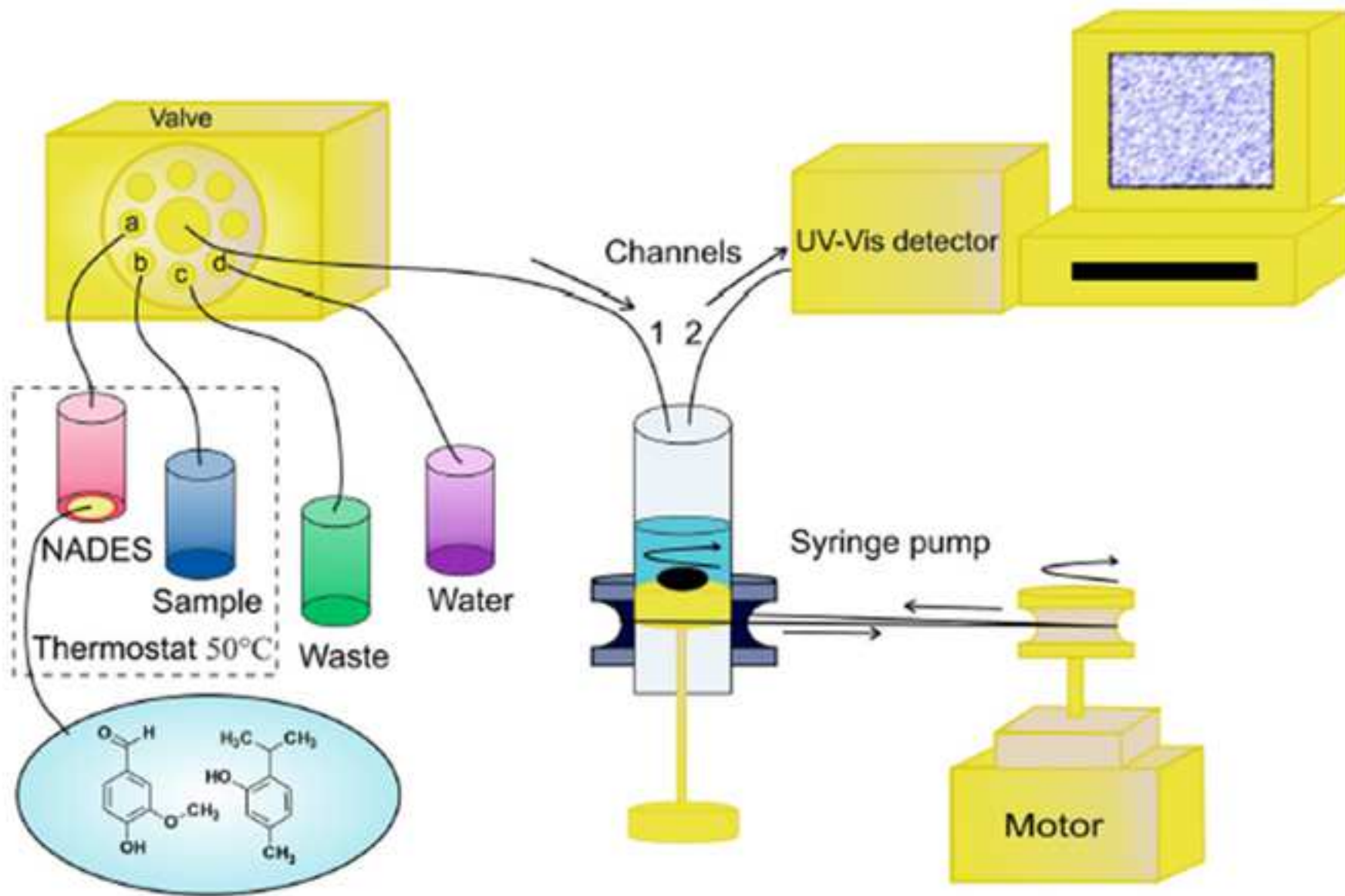
Best regards,

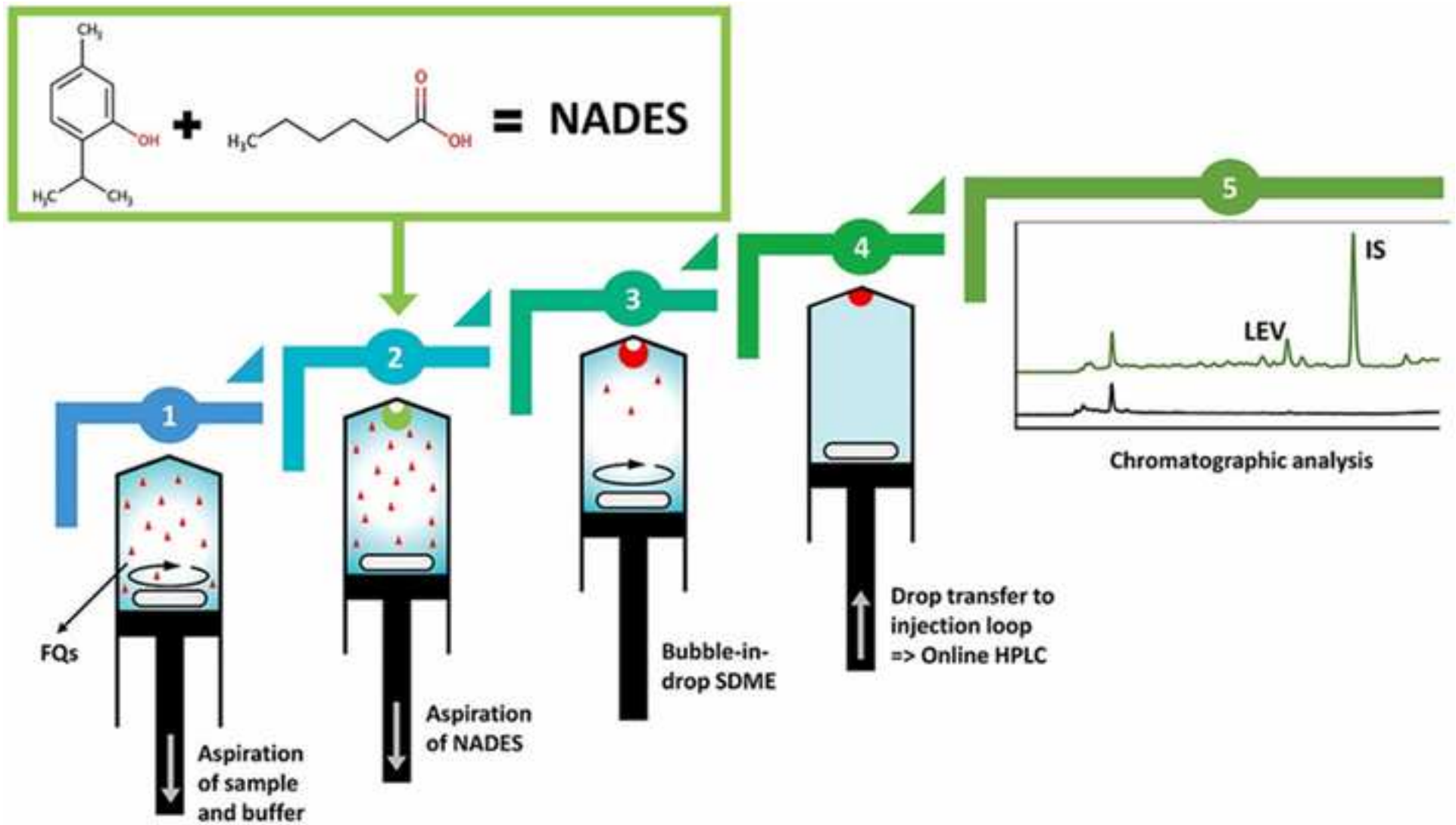
Highlights

1. NADES offer greener alternatives for liquid phase microextraction
2. HF-LPME technique benefits from NADES' environmental friendliness
3. Automation advancements improve efficiency of NADES-based extraction
4. Potential limitation in the utilization of NADES



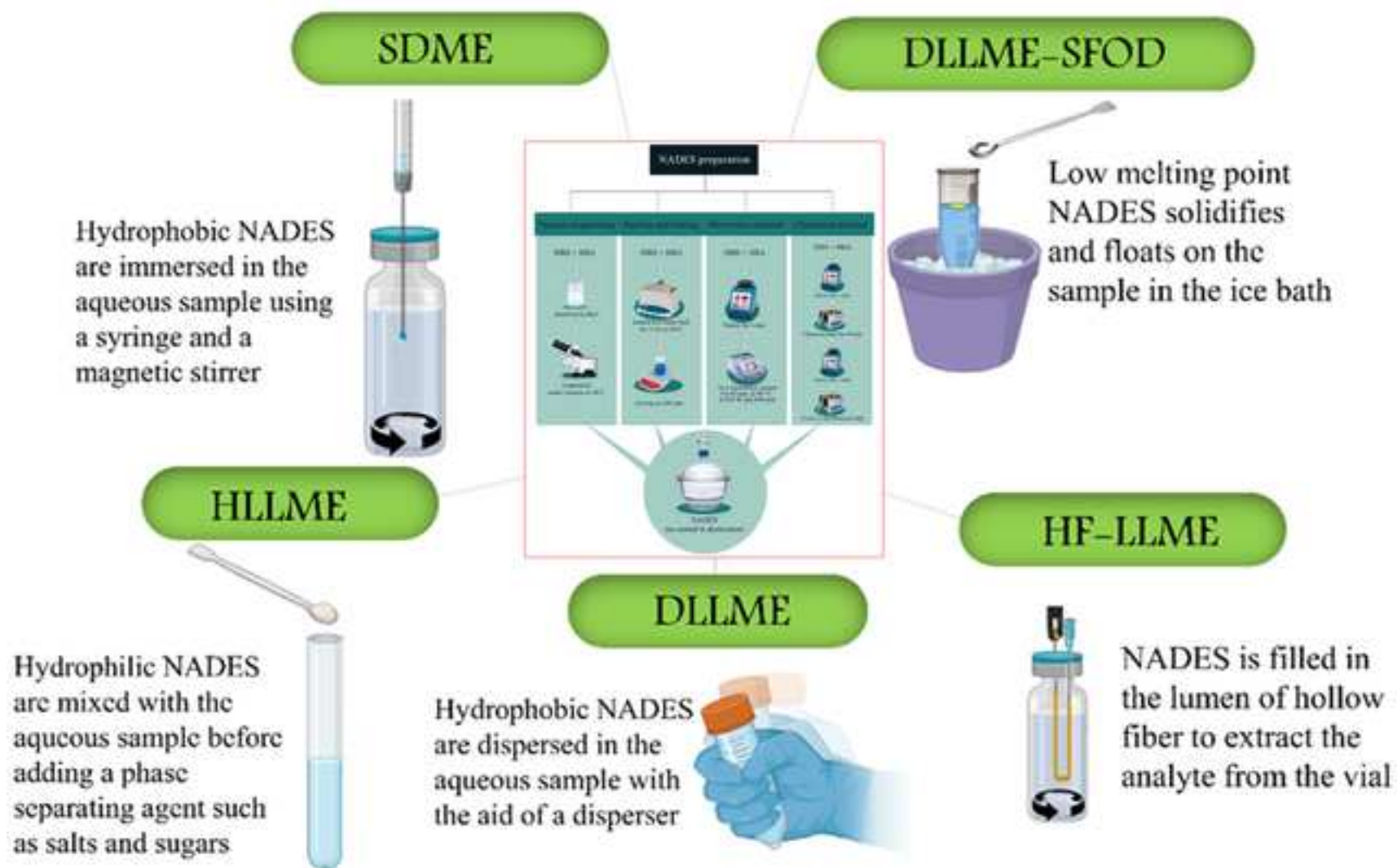






Declaration of interests

The authors declare that they have no competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.



Applications of (natural) deep eutectic solvents in liquid phase microextraction: a review

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8 **List of abbreviation:**

- 9 NADES: Natural deep eutectic solvents,
10 LPME: liquid phase microextraction,
11 GAC: Green Analytical Chemistry,
12 GSP: Green Sample Preparation,
13 BIONPs: bismuth oxide nanoparticles,
14 HBD: hydrogen bond donor,
15 HBA: hydrogen bond acceptor,
16 DSC: Differential scanning calorimetry,
17 TGA: thermogravimetric analysis,
18 LPME: liquid-phase microextraction,
19 DLLME: dispersive liquid-liquid microextraction,
20 HF-LPME: hollow fiber-LPME,
21 EF: enrichment factor,
22 HF-MMLLE: hollow fiber-microporous membrane liquid-liquid microextraction,
23 SALLME: salt-assisted LLME,
24 SULLME: sugar-assisted LLME,
25 SDME: Single-drop microextraction,
26 HS-SDME: headspace SDME,
27 DLLME-SFOD: dispersive liquid-liquid microextraction based on solidification of floating
28 organic droplet,

29 **Abstract**

30 Natural deep eutectic solvents (NADES) have gained significant attention as green solvents
31 due to their unique properties, such as high solubility, low volatility, low toxicity, and
32 tunability. Liquid phase microextraction (LPME) is a sample preparation technique that plays
33 a crucial role in analytical chemistry, and the use of NADES as extraction solvents in LPME
34 offers numerous benefits compared to traditional solvents. NADES can effectively extract
35 bioactive compounds from natural sources without damaging their structure and activity. They
36 can also serve as solvents and catalysts in organic reactions, enhancing the bioavailability of
37 natural compounds. In addition, NADES can be utilized as mobile or stationary phases in
38 chromatographic techniques for separating and analyzing natural compounds. The review
39 highlights the efficiency of NADES in terms of extraction ability, analyte stabilization
40 capacity, and detection compatibility. Moreover, the availability of their components, ease of
41 preparation, low toxicity, cost-effectiveness, and biodegradability make NADES attractive for
42 researchers in the field of analytical chemistry. The applications of NADES in LPME
43 contribute to the principles of green analytical chemistry and green sample preparation by
44 providing a sustainable and environmentally friendly approach to sample preparation. A
45 comprehensive overview of the applications of NADES in liquid phase microextraction is
46 provided, emphasizing their potential for advancing green practices in analytical chemistry.

47 **Keywords**

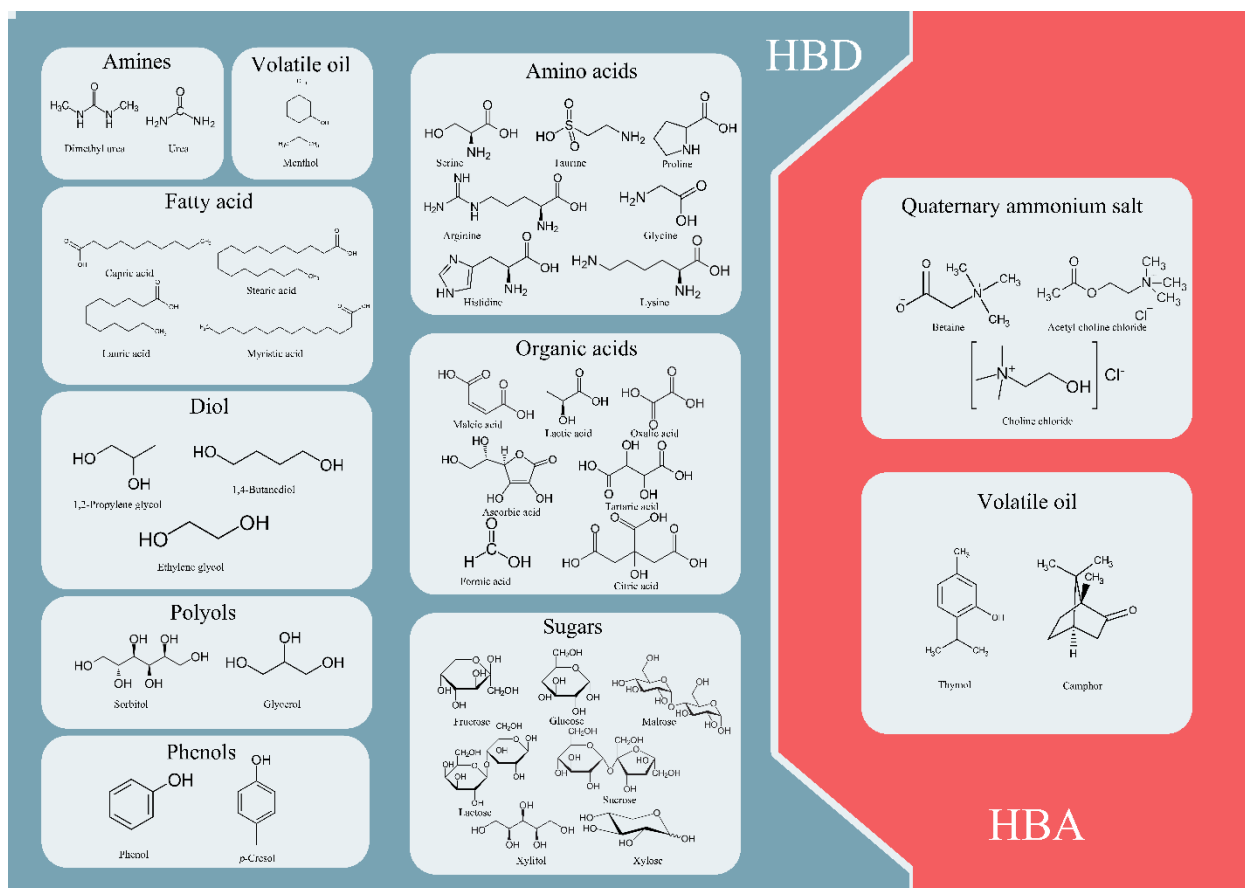
48 Natural deep eutectic solvents; Microextraction; Sample preparation; Analytical chemistry;
49 NADES; Green analytical chemistry

50

51 **1. Introduction**

52 There is a growing interest in the development of new solvents and procedures that are safer
53 for both analysts and the environment [1,2]. This is related to the fact that current organic
54 solvents are highly hazardous, easily vaporized, and combustible. This shift aligns with the
55 principles of green analytical chemistry (GAC) and green sample preparation (GSP) [3–5],
56 which aim to create sustainable solvents, particularly for sample preparation [6,7], a process
57 that can generate significant amounts of waste [8–10]. Natural deep eutectic solvents (NADES)
58 are a novel class of green solvents that captured significant interest in recent years for their
59 potential applications in the domain of research related to natural products. (**Fig. S1**) illustrates
60 the upward trend of NADES publications recently [11].

61 The term “NADES” was coined by Choi et al [12] in 2011. NADES are formed by
62 mixing a hydrogen bond donor (HBD) and a hydrogen bond acceptor (HBA) of natural origin
63 (**Fig. 1**) [13] to form a liquid mixture at room temperature or below [14]. The robust hydrogen
64 bonding interactions between the components lower the melting point of the mixture and drive
65 the formation of NADES. For this reasons, NADES have several unique properties that make
66 them attractive as green solvents. Some of these properties are high solubility, low volatility,
67 low toxicity and tunability. Also, they can dissolve a wide range of compounds, such as
68 proteins, lipids, nucleic acids, metal ions and organic pollutants and bismuth oxide
69 nanoparticles (BIONPs) that are not soluble in water [15–18]. NADES have very low vapor
70 pressure, which reduces the risk of evaporation [19–21]. These solvents are derived from
71 biodegradable compounds, which minimize the environmental and health impacts of solvent
72 use and disposal [22]. Additionally, they can be tailored to suit different applications by
73 changing the type and ratio of the components, which affects the viscosity, polarity, acidity and
74 conductivity of the solvent [23].



75
 76 **Fig. 1.** Names and structures of the most common hydrogen bond donors and acceptors
 77 involved in NADES preparation.

78
 79 NADES have been used for various applications in different fields, such as extraction,
 80 synthesis, separation, electrochemistry and bioavailability enhancement [24]. They are also
 81 able to extract bioactive compounds from natural sources [25], such as plants, algae and fungi,
 82 without damaging their structure and activity [26]. NADES can also act as both solvents and
 83 catalysts for organic reactions, such as esterification, transesterification and aldol condensation
 84 [27–30]. They can improve the bioavailability of natural compounds by increasing their
 85 solubility, stability, permeability, and absorption in biological systems [31]. By creating
 86 complexes or micelles [32–34] with poorly water-soluble drugs, NADES can increase their
 87 solubility and bioavailability [35]. They can also serve as carriers or adjuvants for various drug
 88 delivery systems like nanoparticles, liposomes, or hydrogels. Additionally, NADES can
 89 regulate the absorption and release of drugs by modifying their phase behavior or viscosity
 90 [36]. These solvents could also be used as antibacterial and antifungal agents [37].

91 In the field of analytical chemistry, NADES can separate mixtures of compounds based
 92 on their solubility and affinity to the solvent as mobile phases or stationary phases in

93 chromatographic techniques for separating natural compounds [38–41]. They are also
94 presented as a green alternative in analytical chemistry, showing high extraction ability [42],
95 analyte stabilization capacity [31], and detection compatibility [43] [44]. These advantages
96 make NADES suitable solvent for LPME, which is principally considered green due to the
97 huge reduction in solvent and sample consumption. So, finding the most suitable solvent took
98 massive effort along the years [45]. One major advantage, besides the previously mentioned
99 benefits, is their high polarity, which allows them to dissolve a wide range of substances that
100 are typically insoluble in conventional solvents such as cellulose [46].

101 Several review articles on the microextraction techniques utilizing deep eutectic solvents can
102 be found. Makoś et al. provided an article concentrating in hydrophobic deep eutectic solvents
103 in different microextraction techniques [47]. Nakhle et al. focused on microextraction methods
104 employing deep eutectic solvents as extraction solvents, and exploring the impact of these
105 solvents' properties on extraction efficiency [48]. Andrade et al. presented an overview on the
106 utilization of deep eutectic solvents for the analysis of biological matrices, with a particular
107 emphasis on urine, blood, plasma, and oral fluid. The focus was placed on microextraction
108 techniques, highlighting the various analytical features [49]. Santos et al. explored the
109 application of deep eutectic solvents in LPME and their significant contributions to the field of
110 green chemistry [50]. To the best of our knowledge, this is the first review article to highlight
111 the applications of NADESs in liquid phase microextraction.

112

113 **2. Preparation and characterization of NADES**

114 NADES are prepared by blending specific natural metabolites at specific molar ratios
115 to create a clear liquid at room temperature. Common components of NADES include amino
116 acids, sugars, organic acids, choline salts, essential oil ingredients, and inorganic salts [51–53].
117 The preparation techniques include thermal mixing, vacuum evaporation, ultrasound-based
118 methods, and microwave-based methods. In the thermal mixing method, two components are
119 heated and stirred with or without a predetermined amount of water to obtain a clear liquid
120 [44,54–60]. Vacuum evaporation involves heating the NADES components under reduced
121 pressure to remove excess water [44,54]. Ultrasound-based methods utilize ultrasonic waves
122 to create cavitation and facilitate the formation of NADES [61]. Microwave-based methods
123 use microwave energy to induce molecular agitation and collisions between the components
124 [62,63].

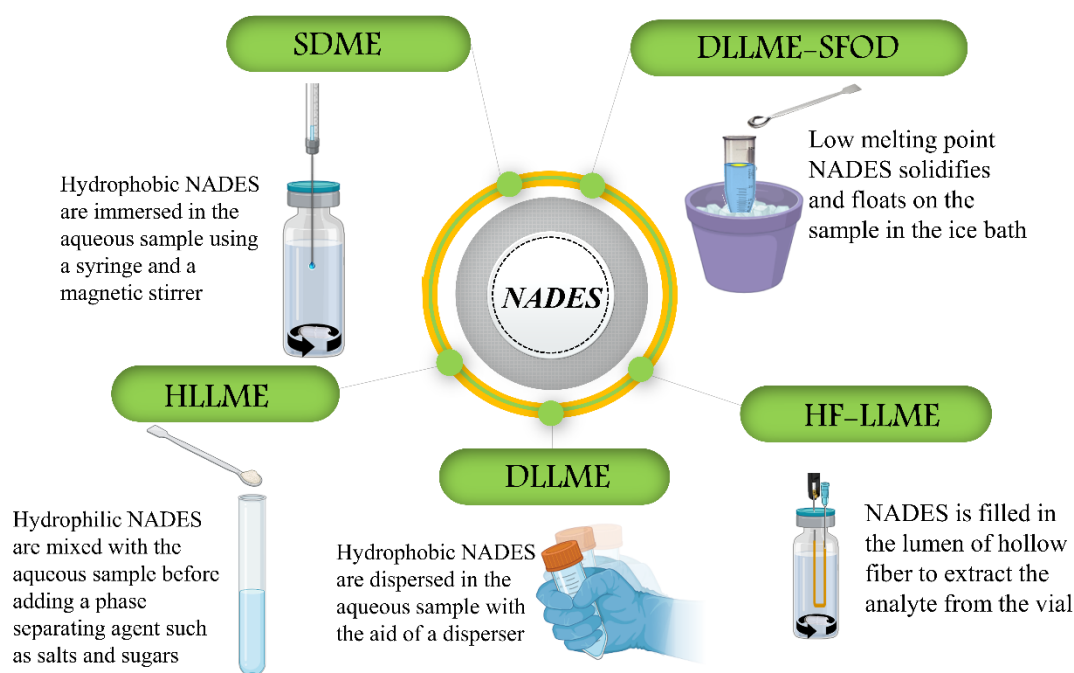
125 The characterization of NADES involves several analytical techniques. Nuclear magnetic
126 resonance (NMR) [23,64], Fourier transform infrared spectroscopy (FTIR)[23], Raman

127 spectroscopy [65,66], and mass spectrometry (MS) [67] are also used to determine the chemical
 128 composition of NADES. NMR, in combination with FTIR, helps identify the constituents and
 129 purity of components [68,69]. FTIR can also be employed to determine NADES' structures
 130 [70,71] while thermogravimetric analysis and differential scanning calorimetry are used to
 131 assess density, thermal features, and stability [44,72]. Density and viscosity measurements
 132 provide important physical property information for designing processes and evaluating
 133 solvent suitability and to determine the best ratio between HBD and HBA [73–75].

134

135 3. Application of NADESs in liquid phase microextraction

136 Despite obvious developments in analytical science and technology, sample preparation
 137 remains the bottleneck of all analytical procedures. Miniaturizing the analytical scale and/or
 138 using safer alternatives instead of hazardous solvents can be used to mitigate the negative
 139 environmental effect of analytical procedures [76,77]. Both hydrophilic and hydrophobic
 140 NADES have been employed in different modes of LPME, as shown in (Fig. 2). In this section,
 141 the role of NADES in liquid phase microextraction approaches are discussed in details.



142

143 **Fig. 2:** Modes on LPME in which NADESs were employed

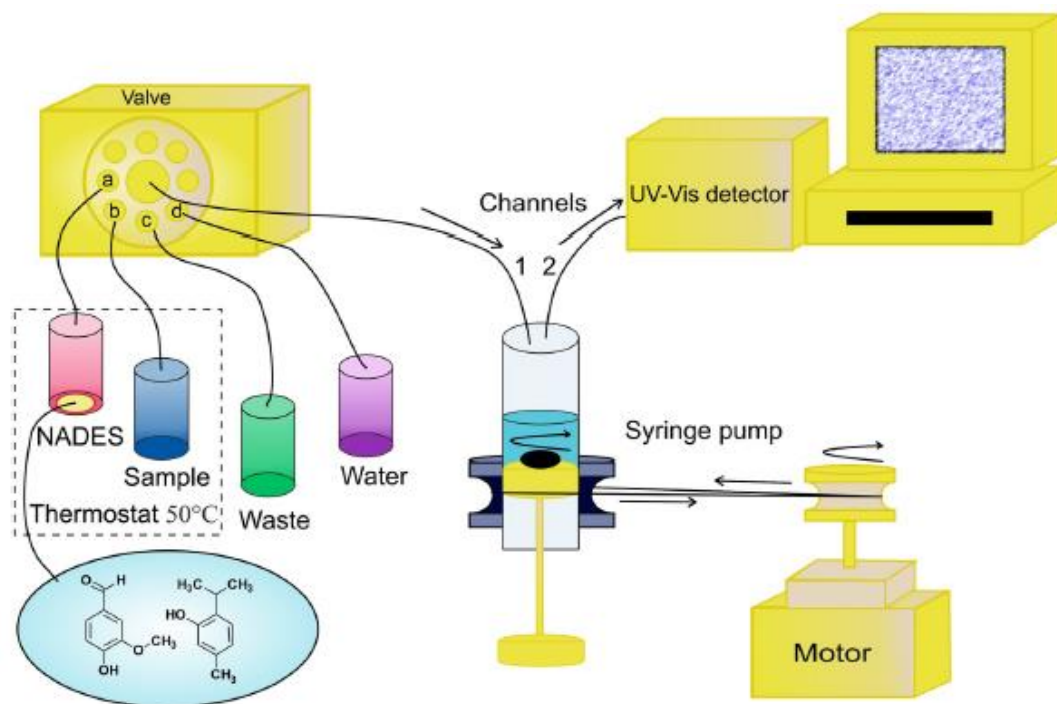
144

145 3.1. Applications of NADES in HF-LPME

146 Sample preparation trends tend to minimize the amount of organic solvent and extraction time.
 147 The liquid-phase microextraction (LPME) approach offers an alternative to typical preparation
 148 procedures [78]. There are different modes of LPME including dispersive liquid-liquid

149 microextraction (DLLME) [79], single drop microextraction (SDME) [80], and hollow fiber–
150 LPME (HF–LPME) [81]. Among these techniques, the HF-LPME has distinct benefits such as
151 low cost, high preconcentration factor, low solvent consumption, and environmental
152 friendliness. The HF-LPME technique is based on the use of different materials such as porous
153 polypropylene hollow fiber, polyvinylidene difluoride, or PTFE, which first extract analytes
154 from an aqueous sample as the donor phase and then back-extract them into the acceptor phase
155 situated in the HF lumen [82]. Organic solvents are often used in the HF-LPME technique, but
156 they have various drawbacks, including volatility, toxicity, instability, and deleterious effects
157 on laboratory workers. Nia et al [83] prepared amino acids hydrophobic NADES in two phase
158 HF-LPME. In this application, NADES was prepared by mixing amino acids (as an HBA) with
159 lactic acid (as an HBD) using a hollow fiber's supported liquid membrane. The lumens were
160 impregnated with extremely stable NADESs (serine: lactic acid). The developed method was
161 successfully applied to extract caffeic acid from green tea, tomato samples and coffee. The
162 enrichment factor was in the range of 418–438. Morelli et al. [84] investigated both hydrophilic
163 and hydrophobic NADESs hollow fiber-microporous membrane liquid-liquid microextraction
164 (HF-MMLLE). The best NADES was composed from thymol and camphor. Selected NADESs
165 were introduced into the porous polypropylene membrane for 10 minutes, substituting widely
166 used solvents (for example, hexane and octanol). The developed method was successfully
167 applied and verified for 11 emergent contaminants from various classes, demonstrating the
168 method's adaptability.

169 Analytical method automation, commonly employed to minimize reagent and sample usage, is
170 a highly effective tool for integrating all stages of necessary analytical procedures onto a single
171 manifold while minimizing human and environmental hazards. Shakirova et al. [85] developed
172 an automated liquid-liquid microextraction process for determining sulfonamides
173 (sulfamethoxazole, sulfamethazine, and sulfapyridine) in urine samples utilizing NADES. The
174 extraction of sulfonamides was based on the synthesis of colored Schiff bases in the presence
175 of vanillin, which served as a derivatization reagent as well as a precursor of NADES (an
176 extractant). Thymol was utilized in this process as both a medium for Schiff base synthesis and
177 a second precursor of the NADES. Mass spectrometry verified the production of the Schiff
178 bases. The microextraction method was automated using the Lab-In-Syringe approach as
179 indicated in (**Fig. 3**).



180

181 **Fig. 3:** manifold for the determination of sulfonamides in urine samples with permission from
 182 [85].

183

184 The developed approach had enough sensitivity to determine the concentration of sulfonamides
 185 at therapeutic levels. In addition to that, this method was ecologically benign, providing full
 186 automation with a sample throughput of six samples/h.

187

188 3.2. Applications of NADES in DLLME

189 DLLME is a miniaturized sample preparation process used in many analytical chemistry
 190 applications [86,87]. In this mode, an immiscible organic solvent is used with an organic
 191 disperser, the two solvents are combined. The organic extractant is dispersed as tiny droplets
 192 by manual shaking resulting in a homogeneous hazy solution. DLMME has several benefits
 193 over other sample preparation approaches in terms of simplicity, affordability, convenience of
 194 use, and speed. However, the right selection of dispersing and extracting solvents (μL scale) is
 195 quite difficult [88]. The pioneers of DLLME mode (Rezaee et al. [89]) developed this mode as
 196 a modification of LLME in an attempt to boost the recovery rate in LLME. DLLME results in
 197 extending the contact surface between the extractant and the sample, and this dispersion
 198 procedure greatly increases extraction kinetics. The sample is then centrifuged to separate the
 199 extractant and break up the emulsion. It worth mentioning that dispersion could be achieved
 200 by using a disperser solvent or by using external mechanical force such as manual shaking,

201 vortex agitation, magnetic stirrer power, ultrasonic power, and microwave irradiation.
202 Traditional DLLME procedures use hazardous halogenated organic solvents such as
203 chloroform, carbon tetrachloride, and chlorobenzene, which can be harmful to human health
204 and the environment. In addition to using long chain alcohols as extractant and hazardous
205 dispersers such as acetonitrile (ACN), methanol, acetone, tetrahydrofuran (THF), ethanol.
206 Therefore, one of the GAC principles that should be adopted in method development is the
207 replacement of harmful solvents with more benign ones. As a result, more environmentally
208 friendly NADESs have recently been offered as a sustainable alternative in DLLME [90]. In
209 general, NADES is made up of two or more natural components (HBD and HBA) blended in
210 a certain ratio to generate a homogeneous mixture with a eutectic point at a lower temperature
211 than the separate substances. The most common components used in synthesis of NADESs are
212 monoterpenes (menthol, thymol, and camphor) [91–102]. These solvents are biodegradable,
213 less hazardous, widely accessible, and simple to make. Monoterpenes such as are considered
214 an ideal choice of extractant because of their poor water solubility [103]. In general,
215 hydrophobic NADESs were used as extractants in DLLME mode however, hydrophilic
216 NADESs could be used as a disperser in the same mode. As reported in Table 1, the use of
217 NADESs in DLLME was successfully applied for the extraction of different analytes from
218 different matrices including water [102], biological samples [104], foods [105], beverages [94]
219 and personal care products [93].

Analyte	Sample	Sample volume (mL)	NADES component	Dispersion mode	Extractant volume (μ L)	Analytical instrument	Linearity range ng/mL	%RSD	Ref
Tetracyclines	Water	5	[ChCl]: [thymol]: [nonanoic acid]	Air assisted DLLME	400	HPLC/UV	18.2-500	\leq 11.2	[102]
Warfarin	Biological samples	10	Borneol: decanoic acid	Air assisted DLLME	60	HPLC/UV	5-500	$<$ 5.87	[104]
Vanadium	Food stuff	2	ChCl: phenol	Ultrasound assisted DLLME	1000	Electrothermal atomic absorption spectrometry (ETAAS)	N/A	3.4%	[106]
Tert-Butylhydroquinone	Soybean Oils	0.2 g	ChCl: sesamol	Ultrasound assisted DLLME	400	HPLC/UV	5-500 mg/kg	$<$ 2.3%	[107]
NSAIDs	Water and milk samples	10	1,1,3,3-tetramethylguanidine chloride: thymol	Ultrasound assisted DLLME	200	HPLC/UV	5-2000	1.11% to 16.9%	[91]
Parabens	Personal care products	5	Menthol: formic acid	Vortex assisted DLLME	80	UHPLC/UV	20-4000	\leq 3.33%	[93]
Mercury	Water samples	9	Decanoic acid: DL-menthol	Vortex assisted DLLME	50	LC/UV-Vis	10-200	\leq 19%	[92]
Alkylphenols, bisphenols and alkylphenol ethoxylates	Microbial-fermented functional beverages and bottled water	10	Methanol: octanoic acid	Vortex assisted DLLME	100	UHPLC-MS	0.4-50	\leq 19.5%	[95]
Sudan I	Food samples	0.2 g	ChCl: sesamol	Vortex assisted DLLME	800	HPLC/UV	0.2-100 mg/kg	$<$ 4.5%	[105]
Beta-blockers	Water samples	9.5	Azelaic acid: thymol	Vortex assisted DLLME	55	HPLC/DAD	0.5-100	$<$ 6%	[108]
Phthalate Esters	Soft drinks	10	Thymol: octanoic acid	Vortex assisted DLLME	125	UPLC-MS/MS	0.10-5.00	$<$ 11.5%	[94]
Phthalate esters	Grape-based beverages	7.5	ChCl: acetic acid	Vortex assisted DLLME	500	Nano-LC/UV	5-403	$<$ 17%	[109]
Benzoic acid and sorbic acid	Condiments	10	L-Menthol Acetic acid: decanoic acid	Vortex assisted DLLME-SFOD	800	HPLC/DAD	70-100000	\leq 5.66%	[96]
Phthalates and one adipate	Water samples	10	Thymol: menthol	Vortex assisted DLLME	100	UHPLC-QqQ-MS/MS	0.100-250	$<$ 14%	[97]
Chloramphenicol	Honey sample	5	Menthol: acetic acid	Vortex assisted DLLME	100	LC/UV	1-100 μ g/kg	\leq 4.5%	[98]
Triarylmethane) dyes	Shrimp and water samples.	10	Thymol and camphor	Vortex assisted DLLME	200	HPLC/DAD	0.2 -200	\leq 2.3	[99]
Acaricides	Egg samples	5	Choline chloride-acetic acid- <i>n</i> -octanol	In-syringe DLLME	74	GC/FID	2.7-4000	\leq 11%	[110]
Phthalic acid esters	Soft drinks and infusions	20	Menthol: acetic acid	Manual agitation assisted DLLME-SFO	100	HPLC/UV	6-1190	1-22 %	[100]
Phthalic acid esters	Water and beverage samples	20	Menthol: acetic acid	Manual agitation assisted DLLME	100	HPLC/UV	4-425	\leq 20%	[101]

222 3.3. Applications of NADES in HLLME

223 HLLME is a method of sample preparation that involves the formation of a homogeneous phase
224 between an aqueous sample and a small amount of a water-miscible extractant, such as
225 acetonitrile, acetone or tetrahydrofuran. The separation of phases is achieved using a phase
226 separating agent (PSA), which may be a salt, sugar, or hydrophobic substance. Depending on
227 the type of PSA used, HLLME can be classified into three categories: salt-assisted LLME
228 (SALLME) [111,112], sugar-assisted LLME (SULLME) [113,114], and hydrophobic
229 substance-assisted or aprotic solvent assisted HLLME [115,116]. The manipulation of
230 physical conditions such as temperature or pH, and the introduction of gas bubbles into the
231 homogeneous system could achieve phase separation [117,118]. It is worth mentioning that
232 HLLME is characterized by infinite contact surface area between the aqueous and organic
233 phases, which permits highly quick and effective extraction [119]. Another advantage of this
234 microextraction process is that there is no need for an evaporation/reconstitution step due to
235 the hydrophilicity of the donor phase. In the standard HLLME approach, hydrophilic organic
236 solvents such as acetonitrile, acetone, ethanol, and propanol are frequently used as extractants.
237 NADESs have recently attracted a lot of attention as a more eco-friendly alternative to the
238 poisonous and volatile organic solvents used in the HLLME process. The most common mode
239 that was used in HLLME is the aprotic solvent-assisted HLLME, which depends on using a
240 water miscible extractant and an aprotic solvent a PSA such as THF, ACN and acetone. Unlike
241 other HLLME modes, this mode gives the ability to use a large sample volume, enhancing
242 sensitivity of the proposed method. Khezeli et al. [120] were the pioneers of this mode. In this
243 work, the NADESs used were prepared by combining choline chloride (ChCl) as an HBA with
244 phenol as an HBD. The developed method was used to successfully extract several organic
245 chemical components from water samples. This procedure produced a homogeneous solution
246 by adding the extraction solvent (the hydrophilic NADES) to the aqueous sample solution
247 (donor phase). Finally, an aprotic solvent (THF) was used to produce phase separation. It has
248 been proposed that introducing an aprotic solvent into a homogeneous solution can greatly
249 diminish the interactions between DES and water molecule because of the π - π and hydrogen
250 bonding interactions between the DES ingredients. Therefore, the DES molecules can self-
251 aggregate and migrate out of the water phase. Shishov et al. [121] proposed another theory in
252 the mechanism of phase separation. They investigated the solvent-assisted HLLME process
253 with hydrophilic DES based on choline and phenol utilizing gas chromatography-mass
254 spectrometry analysis and coulometric Karl-Fischer titration. The results of this study
255 supported the instability of a hydrophilic DES in aqueous conditions. Thus, they hypothesize

256 that hydrophilic DESs based on choline and phenol breaks down in the aqueous phase in the
257 solvent-assisted HLLME process. The findings of this study revealed that the organic phase
258 recovered comprised phenol, THF, and water. As indicated in Table 2 , this mode was
259 successfully applied for extraction various compound from different matrices including water
260 [122], food [123], biological samples [124] and beverages [125]. The most common water
261 miscible NADES used in aprotic solvent-assisted HLLME was composed of phenol and ChCl
262 [123,126–130]. In addition to that, THF was widely used in this mode as PSA
263 [123,126,131,132]. It is worth mentioning that other aprotic solvent were used as PSA in
264 aprotic solvent assisted HLLME such as ACN [133] and acetone [134]. The applications of
265 NADES in HLLME have high potential because of being greener, simpler, cheaper, and more
266 sensitive in comparison with other conventional extraction modes.

267 **Table 2:** Applications of NADES in HLLME

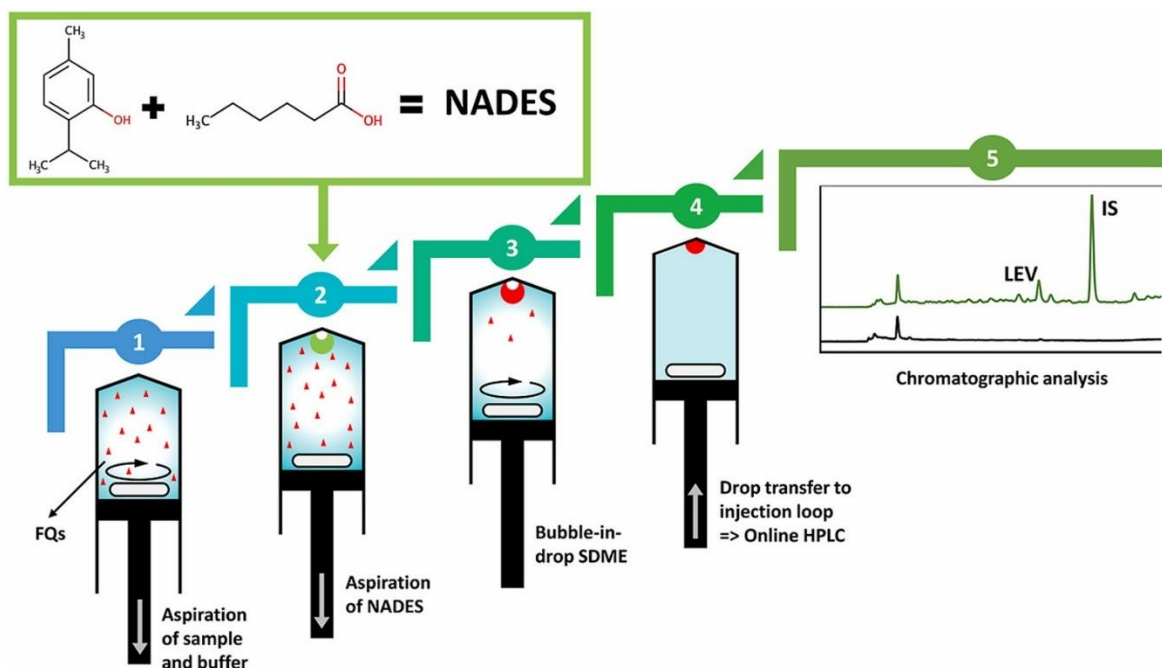
Analyte	Sample	Sample volume (mL)	NADES component	HLLME	PSA	Extractant volume (μL)	PSA(vol /amount) μL	Analytical instrument	Linearity range ng/mL	%RSD	Ref
Copper	olive oil and water samples	15	ChCl: Phenol	Aprotic solvent assisted HLLME	THF	450	450	FAAS	NA	<5.0%	[126]
Arsenic and antimony	Water samples	125	ChCl: oxalic acid	Aprotic solvent assisted HLLME	THF	700	300	Hydride generation-atomic absorption spectrometry	15-570 ng/L	2.1% and 2.7%	[122]
Benzotriazole derivatives and benzothiazole derivatives	Surface water	5	ChCl: Phenol	Aprotic solvent assisted HLLME	THF	1000	500	UHPLC-ESI(+)-QToF-MS	5 -200	1 -8%	[127]
Pesticides	Chinese medicine	10	ChCl: Phenol	Aprotic solvent assisted HLLME	THF	650	550	HPLC/DAD	50-107000	4.7%	[128]
Methyl mercury and total mercury	Water and fish sample	2.5	betaine-sorbitol	Aprotic solvent assisted HLLME	ACN	600	375	Spectrophotometer	0.7–340	1.9–5.5%	[133]
Caffeine	Turkish coffee	5	ChCl: Phenol	Aprotic solvent assisted HLLME	THF	400	800	HPLC/UV	500-100000	2.20%	[129]
Curcumin	Tea and honey samples	5	ChCl: Maltose	Aprotic solvent assisted HLLME	THF	762.5	107.5	Spectrophotometer	0.4–120	\leq 4.3%	[135]
Curcumin	Food and herbal tea	10	ChCl: Phenol	Aprotic solvent assisted HLLME	THF	400	400	Spectrophotometer	NA	1.8 %.	[123]
Malachite green	Aquarium fish water	10	ChCl: Phenol	Aprotic solvent assisted HLLME	THF	500	500	Spectrophotometer	45-900	2.7 %.	[130]
Sulfonamides	Water samples	1.5	ChCl: Phenol	Aprotic solvent assisted HLLME	THF	193	100	HPLC/UV	500–100000	\leq 2.10	[131]
Thiophenols	Water samples	1.5	ChCl:p-cresol	Aprotic solvent assisted HLLME	Acetone	50	50	GC/FID	2-100000	<4.1%	[134]

Polycyclic aromatic hydrocarbons	Water samples	1.5	ChCl: Phenol	Aprotic solvent assisted HLLME	THF	100	100	HPLC/UV	0.1-400	<4.5	[120]
Antidepressants	Pharmaceutical and water samples	6	ChCl: Phenol	Aprotic solvent assisted HLLME	THF	200	430	HPLC/UV	10-8000	3.6-5.7%	[136]
Selenium species	Water and food samples	25	ChCl: Phenol	Aprotic solvent assisted HLLME	THF	500	500	ETAAS	0.2-8	≤4.1	[137]
Phenoxy acid herbicides	Paddy field and water samples	1.5	ChCl:2-chlorophenol	Aprotic solvent assisted HLLME	THF	50	100	HPLC/UV	5-100	≤4.6	[138]
Phthalate	Beverages	10	ChCl: Phenol	Aprotic solvent assisted HLLME	THF	440	440	HPLC/DAD	170-2700	<11%	[125]
Caffeine	Beverages	1	ChCl: Phenol	Aprotic solvent assisted HLLME	THF	50	50	HPLC/UV	100-200000	≤6%	[139]
Mercury	Water and biological samples	10	ChCl: Phenol	Aprotic solvent assisted HLLME	THF	500	500	ETAAS	0.3-10	≤-5.72%	[124]
Cadmium	Food and water samples	50	ChCl: Phenol	Aprotic solvent assisted HLLME	THF	500	600	ETAAS	5-150 ng/ L	3.1%	[132]

269 **3.4. Applications of NADES in single drop microextraction**

270 Single-drop microextraction (SDME) is a highly effective and environmentally
271 sustainable sample pretreatment technique that involves the immersion of an organic solvent
272 microdroplet into the sample with the aid of a microsyringe needle. SDME has gained
273 widespread use in fields such as environmental monitoring, food quality control, and biological
274 analysis, owing to its minimal solvent consumption and high sample-to-extractant phase ratio
275 [140,141]. This technique has streamlined the analytical workflow by integrating extraction
276 and enrichment processes. Furthermore, SDME is particularly well-suited for fluorescence
277 spectroscopy, as the solvent used is transparent in the visible region and does not interfere with
278 direct visual readout or spectral analysis [142,143]. The realm of green analytical chemistry is
279 presently witnessing a huge interest in the creation and utilization of sustainable and eco-
280 friendly solvents. This trend is particularly visible in the SDME field, in which a growing
281 number of innovative solvents has been reported, for instance, ionic liquids, superheated water,
282 deep eutectic solvents, surfactants, and supercritical fluids [144]. An important aspect that
283 could significantly influence the efficacy of the extraction process is the choice of solvent. In
284 particular, the utilization of a solvent with high viscosity can facilitate the suspension of larger
285 and more stable droplets at the needle tip. This property makes NADESs a suitable option for
286 the task, given their favorable attributes such as elevated viscosity at ambient temperature,
287 considerable thermal stability, and low vaporization tendencies [145]. Yousefi et al. have
288 introduced a novel technique for headspace single drop microextraction (HS-SDME) that
289 employs a magnetic bucky gel derived from deep eutectic solvents (DES-MBG) as the
290 extraction medium. This method offers several advantages, including high viscosity, magnetic
291 susceptibility, and adjustable extractability. Additionally, it ensures droplet stability, allowing
292 extraction at high temperatures and rapid agitation rates. This suggests the potential of DES-
293 MBGs to exhibit superior resilience, facilitating the utilization of larger droplet volumes and
294 consequently enhancing extraction efficiency, sensitivity, and detection limits [146]. Yildirim
295 et al. [147] proposed a novel approach for fluoroquinolone analysis in environmental waters
296 via an automated Lab-In-Syringe direct immersion single drop microextraction method
297 coupled online to HPLC with fluorescence detection (**Fig. 4**). The method employed NADES
298 as an extractant within an automatic syringe pump, thus eliminating the utilization of toxic
299 solvents and augmenting the method's sustainability from an environmental perspective. The
300 method's linearity range for fluoroquinolones lied between 0.1 and 5.0 $\mu\text{g/L}$, with
301 quantification limits in the 20-30 ng/L and enrichment factors of 35-45. The trueness of spiked
302 samples ranged from 84.6% to 119.7%, and the method exhibited low RSD values. The

303 method's advantages include its parallel operation with HPLC, low sample consumption, and
 304 environmentally friendly characteristics, aligning it with the principles of green analytical
 305 chemistry [147].



306
 307 **Fig. 4.** A schematic representation for the automation of a lab-in-syringe technique using
 308 NADES-based direct immersion single drop microextraction, which is linked online to HPLC-
 309 FL to determine fluoroquinolones (With permission from [147])

310
 311 **3.5 Applications of NADES in DLLME-SFOD**

312 The DLLME-SFOD approach is a microextraction method that employs a ternary
 313 solvent system (extractant, disperser and sample), in which the extractant is an organic solvent
 314 that solidifies in ice bathes at relatively low temperatures [148]. The injection of a suitable
 315 mixture into an aqueous sample results in the formation of a cloudy solution, which facilitates
 316 phase interaction [149]. Following phase separation and centrifugation, the sample is immersed
 317 in an ice bath and the solidified organic phase is gathered for analysis [150]. This method boasts
 318 high efficiency, enrichment factors, and rapid equilibrium, while necessitating minimal solvent
 319 volume and equipment. Nonetheless, its solvent options are restricted in a narrow range of long
 320 chain alcohols with high melting points in the range 10-25°C. However, deep eutectic solvents
 321 (DESs) are being investigated as a favorable, eco-friendly replacement for this technique
 322 [151,152]. NADES have been utilized in DLLME-SFOD, serving as both disperser and
 323 extracting solvents. An effective example is a NADES consisting of lactic acid, glucose, and
 324 water at a 5:1:3 molar ratio, which has demonstrated efficient dispersion of pesticides from

325 water and white wine through vigorous shaking. The addition of water has resulted in lower
326 viscosity, which has facilitated the dispersion process. The dispersive NADES has achieved
327 recoveries exceeding 90% for analytes tested due to its reduced viscosity and increased
328 polarity, which have improved interactions among the aqueous sample, NADES, and extracting
329 solvent [153]. The developed method offered a strong, efficient, and environmentally friendly
330 alternative for determining pesticides, providing a novel application for NADES in sample
331 preparation, as indicated in **Table 1**. Another study has incorporated menthol and decanoic acid
332 in the preparation of NADES with a molar ratio of 1:2 for the extraction of antidepressants
333 from urine samples prior to GC/MS analysis resulting in recoveries ranging from 74 to 147%
334 [154]. In their research, Taşpınar et al. applied an environmentally friendly approach known as
335 air-assisted DLLME-SFOD, which was designed to extract patulin from both fruit juice and
336 dried fruit. This process involved the injection of NADES as extraction solvents at a volume
337 of 410 μL into a sample solution that has been adjusted to a pH of 5.6. The solution was then
338 drawn into a syringe and immediately reinjected six times to allow for the even dispersal of
339 NADES droplets throughout the aqueous bulk, resulting in a cloudy solution. Afterwards, the
340 tubes were submerged in an ice bath for roughly seven minutes, which enabled the NADES
341 phase to solidify and become easily separable before undergoing UV/Vis spectrophotometric
342 analysis. This method had an LOD of 3.5 $\mu\text{g/L}$ and an EF of 150 [155].

343

344 **4. Limitations of NADES**

345 The interest and the applications of NADES in various fields, particularly in chemical
346 analysis and LPME are increasing. However, NADES are not perfect solvents and have some
347 challenges and limitations that need to be addressed, such as stability, viscosity, water content,
348 and extraction efficiency. NADES are prone to decomposition or degradation over time. The
349 hydrogen-bonding network that exists between the constituents significantly influences the
350 stability of NADES. Hydrogen bonds are responsible for lowering the melting point of NADES
351 [20]. Betaine-urea-water is a NADES that has been used for extracting bioactive compounds
352 from plants. However, this NADES is not stable at room temperature and tends to crystallize
353 after a few days. A recent study by Nava-Ocampo et al. investigated the structural properties
354 and stability of betaine-urea-water using spectroscopic and computational methods. The
355 researchers discovered that the formation of a metastable transparent liquid requires a
356 minimum of two moles of water, whereas a stable NADES necessitates a minimum of three
357 moles of water. They also showed that water plays a crucial role in forming stronger hydrogen
358 bonds between urea and the carbonyl groups of betaine, and in deprotecting the methyl group

359 of betaine from forming intermolecular interactions [156]. NADES tend to have high viscosity
360 compared to conventional solvents, which can limit their mass transfer and diffusion rates. This
361 can reduce their extraction efficiency and increase the energy consumption and processing
362 time. To address this, it is necessary to optimize the composition and ratio of the components
363 of NADES to achieve the desired viscosity. Moreover, some methods can be used to reduce the
364 viscosity of NADES, such as heating, dilution, ultrasonication, or adding co-solvents [13].
365 NADES usually contain a certain amount of water due to their hygroscopic nature or the
366 presence of water in the natural components. Water can affect the polarity and solvation ability
367 of NADES, as well as their interaction with the target compounds. So, it is important to control
368 the water content of NADES according to the specific application and the solubility of the
369 target compounds. Additionally, some techniques can be used to remove or reduce the water
370 content of NADES, such as freeze-drying [157]. NADES may be less environmentally friendly
371 than initially thought, urging a reevaluation of their large-scale applications [158]. According
372 to Popović et al, The cytotoxic effect is primarily influenced by the structure of the HBD, with
373 acidic systems showing the highest cytotoxic effects. Cytotoxicity depends on both the
374 concentration of the NADES system in the cell medium and the chemical composition of the
375 investigated systems [159].

376

377 **5. Perspectives**

378 One of the major limitations in any LPME is phase separation. To overcome this
379 problem, magnetic solvents have been introduced in recent years to shorten the time necessary
380 for phase separation. These magnetic solvents can be quickly separated and collected without
381 the need for time-consuming centrifugation processes, allowing for quick sample preparation.
382 Magnetic solvents are easier to prepare and have higher reproducibility than magnetic
383 materials. Magnetic ionic liquids have a low vapor pressure and good thermal stability, as well
384 as the capacity to respond significantly to external magnetic fields [160,161]. However, they
385 are costly and need drying or a rotary evaporation process [162]. Magnetic deep eutectic
386 solvents (MDESs) not only exhibit paramagnetic characteristics similar to magnetic ionic
387 liquids, but they also offer substantial cost and availability benefits. Most MDESs are currently
388 hydrophilic, which limits their applicability to extracting polar analytes (such as thiophene and
389 aldehydes) in non-polar solvents (such as n-heptane and oil samples) [163,164]. Therefore, the
390 development of hydrophobic MDESs is necessary to extract non-polar analytes from different
391 matrices. For these reasons, MDESs is a new growing area of research for the development
392 green solvents in LPME. Duque et al [165] applied ferrofluid-based NADES in stir bar

393 dispersive liquid microextraction for the determination of UV filters in water samples. This
394 ferrofluid was composed of a hydrophobic NADES (1:5 molar ratio of menthol and thymol as
395 carrier solvent) and oleic acid-coated cobalt ferrite (CoFe_2O_4 @oleic acid) magnetic
396 nanoparticles. CoFe_2O_4 MNPs were first synthesized through wet chemical coprecipitation
397 using an adapted procedure [166], and then coated with oleic acid. In this case, 100 mL of 0.4
398 M FeCl_3 aqueous solution was combined with 100 mL of 0.2 M CoCl_2 aqueous solution. Then,
399 100 mL of a 3 M sodium hydroxide aqueous solution was added dropwise at 80°C , under
400 continuous stirring. The reaction mixture was then agitated at the same temperature for 1 hour
401 after 2 mL of oleic acid was added. After carefully cooling the black precipitate result to
402 ambient temperature, the MNPs were cleaned twice with ultrapure water and once with ethanol.
403 Finally, the precipitate was dried overnight at 100°C and ground into a fine powder. A stable
404 ferrofluid was prepared by weighing 25 mg of CoFe_2O_4 @OA MNPs in a microcentrifuge tube
405 and 1 mL of NADES was added. The resulting mixture was sonicated for 40 min. The results
406 indicated that the developed analytical method produced comparable findings, demonstrating
407 the promise of this ferrofluid as a less expensive and more environmentally friendly alternative
408 to MILs in future analytical procedures [166].

409

410 **6. Conclusion**

411 NADESs have emerged as promising alternatives for liquid phase microextraction
412 applications. NADES offer unique advantages such as high polarity, hydrophilicity, and
413 environmentally friendly nature, making them suitable for liquid phase microextraction in
414 diverse fields, including pharmaceutical, environmental, and food analysis. NADES have been
415 successfully employed in different modes, including HF-LPME, DLLME, and SDME. These
416 techniques aim to minimize the use of organic solvents, reduce extraction time, and enhance
417 the preconcentration factor. NADES have shown promise in improving the efficiency and
418 environmental friendliness of LPME processes. By replacing traditional solvents with NADES,
419 researchers have achieved successful extraction of analytes from aqueous samples. Rising
420 interest in NADES for analysis and LPME faces challenges in stability, viscosity, water
421 content, and extraction efficiency. Further research and development in the synthesis methods,
422 characterization techniques, and application of NADES are warranted to fully explore their
423 potential in liquid phase microextraction and contribute to sustainable analytical practices. The
424 automation of liquid-liquid microextraction processes using NADES has proven to be a
425 valuable approach in minimizing reagent and sample usage while reducing human and
426 environmental hazards.

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431

432 **Declaration of interests**

433 The authors declare that they have no competing financial interests or personal
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435

436 **Author contributions**

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Applications of (natural) deep eutectic solvents in liquid phase microextraction: a review

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8 **List of abbreviation:**

- 9 NADES: Natural deep eutectic solvents,
10 LPME: liquid phase microextraction,
11 GAC: Green Analytical Chemistry,
12 GSP: Green Sample Preparation,
13 BIONPs: bismuth oxide nanoparticles,
14 HBD: hydrogen bond donor,
15 HBA: hydrogen bond acceptor,
16 DSC: Differential scanning calorimetry,
17 TGA: thermogravimetric analysis,
18 LPME: liquid-phase microextraction,
19 DLLME: dispersive liquid-liquid microextraction,
20 HF-LPME: hollow fiber-LPME,
21 EF: enrichment factor,
22 HF-MMLLE: hollow fiber-microporous membrane liquid-liquid microextraction,
23 SALLME: salt-assisted LLME,
24 SULLME: sugar-assisted LLME,
25 SDME: Single-drop microextraction,
26 HS-SDME: headspace SDME,
27 DLLME-SFOD: dispersive liquid-liquid microextraction based on solidification of floating
28 organic droplet,

29 **Abstract**

30 Natural deep eutectic solvents (NADES) have gained significant attention as green solvents
31 due to their unique properties, such as high solubility, low volatility, low toxicity, and
32 tunability. ~~LPME~~Liquid phase microextraction (LPME) is a sample preparation technique that
33 plays a crucial role in analytical chemistry, and the use of NADES as extraction solvents in
34 LPME offers numerous benefits compared to traditional solvents. NADES can effectively
35 extract bioactive compounds from natural sources without damaging their structure and
36 activity. They can also serve as solvents and catalysts in organic reactions, enhancing the
37 bioavailability of natural compounds. In addition, NADES can be utilized as mobile or
38 stationary phases in chromatographic techniques for separating and analyzing natural
39 compounds. The review highlights the efficiency of NADES in terms of extraction ability,
40 analyte stabilization capacity, and detection compatibility. Moreover, the availability of their
41 components, ease of preparation, low toxicity, cost-effectiveness, and biodegradability make
42 NADES attractive for researchers in the field of analytical chemistry. The applications of
43 NADES in LPME contribute to the principles of green analytical chemistry and green sample
44 preparation by providing a sustainable and environmentally friendly approach to sample
45 preparation. A comprehensive overview of the applications of NADES in liquid phase
46 microextraction is provided, emphasizing their potential for advancing green practices in
47 analytical chemistry.

48 **Keywords**

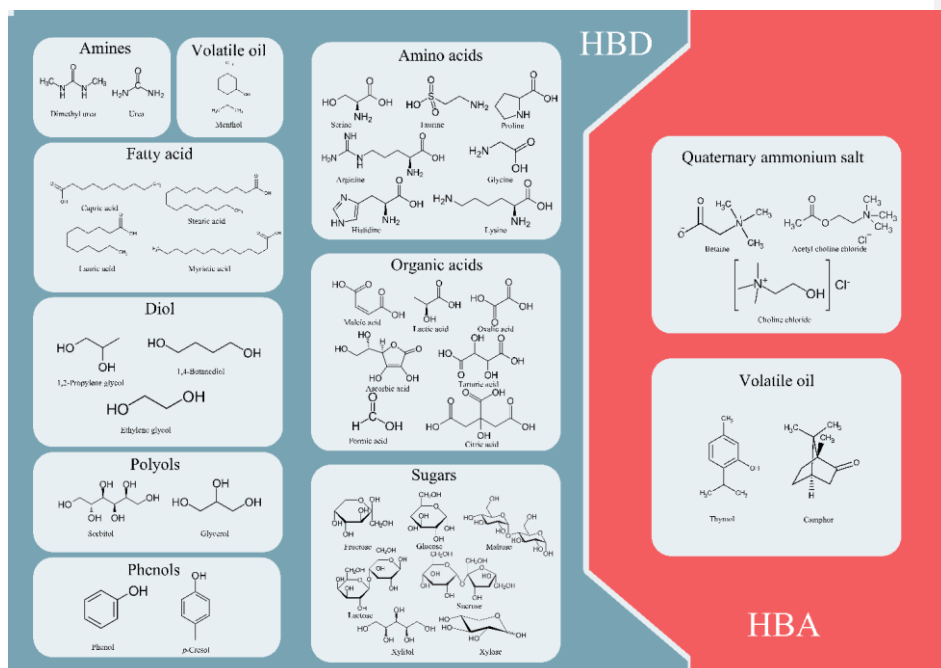
49 Natural deep eutectic solvents; Microextraction; Sample preparation; Analytical chemistry;
50 NADES; Green analytical chemistry

51

52 **1. Introduction**

53 There is a growing interest in the development of new solvents and procedures that are safer
54 for both analysts and the environment [1,2]. This is related to the fact that current organic
55 solvents are highly hazardous, easily vaporized, and combustible. This shift aligns with the
56 principles of green analytical chemistry (GAC) and green sample preparation (GSP) [3–5],
57 which aim to create sustainable solvents, particularly for sample preparation [6,7], a process
58 that can generate significant amounts of waste [8–10]. Natural deep eutectic solvents (NADES)
59 are a novel class of green solvents that captured significant interest in recent years for their
60 potential applications in the domain of research related to natural products. **(Fig. S1)** illustrates
61 the upward trend of NADES publications recently [11].

62 The term “NADES” was coined by Choi et al [12] in 2011. NADES are formed by
63 mixing a hydrogen bond donor (HBD) and a hydrogen bond acceptor (HBA) of natural origin
64 **(Fig. 1)** [13] to form a liquid mixture at room temperature or below [14]. The robust hydrogen
65 bonding interactions between the components lower the melting point of the mixture and drive
66 the formation of NADES. For this reasons, NADES have several unique properties that make
67 them attractive as green solvents. Some of these properties are high solubility, low volatility,
68 low toxicity and tunability. Also, they can dissolve a wide range of compounds, such as
69 proteins, lipids, nucleic acids, metal ions and organic pollutants and bismuth oxide
70 nanoparticles (BIONPs) that are not soluble in water [15–18]. NADES have very low vapor
71 pressure, which reduces the risk of evaporation [19–21]. These solvents are derived from
72 biodegradable compounds, which minimize the environmental and health impacts of solvent
73 use and disposal [22]. Additionally, they can be tailored to suit different applications by
74 changing the type and ratio of the components, which affects the viscosity, polarity, acidity and
75 conductivity of the solvent [23].



76
77 **Fig. 1.** Names and structures of the most common hydrogen bond donors and acceptors
78 involved in NADES preparation.

79
80 NADES have been used for various applications in different fields, such as extraction,
81 synthesis, separation, electrochemistry and bioavailability enhancement [24]. They are also
82 able to extract bioactive compounds from natural sources [25], such as plants, algae and fungi,
83 without damaging their structure and activity [26]. NADES can also act as both solvents and
84 catalysts for organic reactions, such as esterification, transesterification and aldol condensation
85 [27–30]. They can improve the bioavailability of natural compounds by increasing their
86 solubility, stability, permeability, and absorption in biological systems [31]. By creating
87 complexes or micelles [32–34] with poorly water-soluble drugs, NADES can increase their
88 solubility and bioavailability [35]. They can also serve as carriers or adjuvants for various drug
89 delivery systems like nanoparticles, liposomes, or hydrogels. Additionally, NADES can
90 regulate the absorption and release of drugs by modifying their phase behavior or viscosity
91 [36]. These solvents could also be used as antibacterial and antifungal agents [37].

92 In the field of analytical chemistry, NADES can separate mixtures of compounds based
93 on their solubility and affinity to the solvent as mobile phases or stationary phases in

94 ~~chromatographic techniques for separating natural compounds [37–40]. They are also~~
95 ~~presented as a green alternative in analytical chemistry, showing high extraction ability [41],~~
96 ~~analyte stabilization capacity. In the field of analytical chemistry, NADES can separate~~
97 ~~mixtures of compounds based on their solubility and affinity to the solvent as mobile phases or~~
98 ~~stationary phases in chromatographic techniques for separating natural compounds [38–41].~~
99 ~~They are also presented as a green alternative in analytical chemistry, showing high extraction~~
100 ~~ability [42], analyte stabilization capacity [31], and detection compatibility [42]–[43]. These~~
101 ~~advantages make NADES suitable solvent for LPME, which is principally considered green~~
102 ~~due to the huge reduction in solvent and sample consumption. So, finding the most suitable~~
103 ~~solvent took massive effort along the years [44]. One major advantage, besides the previously~~
104 ~~mentioned benefits, is their high polarity, which allows them to dissolve a wide range of~~
105 ~~substances that are typically insoluble in conventional solvents such as cellulose [45].~~

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110 ~~polarity, which allows them to dissolve a wide range of substances that are typically insoluble~~
111 ~~in conventional solvents such as cellulose [46].~~

112 Several review articles on the microextraction techniques utilizing deep eutectic solvents can
113 be found. Makoś et al. provided an article concentrating in hydrophobic deep eutectic solvents
114 in different microextraction techniques [46]–[47]. Nakhle et al. focused on microextraction
115 methods employing deep eutectic solvents as extraction solvents, and exploring the impact of
116 these solvents' properties on extraction efficiency [47]–[48]. Andrade et al. presented an
117 overview on the utilization of deep eutectic solvents for the analysis of biological matrices,
118 with a particular emphasis on urine, blood, plasma, and oral fluid. The focus was placed on
119 microextraction techniques, highlighting the various analytical features [48]–[49]. Santos et al.
120 explored the application of deep eutectic solvents in LPME and their significant contributions
121 to the field of green chemistry [49]–[50]. To the best of our knowledge, this is the first review
122 article to highlight the applications of NADESs in liquid phase microextraction.

123 124 **2. Preparation and characterization of NADES**

125 NADES are prepared by blending specific natural metabolites at specific molar ratios
126 to create a clear liquid at room temperature. Common components of NADES include amino
127 acids, sugars, organic acids, choline salts, essential oil ingredients, and inorganic salts [50–52].

128 ~~The preparation techniques include thermal mixing, vacuum evaporation, ultrasound-based~~
129 ~~methods, and microwave-based methods. In the thermal mixing method, two components are~~
130 ~~heated and stirred with or without a predetermined amount of water to obtain a clear liquid~~
131 ~~[43,53–59]. Vacuum evaporation involves heating the NADES components under reduced~~
132 ~~pressure to remove excess water [43,53]. Ultrasound-based methods utilize ultrasonic waves~~
133 ~~to create cavitation and facilitate the formation of NADES [60]. Microwave-based methods~~
134 ~~use microwave energy to induce molecular agitation and collisions between the components~~
135 ~~[61,62][51–53].~~ The preparation techniques include thermal mixing, vacuum evaporation,
136 ultrasound-based methods, and microwave-based methods. In the thermal mixing method, two
137 components are heated and stirred with or without a predetermined amount of water to obtain
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139 reduced pressure to remove excess water [44,54]. Ultrasound-based methods utilize ultrasonic
140 waves to create cavitation and facilitate the formation of NADES [61]. Microwave-based
141 methods use microwave energy to induce molecular agitation and collisions between the
142 components [62,63].

143 ~~The characterization of NADES involves several analytical techniques. Nuclear magnetic~~
144 ~~resonance (NMR) [23,63], Fourier transform infrared spectroscopy (FTIR),~~ The characterization
145 of NADES involves several analytical techniques. Nuclear magnetic resonance (NMR)
146 [23,64], Fourier transform infrared spectroscopy (FTIR)[23], Raman spectroscopy [64,65], and
147 mass spectrometry (MS) [66] are also used to determine the chemical composition of NADES.
148 ~~NMR, in combination with FTIR, helps identify the constituents and purity of components~~
149 ~~[67,68]. FTIR can also be employed to determine NADES' structures [69,70] while~~
150 ~~thermogravimetric analysis and differential scanning calorimetry are used to assess density,~~
151 ~~thermal features, and stability [43,71]. Density and viscosity measurements provide important~~
152 ~~physical property information for designing processes and evaluating solvent suitability and to~~
153 ~~determine the best ratio between HBD and HBA [72–74].~~

155 **3. Application of NADESs in liquid phase microextraction**

156 ~~Despite obvious developments in analytical science and technology, sample preparation~~
157 ~~remains the bottleneck of all analytical procedures. Miniaturizing the analytical scale and/or~~
158 ~~using safer alternatives instead of hazardous solvents can be used to mitigate the negative~~
159 ~~environmental effect of analytical procedures [75,76].~~ Raman spectroscopy [65,66], and mass
160 spectrometry (MS) [67] are also used to determine the chemical composition of NADES. NMR,
161 in combination with FTIR, helps identify the constituents and purity of components [68,69].

FTIR can also be employed to determine NADES' structures [70,71] while thermogravimetric analysis and differential scanning calorimetry are used to assess density, thermal features, and stability [44,72]. Density and viscosity measurements provide important physical property information for designing processes and evaluating solvent suitability and to determine the best ratio between HBD and HBA [73–75].

3. Application of NADESs in liquid phase microextraction

Despite obvious developments in analytical science and technology, sample preparation remains the bottleneck of all analytical procedures. Miniaturizing the analytical scale and/or using safer alternatives instead of hazardous solvents can be used to mitigate the negative environmental effect of analytical procedures [76,77]. Both hydrophilic and hydrophobic NADES have been employed in different modes of LPME, as shown in (Fig. 2). In this section, the role of NADES in liquid phase microextraction approaches are discussed in details.

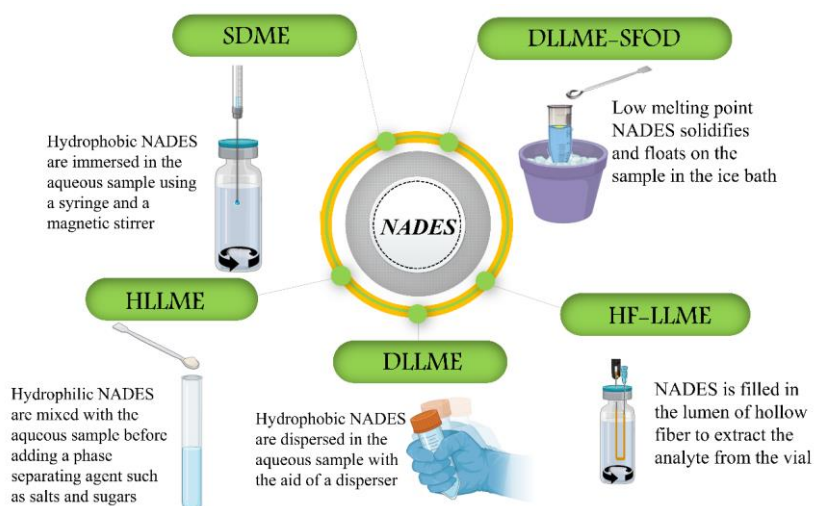


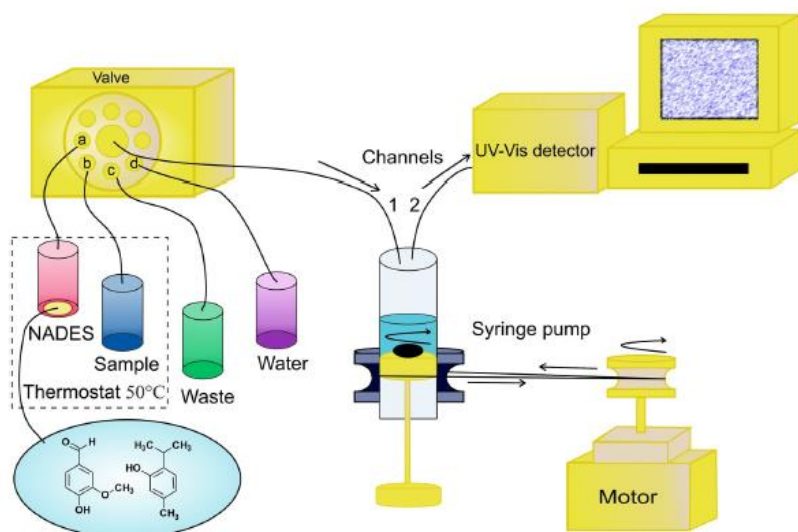
Fig. 2: Modes on LPME in which NADESs were employed

3.1. Applications of NADES in HF-LPME

Sample preparation trends tend to minimize the amount of organic solvent and extraction time. The liquid-phase microextraction (LPME) approach offers an alternative to typical preparation procedures [77]. There are different modes of LPME including dispersive liquid-liquid microextraction (DLLME) [78], single drop microextraction (SDME) [79], and hollow fiber-LPME (HF-LPME) [80]. Among these techniques, the HF-LPME has distinct benefits such as

184 ~~low cost, high preconcentration factor, low solvent consumption, and environmental~~
185 ~~friendliness. The HF-LPME technique is based on the use of different materials such as porous~~
186 ~~polypropylene hollow fiber, polyvinylidene difluoride, or PTFE, which first extract analytes~~
187 ~~from an aqueous sample as the donor phase and then back-extract them into the acceptor phase~~
188 ~~situated in the HF lumen [81]. Organic solvents are often used in the HF-LPME technique, but~~
189 ~~they have various drawbacks, including volatility, toxicity, instability, and deleterious effects~~
190 ~~on laboratory workers. Nia et al [82] prepared amino acids hydrophobic NADES in two phase~~
191 ~~HF-LPME. In this application, NADES was prepared by mixing amino acids (as an HBA) with~~
192 ~~lactic acid (as an HBD) using a hollow fiber's supported liquid membrane. The lumens were~~
193 ~~impregnated with extremely stable NADESs (serine: lactic acid). The developed method was~~
194 ~~successfully applied to extract caffeic acid from green tea, tomato samples and coffee. The~~
195 ~~enrichment factor was in the range of 418–438. Morelli et al. [83] investigated both hydrophilic~~
196 ~~and hydrophobic NADESs hollow fiber-microporous membrane liquid-liquid microextraction~~
197 ~~(HF-MMLLE)-[78]. There are different modes of LPME including dispersive liquid-liquid~~
198 ~~microextraction (DLLME) [79], single drop microextraction (SDME) [80], and hollow fiber-~~
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212 ~~and hydrophobic NADESs hollow fiber-microporous membrane liquid-liquid microextraction~~
213 ~~(HF-MMLLE). The best NADES was composed from thymol and camphor. Selected NADESs~~
214 ~~were introduced into the porous polypropylene membrane for 10 minutes, substituting widely~~
215 ~~used solvents (for example, hexane and octanol). The developed method was successfully~~
216 ~~applied and verified for 11 emergent contaminants from various classes, demonstrating the~~
217 ~~method's adaptability.~~

218 Analytical method automation, commonly employed to minimize reagent and sample usage, is
 219 a highly effective tool for integrating all stages of necessary analytical procedures onto a single
 220 manifold while minimizing human and environmental hazards. Shakirova et al. [84] Analytical
 221 method automation, commonly employed to minimize reagent and sample usage, is a highly
 222 effective tool for integrating all stages of necessary analytical procedures onto a single
 223 manifold while minimizing human and environmental hazards. Shakirova et al. [85] developed
 224 an automated liquid-liquid microextraction process for determining sulfonamides
 225 (sulfamethoxazole, sulfamethazine, and sulfapyridine) in urine samples utilizing NADES. The
 226 extraction of sulfonamides was based on the synthesis of colored Schiff bases in the presence
 227 of vanillin, which served as a derivatization reagent as well as a precursor of NADES (an
 228 extractant). Thymol was utilized in this process as both a medium for Schiff base synthesis and
 229 a second precursor of the NADES. Mass spectrometry verified the production of the Schiff
 230 bases. The microextraction method was automated using the Lab-In-Syringe approach as
 231 indicated in (Fig. 3).



232
 233 **Fig. 3:** manifold for the determination of sulfonamides in urine samples with permission from
 234 [8485].

Field Code Changed

236 The developed approach had enough sensitivity to determine the concentration of sulfonamides
 237 at therapeutic levels. In addition to that, this method was ecologically benign, providing full
 238 automation with a sample throughput of six samples/h.

239

240 3.2. Applications of NADES in DLLME

241 DLLME is a miniaturized sample preparation process used in many analytical chemistry
242 applications [85,86]. ~~In this mode, an immiscible organic solvent is used with an organic~~
243 ~~disperser, the two solvents are combined. The organic extractant is dispersed as tiny droplets~~
244 ~~by manual shaking resulting in a homogeneous hazy solution. DLLME has several benefits~~
245 ~~over other sample preparation approaches in terms of simplicity, affordability, convenience of~~
246 ~~use, and speed. However, the right selection of dispersing and extracting solvents (μL scale) is~~
247 ~~quite difficult [87]. The pioneers of DLLME mode (Rezaee et al. [88]) developed this mode as~~
248 ~~a modification of LLME in an attempt to boost the recovery rate in LLME. DLLME results in~~
249 ~~extending the contact surface between the extractant and the sample, and this dispersion~~
250 ~~procedure greatly increases extraction kinetics. The sample is then centrifuged to separate the~~
251 ~~extractant and break up the emulsion. It worth mentioning that dispersion could be achieved~~
252 ~~by using a disperser solvent or by using external mechanical force such as manual shaking,~~
253 ~~vortex agitation, magnetic stirrer power, ultrasonic power, and microwave irradiation.~~
254 ~~Traditional DLLME procedures use hazardous halogenated organic solvents such as~~
255 ~~chloroform, carbon tetrachloride, and chlorobenzene, which can be harmful to human health~~
256 ~~and the environment. In addition to using long chain alcohols as extractant and hazardous~~
257 ~~dispersers such as acetonitrile (ACN), methanol, acetone, tetrahydrofuran (THF), ethanol.~~
258 ~~Therefore, one of the GAC principles that should be adopted in method development is the~~
259 ~~replacement of harmful solvents with more benign ones. As a result, more environmentally~~
260 ~~friendly NADESs have recently been offered as a sustainable alternative in DLLME. In~~
261 ~~general, NADES is made up of two or more natural components (HBD and HBA) blended in~~
262 ~~a certain ratio to generate a homogeneous mixture with a eutectic point at a lower temperature~~
263 ~~than the separate substances. The most common components used in synthesis of NADESs are~~
264 ~~monoterpenes (menthol, thymol, and camphor) [89–100]. These solvents are biodegradable,~~
265 ~~less hazardous, widely accessible, and simple to make. Monoterpenes such as are considered~~
266 ~~an ideal choice of extractant because of their poor water solubility [101]. In general,~~
267 ~~hydrophobic NADESs were used as extractants in DLLME mode however, hydrophilic~~
268 ~~NADESs could be used as a disperser in the same mode. As reported in Table 1, the use of~~
269 ~~NADESs in DLLME was successfully applied for the extraction of different analytes from~~
270 ~~different matrices including water [100], biological samples [102], foods [103], beverages [92]~~
271 ~~and personal care products [94][86,87]. In this mode, an immiscible organic solvent is used~~
272 ~~with an organic disperser, the two solvents are combined. The organic extractant is dispersed~~

273 as tiny droplets by manual shaking resulting in a homogeneous hazy solution. DLMME has
274 several benefits over other sample preparation approaches in terms of simplicity, affordability,
275 convenience of use, and speed. However, the right selection of dispersing and extracting
276 solvents (μL scale) is quite difficult [88]. The pioneers of DLLME mode (Rezaee et al. [89])
277 developed this mode as a modification of LLME in an attempt to boost the recovery rate in
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288 is the replacement of harmful solvents with more benign ones. As a result, more
289 environmentally friendly NADESs have recently been offered as a sustainable alternative in
290 DLLME [90]. In general, NADES is made up of two or more natural components (HBD and
291 HBA) blended in a certain ratio to generate a homogeneous mixture with a eutectic point at a
292 lower temperature than the separate substances. The most common components used in
293 synthesis of NADESs are monoterpenes (menthol, thymol, and camphor) [91–102]. These
294 solvents are biodegradable, less hazardous, widely accessible, and simple to make.
295 Monoterpenes such as are considered an ideal choice of extractant because of their poor water
296 solubility [103]. In general, hydrophobic NADESs were used as extractants in DLLME mode
297 however, hydrophilic NADESs could be used as a disperser in the same mode. As reported in
298 Table 1, the use of NADESs in DLLME was successfully applied for the extraction of different
299 analytes from different matrices including water [102], biological samples [104], foods [105],
300 beverages [94] and personal care products [93].

301 **Table 1:** Application of NADES in DLLME

Analyte	Sample	Sample volume (mL)	NADES component	Dispersion mode	Extractant volume (μL)	Analytical instrument	Linearity range ng/mL	%RSD	Ref
Tetracyclines	Water	5	[ChCl]: [thymol]: [nonanoic acid]	Air assisted DLLME	400	HPLC/UV	18.2-500	≤11.2	[100] [102]
Warfarin	Biological samples	10	Borneol: decanoic acid	Air assisted DLLME	60	HPLC/UV	5-500	<5.87	[102] [104]
Vanadium	Food stuff	2	ChCl: phenol	Ultrasound assisted DLLME	1000	Electrothermal atomic absorption spectrometry (ETAAS)	N/A	3.4%	[104] [106]
Tert-Butylhydroquinone	Soybean Oils	0.2 g	ChCl: sesamol	Ultrasound assisted DLLME	400	HPLC/UV	5-500 mg/kg	<2.3%	[105] [107]
NSAIDs	Water and milk samples	10	1,1,3,3-tetramethylguanidine chloride: thymol	Ultrasound assisted DLLME	200	HPLC/UV	5-2000	1.11% to 16.9%	[89] [91]
Parabens	Personal care products	5	Menthol: formic acid	Vortex assisted DLLME	80	UHPLC/UV	20-4000	≤3.33%	[91] [93]
Mercury	Water samples	9	Decanoic acid: DL-menthol	Vortex assisted DLLME	50	LC/UV-Vis	10-200	≤19%	[90] [92]
Alkylphenols, bisphenols and alkylphenol ethoxylates	Microbial-fermented functional beverages and bottled water	10	Methanol: octanoic acid	Vortex assisted DLLME	100	UHPLC-MS	0.4-50	≤19.5%	[93] [95]
Sudan I	Food samples	0.2 g	ChCl: sesamol	Vortex assisted DLLME	800	HPLC/UV	0.2-100 mg/kg	<4.5%	[103] [105]
Beta-blockers	Water samples	9.5	Azelaic acid: thymol	Vortex assisted DLLME	55	HPLC/DAD	0.5-100	<6%	[106] [108]
Phthalate Esters	Soft drinks	10	Thymol: octanoic acid	Vortex assisted DLLME	125	UPLC-MS/MS	0.10-5.00	<11.5%	[92] [94]
Phthalate esters	Grape-based beverages	7.5	ChCl: acetic acid	Vortex assisted DLLME	500	Nano-LC/UV	5-403	<17%	[107] [109]
Benzoic acid and sorbic acid	Condiments	10	L-Menthol Acetic acid: decanoic acid	Vortex assisted DLLME-SFOD	800	HPLC/DAD	70-100000	≤5.66%	[94] [96]
Phthalates and one adipate	Water samples	10	Thymol: menthol	Vortex assisted DLLME	100	UHPLC-QqQ-MS/MS	0.100-250	<14%	[95] [97]
Chloramphenicol	Honey sample	5	Menthol: acetic acid	Vortex assisted DLLME	100	LC/UV	1-100 μg/kg	≤4.5%	[96] [98]
Triarylmethane) dyes	Shrimp and water samples.	10	Thymol and camphor	Vortex assisted DLLME	200	HPLC/DAD	0.2-200	≤2.3	[97] [99]
Acaricides	Egg samples	5	Choline chloride-acetic acid- <i>n</i> -octanol	In-syringe DLLME	74	GC/FID	2.7-4000	≤11%	[108] [110]
Phthalic acid esters	Soft drinks and infusions	20	Menthol: acetic acid	Manual agitation assisted DLLME-SFO	100	HPLC/UV	6-1190	1-22 %	[98] [100]
Phthalic acid esters	Water and beverage samples	20	Menthol: acetic acid	Manual agitation assisted DLLME	100	HPLC/UV	4-425	≤ 20%	[99] [101]

302

3.3. Applications of NADES in HLLME

HLLME is a method of sample preparation that involves the formation of a homogeneous phase between an aqueous sample and a small amount of a water-miscible extractant, such as acetonitrile, acetone or tetrahydrofuran. The separation of phases is achieved using a phase separating agent (PSA), which may be a salt, sugar, or hydrophobic substance. Depending on the type of PSA used, HLLME can be classified into three categories: salt-assisted LLME (SALLME) [109,110], sugar-assisted LLME (SULLME) [111,112], and hydrophobic substance-assisted or aprotic solvent-assisted HLLME [113,114]. Besides, the manipulation of physical conditions such as temperature, pH of the system, and, introducing gas bubbles to the homogeneous system could achieve phase separation [115]. It is worth mentioning that HLLME is characterized by infinite contact surface area between the aqueous and organic phases, which permits highly quick and effective extraction [116]. Another advantage of this microextraction process is that there is no need for an evaporation/reconstitution step due to the hydrophilicity of the donor phase. In the standard HLLME approach, hydrophilic organic solvents such as acetonitrile, acetone, ethanol, and propanol are frequently used as extractants. NADESs have recently attracted a lot of attention as a more eco-friendly alternative to the poisonous and volatile organic solvents used in the HLLME process. The most common mode that was used in HLLME is the aprotic solvent-assisted HLLME, which depends on using a water-miscible extractant and an aprotic solvent a PSA such as THF, ACN and acetone. Unlike other HLLME modes, this mode gives the ability to use a large sample volume, enhancing sensitivity of the proposed method. Khezeli et al. [117] were the pioneers of this mode. In this work, the NADESs used were prepared by combining choline chloride (ChCl) as an HBA with phenol as an HBD. The developed method was used to successfully extract several organic chemical components from water samples. This procedure produced a homogeneous solution by adding the extraction solvent (the hydrophilic NADES) to the aqueous sample solution (donor phase). Finally, an aprotic solvent (THF) was used to produce phase separation. It has been proposed that introducing an aprotic solvent into a homogeneous solution can greatly diminish the interactions between DES and water molecule because of the $\pi-\pi$ and hydrogen bonding interactions between the DES ingredients. Therefore, the DES molecules can self-aggregate and migrate out of the water phase. Shishov et al. [118] proposed another theory in the mechanism of phase separation. They investigated the solvent-assisted HLLME process with hydrophilic DES based on choline and phenol utilizing gas chromatography mass spectrometry analysis and coulometric Karl Fischer titration. The results of this study supported the instability of a hydrophilic DES in aqueous conditions. Thus, they hypothesize

337 ~~that hydrophilic DESs based on choline and phenol breaks down in the aqueous phase in the~~
338 ~~solvent assisted HLLME process. The findings of this study revealed that the organic phase~~
339 ~~recovered comprised phenol, THF, and water. As indicated in Table 2 , this mode was~~
340 ~~successfully applied for extraction various compound from different matrices including water~~
341 ~~[119], food [120], biological samples [121] and beverages [122]. The most common water~~
342 ~~miscible NADES used in aprotic solvent assisted HLLME was composed of phenol and ChCl~~
343 ~~[120,123-127]. In addition to that, THF was widely used in this mode as PSA~~
344 ~~[120,123,128,129]. It is worth mentioning that other aprotic solvent were used as PSA in~~
345 ~~aprotic solvent assisted HLLME such as ACN [130] and acetone [131]. The applications of~~
346 ~~NADES in HLLME have high potential because of being greener, simpler, cheaper, and more~~
347 ~~sensitive in comparison with other conventional extraction modes.~~

3.3. Applications of NADES in HLLME

HLLME is a method of sample preparation that involves the formation of a homogeneous phase between an aqueous sample and a small amount of a water-miscible extractant, such as acetonitrile, acetone or tetrahydrofuran. The separation of phases is achieved using a phase separating agent (PSA), which may be a salt, sugar, or hydrophobic substance. Depending on the type of PSA used, HLLME can be classified into three categories: salt-assisted LLME (SALLME) [111,112], sugar-assisted LLME (SULLME) [113,114], and hydrophobic substance-assisted or aprotic solvent assisted HLLME [115,116]. The manipulation of physical conditions such as temperature or pH, and the introduction of gas bubbles into the homogeneous system could achieve phase separation [117,118]. It is worth mentioning that HLLME is characterized by infinite contact surface area between the aqueous and organic phases, which permits highly quick and effective extraction [119]. Another advantage of this microextraction process is that there is no need for an evaporation/reconstitution step due to the hydrophilicity of the donor phase. In the standard HLLME approach, hydrophilic organic solvents such as acetonitrile, acetone, ethanol, and propanol are frequently used as extractants. NADESs have recently attracted a lot of attention as a more eco-friendly alternative to the poisonous and volatile organic solvents used in the HLLME process. The most common mode that was used in HLLME is the aprotic solvent-assisted HLLME, which depends on using a water miscible extractant and an aprotic solvent a PSA such as THF, ACN and acetone. Unlike other HLLME modes, this mode gives the ability to use a large sample volume, enhancing sensitivity of the proposed method. Khezeli et al. [120] were the pioneers of this mode. In this work, the NADESs used were prepared by combining choline chloride (ChCl) as an HBA with phenol as an HBD. The developed method was used to successfully extract several organic chemical components from water samples. This procedure produced a homogeneous solution by adding the extraction solvent (the hydrophilic NADES) to the aqueous sample solution (donor phase). Finally, an aprotic solvent (THF) was used to produce phase separation. It has been proposed that introducing an aprotic solvent into a homogeneous solution can greatly diminish the interactions between DES and water molecule because of the π - π and hydrogen bonding interactions between the DES ingredients. Therefore, the DES molecules can self-aggregate and migrate out of the water phase. Shishov et al. [121] proposed another theory in the mechanism of phase separation. They investigated the solvent-assisted HLLME process with hydrophilic DES based on choline and phenol utilizing gas chromatography-mass spectrometry analysis and coulometric Karl-Fischer titration. The results of this study supported the instability of a hydrophilic DES in aqueous conditions. Thus, they hypothesize

383 that hydrophilic DESs based on choline and phenol breaks down in the aqueous phase in the
384 solvent-assisted HLLME process. The findings of this study revealed that the organic phase
385 recovered comprised phenol, THF, and water. As indicated in Table 2 , this mode was
386 successfully applied for extraction various compound from different matrices including water
387 [122], food [123], biological samples [124] and beverages [125]. The most common water
388 miscible NADES used in aprotic solvent-assisted HLLME was composed of phenol and ChCl
389 [123,126–130]. In addition to that, THF was widely used in this mode as PSA
390 [123,126,131,132]. It is worth mentioning that other aprotic solvent were used as PSA in
391 aprotic solvent assisted HLLME such as ACN [133] and acetone [134]. The applications of
392 NADES in HLLME have high potential because of being greener, simpler, cheaper, and more
393 sensitive in comparison with other conventional extraction modes.

394 **Table 2: Applications of NADES in HLLME**

Analyte	Sample	Sample volume (mL)	NADES component	HLLME	PSA	Extractant volume (μL)	PSA(vol /amount) μL	Analytical instrument	Linearity range ng/mL	%RSD	Ref
Copper	olive oil and water samples	15	ChCl: Phenol	Aprotic solvent assisted HLLME	THF	450	450	FAAS	NA	<5.0%	[123][126]
Arsenic and antimony	Water samples	125	ChCl: oxalic acid	Aprotic solvent assisted HLLME	THF	700	300	Hydride generation-atomic absorption spectrometry	15-570 ng/L	2.1% and 2.7%	[119][122]
Benzotriazole derivatives and benzothiazole derivatives	Surface water	5	ChCl: Phenol	Aprotic solvent assisted HLLME	THF	1000	500	UHPLC-ESI(+)-QToF-MS	5 -200	1 -8%	[124][127]
Pesticides	Chinese medicine	10	ChCl: Phenol	Aprotic solvent assisted HLLME	THF	650	550	HPLC/DAD	50-107000	4.7%	[125][128]
Methyl mercury and total mercury	Water and fish sample	2.5	betaine-sorbitol	Aprotic solvent assisted HLLME	ACN	600	375	Spectrophotometer	0.7–340	1.9–5.5%	[130][133]
Caffeine	Turkish coffee	5	ChCl: Phenol	Aprotic solvent assisted HLLME	THF	400	800	HPLC/UV	500-100000	2.20%	[126][129]
Curcumin	Tea and honey samples	5	ChCl: Maltose	Aprotic solvent assisted HLLME	THF	762.5	107.5	Spectrophotometer	0.4–120	≤4.3%	[132][135]
Curcumin	Food and herbal tea	10	ChCl: Phenol	Aprotic solvent assisted HLLME	THF	400	400	Spectrophotometer	NA	1.8 %.	[120][123]
Malachite green	Aquarium fish water	10	ChCl: Phenol	Aprotic solvent	THF	500	500	Spectrophotometer	45-900	2.7 %.	[127][130]

Sulfonamides	Water samples	1.5	ChCl: Phenol	assisted HLLME Aprotic solvent assisted HLLME	THF	193	100	HPLC/UV	500– 100000	≤2.10	[128] [131]
Thiophenols	Water samples	1.5	ChCl:p-cresol	Aprotic solvent assisted HLLME	Acetone	50	50	GC/FID	2-100000	<4.1%	[131] [134]
Polycyclic aromatic hydrocarbons	Water samples	1.5	ChCl: Phenol	Aprotic solvent assisted HLLME	THF	100	100	HPLC/UV	0.1-400	<4.5	[117] [120]
Antidepressants	Pharmaceutical and water samples	6	ChCl: Phenol	Aprotic solvent assisted HLLME	THF	200	430	HPLC/UV	10-8000	3.6-5.7%	[133] [136]
Selenium species	Water and food samples	25	ChCl: Phenol	Aprotic solvent assisted HLLME	THF	500	500	ETAAS	0.2-8	≤4.1	[134] [137]
Phenoxy acid herbicides	Paddy field and water samples	1.5	ChCl:2- chlorophenol	Aprotic solvent assisted HLLME	THF	50	100	HPLC/UV	5–100	≤4.6	[135] [138]
Phthalate	Beverages	10	ChCl: Phenol	Aprotic solvent assisted HLLME	THF	440	440	HPLC/DAD	170-2700	<11%	[122] [125]
Caffeine	Beverages	1	ChCl: Phenol	Aprotic solvent assisted HLLME	THF	50	50	HPLC/UV	100- 200000	≤6%	[136] [139]
Mercury	Water and biological samples	10	ChCl: Phenol	Aprotic solvent assisted HLLME	THF	500	500	ETAAS	0.3-10	≤–5.72%	[121] [124]

	Cadmium	Food and water samples	50	ChCl: Phenol	Aprotic solvent assisted HLLME	THF	500	600	ETAAS	5–150 ng/L	3.1%	[129] [132]
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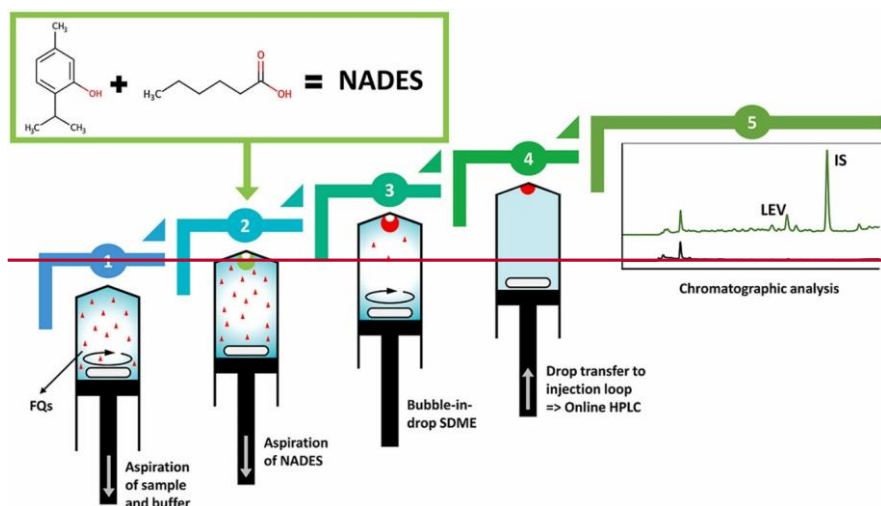
395

396 3.4. Applications of NADES in single drop microextraction

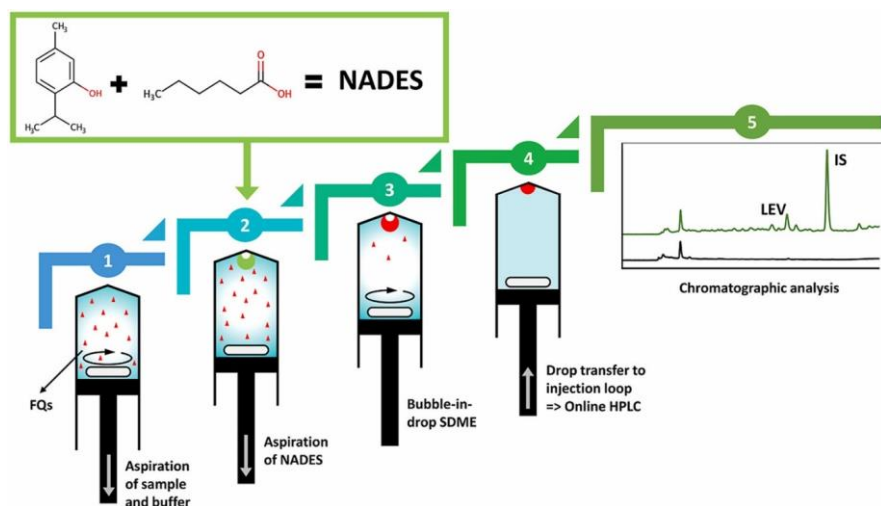
397 Single-drop microextraction (SDME) is a highly effective and environmentally
398 sustainable sample pretreatment technique that involves the immersion of an organic solvent
399 microdroplet into the sample with the aid of a microsyringe needle. SDME has gained
400 widespread use in fields such as environmental monitoring, food quality control, and biological
401 analysis, owing to its minimal solvent consumption and high sample-to-extractant phase ratio
402 [137,138]-[140,141]. This technique has streamlined the analytical workflow by integrating
403 extraction and enrichment processes. Furthermore, SDME is particularly well-suited for
404 fluorescence spectroscopy, as the solvent used is transparent in the visible region and does not
405 interfere with direct visual readout or spectral analysis [139,140]-[142,143]. The realm of green
406 analytical chemistry is presently witnessing a huge interest in the creation and utilization of
407 sustainable and eco-friendly solvents. This trend is particularly visible in the SDME field, in
408 which a growing number of innovative solvents has been reported, for instance, ionic liquids,
409 superheated water, deep eutectic solvents, surfactants, and supercritical fluids [141]-[144]. An
410 important aspect that could significantly influence the efficacy of the extraction process is the
411 choice of solvent. In particular, the utilization of a solvent with high viscosity can facilitate the
412 suspension of larger and more stable droplets at the needle tip. This property makes NADESs
413 a suitable option for the task, given their favorable attributes such as elevated viscosity at
414 ambient temperature, considerable thermal stability, and low vaporization tendencies
415 [142]-[145]. Yousefi et al. have introduced a novel technique for headspace single drop
416 microextraction (HS-SDME) that employs a magnetic bucky gel derived from deep eutectic
417 solvents (DES-MBG) as the extraction medium. This method offers several advantages,
418 including high viscosity, magnetic susceptibility, and adjustable extractability. Additionally, it
419 ensures droplet stability, allowing extraction at high temperatures and rapid agitation rates. This
420 suggests the potential of DES-MBGs to exhibit superior resilience, facilitating the utilization
421 of larger droplet volumes and consequently enhancing extraction efficiency, sensitivity, and
422 detection limits [143]-[146]. Yıldırım et al. [144][147] proposed a novel approach for
423 fluoroquinolone analysis in environmental waters via an automated Lab-In-Syringe direct
424 immersion single drop microextraction method coupled online to HPLC with fluorescence
425 detection (Fig. 4). The method employed NADES as an extractant within an automatic syringe
426 pump, thus eliminating the utilization of toxic solvents and augmenting the method's
427 sustainability from an environmental perspective. The method's linearity range for
428 fluoroquinolones lied between 0.1 and 5.0 µg/L, with quantification limits in the 20-30 ng/L
429 and enrichment factors of 35-45. The trueness of spiked samples ranged from 84.6% to 119.7%,

430 and the method exhibited low RSD values. The method's advantages include its parallel
431 operation with HPLC, low sample consumption, and environmentally friendly characteristics,
432 aligning it with the principles of green analytical chemistry [144,147].

Field Code Changed



433
434 **Fig. 4.** A schematic representation for the automation of a lab-in-syringe technique using
435 NADES-based direct immersion single drop microextraction, which is linked online to HPLC-
436 FL to determine fluoroquinolones (With permission from [144])



437
438 **Fig. 4.** A schematic representation for the automation of a lab-in-syringe technique using
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440 FL to determine fluoroquinolones (With permission from [147])

441

442 3.5 Applications of NADES in DLLME-SFOD

443 The DLLME-SFOD approach is a microextraction method that employs a ternary
444 solvent system (extractant, disperser and sample), in which the extractant is an organic solvent
445 that solidifies in ice bathes at relatively low temperatures [145],[148]. The injection of a
446 suitable mixture into an aqueous sample results in the formation of a cloudy solution, which
447 facilitates phase interaction [146],[149]. Following phase separation and centrifugation, the
448 sample is immersed in an ice bath and the solidified organic phase is gathered for analysis
449 [147],[150]. This method boasts high efficiency, enrichment factors, and rapid equilibrium,
450 while necessitating minimal solvent volume and equipment. Nonetheless, its solvent options
451 are restricted in a narrow range of long chain alcohols with high melting points in the range
452 10-25°C. However, deep eutectic solvents (DESs) are being investigated as a favorable, eco-
453 friendly replacement for this technique [148,149],[151,152]. NADES have been utilized in
454 DLLME-SFOD, serving as both disperser and extracting solvents. An effective example is a
455 NADES consisting of lactic acid, glucose, and water at a 5:1:3 molar ratio, which has
456 demonstrated efficient dispersion of pesticides from water and white wine through vigorous
457 shaking. The addition of water has resulted in lower viscosity, which has facilitated the
458 dispersion process. The dispersive NADES has achieved recoveries exceeding 90% for
459 analytes tested due to its reduced viscosity and increased polarity, which have improved
460 interactions among the aqueous sample, NADES, and extracting solvent [150],[153]. The
461 developed method offered a strong, efficient, and environmentally friendly alternative for
462 determining pesticides, providing a novel application for NADES in sample preparation, as
463 indicated in **Table 1**. Another study has incorporated menthol and decanoic acid in the
464 preparation of NADES with a molar ratio of 1:2 for the extraction of antidepressants from urine
465 samples prior to GC/MS analysis resulting in recoveries ranging from 74 to 147% [151],[154].
466 In their research, Taşpınar et al. applied an environmentally friendly approach known as air-
467 assisted DLLME-SFOD, which was designed to extract patulin from both fruit juice and dried
468 fruit. This process involved the injection of NADES as extraction solvents at a volume of 410
469 µL into a sample solution that has been adjusted to a pH of 5.6. The solution was then drawn
470 into a syringe and immediately reinjected six times to allow for the even dispersal of NADES
471 droplets throughout the aqueous bulk, resulting in a cloudy solution. Afterwards, the tubes were
472 submerged in an ice bath for roughly seven minutes, which enabled the NADES phase to
473 solidify and become easily separable before undergoing UV/Vis spectrophotometric analysis.
474 This method had an LOD of 3.5 µg/L and an EF of 150 [152],[155].

Field Code Changed

475

476 4. Limitations of NADES

477 The interest and the applications of NADES in various fields, particularly in chemical
478 analysis and LPME are increasing. However, NADES are not perfect solvents and have some
479 challenges and limitations that need to be addressed, such as stability, viscosity, water content,
480 and extraction efficiency. NADES are prone to decomposition or degradation over time. The
481 hydrogen-bonding network that exists between the constituents significantly influences the
482 stability of NADES. Hydrogen bonds are responsible for lowering the melting point of NADES
483 [20]. Betaine-urea-water is a NADES that has been used for extracting bioactive compounds
484 from plants. However, this NADES is not stable at room temperature and tends to crystallize
485 after a few days. A recent study by Nava-Ocampo et al. investigated the structural properties
486 and stability of betaine-urea-water using spectroscopic and computational methods. The
487 researchers discovered that the formation of a metastable transparent liquid requires a
488 minimum of two moles of water, whereas a stable NADES necessitates a minimum of three
489 moles of water. They also showed that water plays a crucial role in forming stronger hydrogen
490 bonds between urea and the carbonyl groups of betaine, and in deprotecting the methyl group
491 of betaine from forming intermolecular interactions [153],[156]. NADES tend to have high
492 viscosity compared to conventional solvents, which can limit their mass transfer and diffusion
493 rates. This can reduce their extraction efficiency and increase the energy consumption and
494 processing time. To address this, it is necessary to optimize the composition and ratio of the
495 components of NADES to achieve the desired viscosity. Moreover, some methods can be used
496 to reduce the viscosity of NADES, such as heating, dilution, ultrasonication, or adding co-
497 solvents [13]. NADES usually contain a certain amount of water due to their hygroscopic
498 nature or the presence of water in the natural components. Water can affect the polarity and
499 solvation ability of NADES, as well as their interaction with the target compounds. So, it is
500 important to control the water content of NADES according to the specific application and the
501 solubility of the target compounds. Additionally, some techniques can be used to remove or
502 reduce the water content of NADES, such as freeze-drying [154],[157]. NADES may be less
503 environmentally friendly than initially thought, urging a reevaluation of their large-scale
504 applications [155],[158]. According to Popović et al, The cytotoxic effect is primarily
505 influenced by the structure of the HBD, with acidic systems showing the highest cytotoxic
506 effects. Cytotoxicity depends on both the concentration of the NADES system in the cell
507 medium and the chemical composition of the investigated systems [156],[159].

508

Field Code Changed

5. Perspectives

One of the major limitations in any LPME is phase separation. To overcome this problem, magnetic solvents have been introduced in recent years to shorten the time necessary for phase separation. These magnetic solvents can be quickly separated and collected without the need for time-consuming centrifugation processes, allowing for quick sample preparation. Magnetic solvents are easier to prepare and have higher reproducibility than magnetic materials. Magnetic ionic liquids have a low vapor pressure and good thermal stability, as well as the capacity to respond significantly to external magnetic fields [157,158]. However, they are costly and need drying or a rotary evaporation process [159]. Magnetic deep eutectic solvents (MDESs) not only exhibit paramagnetic characteristics similar to magnetic ionic liquids, but they also offer substantial cost and availability benefits. Most MDESs are currently hydrophilic, which limits their applicability to extracting polar analytes (such as thiophene and aldehydes) in non-polar solvents (such as n-heptane and oil samples) [160,161]. Therefore, the development of hydrophobic MDESs is necessary to extract non-polar analytes from different matrices. For these reasons, MDESs is a new growing area of research for the development green solvents in LPME. Duque et al [162] applied ferrofluid based NADES in stir bar dispersive liquid microextraction for the determination of UV filters in water samples. This ferrofluid was composed of a hydrophobic NADES (1:5 molar ratio of menthol and thymol as carrier solvent) and oleic acid-coated cobalt ferrite (CoFe_2O_4 @oleic acid) magnetic nanoparticles. CoFe_2O_4 MNPs were first synthesized through wet chemical coprecipitation using an adapted procedure [163], and then coated with oleic acid. In this case, 100 mL of 0.4 M FeCl_3 aqueous solution was combined with 100 mL of 0.2 M CoCl_2 aqueous solution. Then, 100 mL of a 3 M sodium hydroxide aqueous solution was added dropwise at 80°C, under continuous stirring. The reaction mixture was then agitated at the same temperature for 1 hour after 2 mL of oleic acid was added. After carefully cooling the black precipitate result to ambient temperature, the MNPs were cleaned twice with ultrapure water and once with ethanol. Finally, the precipitate was dried overnight at 100°C and ground into a fine powder. A stable ferrofluid was prepared by weighing 25 mg of CoFe_2O_4 @OA MNPs in a microcentrifuge tube and 1 mL of NADES was added. The resulting mixture was sonicated for 40 min. The results indicated that the developed analytical method produced comparable findings, demonstrating the promise of this ferrofluid as a less expensive and more environmentally friendly alternative to MILs in future analytical procedures [163].

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573 to MILs in future analytical procedures [166].

574 575 **6. Conclusion**

576 NADESs have emerged as promising alternatives for liquid phase microextraction
577 applications. NADES offer unique advantages such as high polarity, hydrophilicity, and
578 environmentally friendly nature, making them suitable for liquid phase microextraction in
579 diverse fields, including pharmaceutical, environmental, and food analysis. NADES have been
580 successfully employed in different modes, including HF-LPME, DLLME, and SDME. These
581 techniques aim to minimize the use of organic solvents, reduce extraction time, and enhance
582 the preconcentration factor. NADES have shown promise in improving the efficiency and
583 environmental friendliness of LPME processes. By replacing traditional solvents with NADES,
584 researchers have achieved successful extraction of analytes from aqueous samples. Rising
585 interest in NADES for analysis and LPME faces challenges in stability, viscosity, water
586 content, and extraction efficiency. Further research and development in the synthesis methods,
587 characterization techniques, and application of NADES are warranted to fully explore their
588 potential in liquid phase microextraction and contribute to sustainable analytical practices. The
589 automation of liquid-liquid microextraction processes using NADES has proven to be a
590 valuable approach in minimizing reagent and sample usage while reducing human and
591 environmental hazards.

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596

597 **Declaration of interests**

598 The authors declare that they have no competing financial interests or personal
599 relationships that could have appeared to influence the work reported in this paper.

600

601 **Author contributions**

602 All Authors contributed equally to Conceptualization; Investigation; Project
603 administration; Resources; Supervision; Roles/Writing - original draft; and Writing - review &
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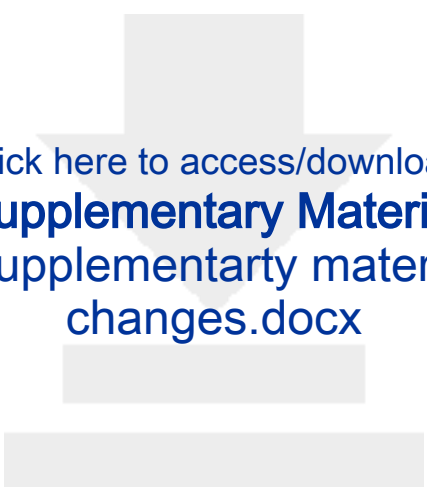


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Table 1: Application of NADES in DLLME

Analyte	Sample	Sample volume (mL)	NADES component	Dispersion mode	Extractant volume (μ L)	Analytical instrument	Linearity range ng/mL	%RSD	Ref
Tetracyclines	Water	5	[ChCl]: [thymol]: [nonanoic acid]	Air assisted DLLME	400	HPLC/UV	18.2-500	\leq 11.2	[100]
Warfarin	Biological samples	10	Borneol: decanoic acid	Air assisted DLLME	60	HPLC/UV	5–500	$<$ 5.87	[102]
Vanadium	Food stuff	2	ChCl: phenol	Ultrasound assisted DLLME	1000	Electrothermal atomic absorption spectrometry (ETAAS)	N/A	3.4%	[104]
Tert-Butylhydroquinone	Soybean Oils	0.2 g	ChCl: sesamol	Ultrasound assisted DLLME	400	HPLC/UV	5-500 mg/kg	$<$ 2.3%	[105]
NSAIDs	Water and milk samples	10	1,1,3,3-tetramethylguanidine chloride: thymol	Ultrasound assisted DLLME	200	HPLC/UV	5–2000	1.11% to 16.9%	[89]
Parabens	Personal care products	5	Menthol: formic acid	Vortex assisted DLLME	80	UHPLC/UV	20–4000	\leq 3.33%	[91]
Mercury	Water samples	9	Decanoic acid: DL-menthol	Vortex assisted DLLME	50	LC/UV–Vis	10–200	\leq 19%	[90]
Alkylphenols, bisphenols and alkylphenol ethoxylates	Microbial-fermented functional beverages and bottled water	10	Methanol: octanoic acid	Vortex assisted DLLME	100	UHPLC-MS	0.4-50	\leq 19.5%	[93]
Sudan I	Food samples	0.2 g	ChCl: sesamol	Vortex assisted DLLME	800	HPLC/UV	0.2–100 mg /kg	$<$ 4.5%	[103]
Beta-blockers	Water samples	9.5	Azelaic acid: thymol	Vortex assisted DLLME	55	HPLC/DAD	0.5-100	$<$ 6%	[106]
Phthalate Esters	Soft drinks	10	Thymol: octanoic acid	Vortex assisted DLLME	125	UPLC-MS/MS	0.10–5.00	$<$ 11.5%	[92]
Phthalate esters	Grape-based beverages	7.5	ChCl: acetic acid	Vortex assisted DLLME	500	Nano-LC/UV	5-403	$<$ 17%	[107]
Benzoic acid and sorbic acid	Condiments	10	L-Menthol Acetic acid: decanoic acid	Vortex assisted DLLME-SFOD	800	HPLC/DAD	70-100000	\leq 5.66%	[94]
Phthalates and one adipate	Water samples	10	Thymol: menthol	Vortex assisted DLLME	100	UHPLC-QqQ-MS/MS	0.100–250	$<$ 14%	[95]
Chloramphenicol	Honey sample	5	Menthol: acetic acid	Vortex assisted DLLME	100	LC/UV	1–100 μ g /kg	\leq 4.5%	[96]

Triarylmethane) dyes	Shrimp and water samples.	10	Thymol and camphor	Vortex assisted DLLME	200	HPLC/DAD	0.2 -200	≤2.3	[97]
Acaricides	Egg samples	5	Choline chloride-acetic acid- <i>n</i> -octanol	In-syringe DLLME	74	GC/FID	2.7-4000	≤11%	[108]
Phthalic acid esters	Soft drinks and infusions	20	Menthol: acetic acid	Manual agitation assisted DLLME-SFO	100	HPLC/UV	6-1190	1-22 %	[98]
Phthalic acid esters	Water and beverage samples	20	Menthol: acetic acid	Manual agitation assisted DLLME	100	HPLC/UV	4-425	≤ 20%	[99]

Table 2: Applications of NADES in HLLME

Analyte	Sample	Sample volume (mL)	NADES component	HLLME	PSA	Extractant volume (μ L)	PSA(vol /amount) μ L	Analytical instrument	Linearity range ng/mL	%RSD	Ref
Copper	olive oil and water samples	15	ChCl: Phenol	Aprotic solvent assisted HLLME	THF	450	450	FAAS	NA	<5.0%	[123]
Arsenic and antimony	Water samples	125	ChCl: oxalic acid	Aprotic solvent assisted HLLME	THF	700	300	Hydride generation-atomic absorption spectrometry	15-570 ng/L	2.1% and 2.7%	[119]
Benzotriazole derivatives and benzothiazole derivatives	Surface water	5	ChCl: Phenol	Aprotic solvent assisted HLLME	THF	1000	500	UHPLC-ESI(+)-QToF-MS	5 -200	1 -8%	[124]
Pesticides	Chinese medicine	10	ChCl: Phenol	Aprotic solvent assisted HLLME	THF	650	550	HPLC/DAD	50-107000	4.7%	[125]
Methyl mercury and total mercury	Water and fish sample	2.5	betaine-sorbitol	Aprotic solvent assisted HLLME	ACN	600	375	Spectrophotometer	0.7–340	1.9–5.5%	[130]
Caffeine	Turkish coffee	5	ChCl: Phenol	Aprotic solvent assisted HLLME	THF	400	800	HPLC/UV	500-100000	2.20%	[126]
Curcumin	Tea and honey samples	5	ChCl: Maltose	Aprotic solvent assisted HLLME	THF	762.5	107.5	Spectrophotometer	0.4–120	\leq 4.3%	[132]
Curcumin	Food and herbal tea	10	ChCl: Phenol	Aprotic solvent assisted HLLME	THF	400	400	Spectrophotometer	NA	1.8 %.	[120]
Malachite green	Aquarium fish water	10	ChCl: Phenol	Aprotic solvent assisted HLLME	THF	500	500	Spectrophotometer	45-900	2.7 %.	[127]
Sulfonamides	Water samples	1.5	ChCl: Phenol	Aprotic solvent assisted HLLME	THF	193	100	HPLC/UV	500–100000	\leq 2.10	[128]
Thiophenols	Water samples	1.5	ChCl:p-cresol	Aprotic solvent assisted HLLME	Acetone	50	50	GC/FID	2-100000	<4.1%	[131]

Polycyclic aromatic hydrocarbons	Water samples	1.5	ChCl: Phenol	Aprotic solvent assisted HLLME	THF	100	100	HPLC/UV	0.1-400	<4.5	[117]
Antidepressants	Pharmaceutical and water samples	6	ChCl: Phenol	Aprotic solvent assisted HLLME	THF	200	430	HPLC/UV	10-8000	3.6-5.7%	[133]
Selenium species	Water and food samples	25	ChCl: Phenol	Aprotic solvent assisted HLLME	THF	500	500	ETAAS	0.2-8	≤4.1	[134]
Phenoxy acid herbicides	Paddy field and water samples	1.5	ChCl:2-chlorophenol	Aprotic solvent assisted HLLME	THF	50	100	HPLC/UV	5–100	≤4.6	[135]
Phthalate	Beverages	10	ChCl: Phenol	Aprotic solvent assisted HLLME	THF	440	440	HPLC/DAD	170-2700	<11%	[122]
Caffeine	Beverages	1	ChCl: Phenol	Aprotic solvent assisted HLLME	THF	50	50	HPLC/UV	100-200000	≤6%	[136]
Mercury	Water and biological samples	10	ChCl: Phenol	Aprotic solvent assisted HLLME	THF	500	500	ETAAS	0.3-10	≤5.72%	[121]
Cadmium	Food and water samples	50	ChCl: Phenol	Aprotic solvent assisted HLLME	THF	500	600	ETAAS	5–150 ng/ L	3.1%	[129]

Declaration of interests

The authors declare that they have no competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.