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Review article

Deep eutectic solvents: Preparation, properties, and food applications

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ABSTRACT

Deep Eutectic Solvents (DESs) emerge as innovative 21st-century solvents, supplanting traditional ones like ethanol and n-hexane. Renowned for their non-toxic, biodegradable, and water-miscible nature with reduced volatility, DESs are mostly synthesized through heating and stirring method. Physicochemical properties such as polarity, viscosity, density and surface tension of DESs influenced their application. This review paper gives the overview of application of eco-benign DESs in fruits, vegetables, cereals, pulses, spices, herbs, plantation crops, oil seed crops, medicinal and aromatic plants, seaweed, and milk for the extraction of bioactive compounds. Also, it gives insight of determination of pesticides, insecticides, hazardous and toxic compounds, removal of heavy metals, detection of illegal milk additive, purification of antibiotics and preparation of packaging film. Methodologies for separating bioactive compounds from DESs extracts are systematically examined. Further, safety regulations of DESs are briefly discussed and reviewed literature reveals prevalent utilization of DES-based bioactive compound rich extracts in cosmetics, indicating untapped potential of their application in the food industry.

1. Introduction

Extraction, an earliest method for the separation of desired components from agricultural waste is still used in laboratories and industries [1]. Traditional organic solvents like ethanol, n-hexane, and methanol, employed in this process are toxic, hazardous, potentially explosive, highly flammable and causes environmental pollution [2]. The residues of organic solvents remained in extract and act as impurities which is well known for their reproductive hazardous, neurotoxic and carcinogenic nature [3]. Their interaction with oxides of nitrogen (came from chemical manufacturing industries) leads to formation of ground level ozone (bad ozone), posing

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respiratory threat and also, aggravating conditions for asthma patients [4]. However, food, cosmetic, biofuel, pharmaceutical, nutraceutical as well as chemical industry has been depending on these petroleum originated solvents [5]. To cope up with these problems, several research have been carried out in order to find a 'green solvent' which has substantial benefits over organic solvent.

Water, supercritical fluids (SCF), ionic liquids (ILs) and deep eutectic solvents (DESs) are well known green solvents. However, some limitations are associated with them. Water is not fit for the extraction of non-polar constituents whereas SCF (like carbon dioxide), is not a good solvent for polar compounds. Synthetic ILs are prepared from petroleum which impede its application in food products and also Food and Drug Administration (FDA), Codex Alimentarius as well as European Union Legislation have not regulated its use in food industry [6,7]. Moreover, ILs and DESs cannot be employed in chemical industry due to high price of ILs, solid form of many DESs at room temperature, and deleterious effect of these solvents on humans. DESs are a mixture of two or more components which are individually solid at ambient temperature but converts to liquid after mixing due to the development of intermolecular hydrogen bond that renders them in liquid state [8]. Other than its application as an extraction solvent for bioactive compounds and food colorants from natural sources, it has other uses in food discipline such as in extraction of undesired compounds (such as metals from tobacco, lettuce leaves, edible oil etc.), improving mechanical properties (such as flexibility, elasticity etc.) of food packaging films, anti-freezing agent for frozen food industries, encapsulation of low bioavailable bioactive compounds, enhancer for organoleptic properties [9], extraction of synthetic phenolics (Tert-Butylhydroquinone in edible oil) and protein from oats, soybean, bamboo shoots etc, detection of aflatoxin in crops like peanut, millet etc. and detection of hazardous chemicals present in drinking water [10,11]. DESs has uses in other areas also like membrane preparation of ultrafiltration as well as nanofiltration [12], separation of azeotropic methanol - methyl *tert*-butyl ether and water-ethanol mixture by using pervaporation chitosan-based DESs membranes [13–15] and enhancement of mechanical stability and plasticity of chitosan film as DESs has great ability to dissolve chitosan effectively. DESs also used for the conversion of chitin powder into chitin nanocrystals and nanofibers [16].

Abbott and co-workers discovered first Deep Eutectic Solvent in 2003 by mixing choline chloride (ChCl) and urea (Ur) in the molar ratio of 1:2 (also known as reline) whose melting point (MP) was 12 °C, lower than the MP of ChCl (i.e. 302 °C) and Ur (i.e. 133 °C) [17]. It is supposed that high MP depression of eutectic mixture may be due to charge delocalization e.g. halide anion (HBA) to HBD via hydrogen bond formation [18]. Deep Eutectic Solvents (DESs) are mainly categorized into four groups i.e. organic salts + metal salts (type 1), organic salts + metal hydrates (type 2), organic salts + hydrogen bond donor (HBD) (type 3) and metal chlorides + HBD (type 4) [19]. Later, Choi, van Spronsen, Dai, Verberne, Hollmann, Arends, Witkamp and Verpoorte [20] described the term 'Natural Deep Eutectic Solvents' (NADESs) comprising of quaternary ammonium salts and natural substances such as amino acids, polyols, sugars, organic acids, amides, amines and diols. In type 3, second element is mainly natural compounds or primary metabolites which are used by plants for its own survival such as organic acids, sugars etc. [21,22]. It is considered that these solvents are present in all living cells as third class of liquids other than water and lipids which help them to fight against odd conditions such as drought [23]. NADESs shows better extraction properties than DESs, solubilises polar as well as non-polar compounds and also acts as a stable media for oxidation sensitive compounds [24].

Till now, researchers have done intensive experiments that depict the advantages of DESs. As far we know, no review was published that separately discussed the use of DESs in agriculture and its byproducts in various perspectives. The present review fills the gap of existing literature by presenting the use of DESs in fruits, vegetables, cereals, pulses, spices, herbs, plantation crops, oil seed crops, medicinal and aromatic plants, seaweed and milk, discussing each in separate section and from various perspectives such as extraction of bioactive compounds, determination of pesticides, insecticides, hazardous and toxic compounds, removal of heavy metals, detection of illegal milk additive, purification of antibiotics and preparation of packaging film. Along with it, recovery methods and safety regulations of DESs are also discussed by keeping in mind that the knowledge of these properties is utmost important as the extract obtained from these avant-gardes solvents has the potential to be utilized directly in food, cosmetics, and pharmaceutical products.

2. DESs preparation methods

There are various methods for the preparation of Deep Eutectic Solvents (DESs) such as heating and stirring (also known as thermal mixing), microwave, ultrasonication, grinding, freeze drying and vacuum evaporation [25]. One of the widely preferred methods is heating and stirring which involves mixing of individual components with or without known amount of water followed by heating in water bath or can be done on a hot plate (50–100 °C) until a clear homogenous liquid is obtained. This method is one of the simplest, cheap and safe but requires more time for preparation [26,27]. In microwave assisted synthesis of DESs, individual components are mixed in glass bottles and exposed to microwaves for a few seconds (less than 30 s at 180 W) that makes this method ultra-fast [28]. Similarly, in ultrasound (US) assisted synthesis, individual components along with known amount of distilled water (10, 30, 75 % w/w) is added in a glass vial consisting of screw cap and treated with US waves (37 KHz, 30 W) at 50 °C till a clear homogenous liquid is formed [29]. Under grinding method, components are mixed and ground in pestle-mortar at room temperature till clear solution is formed. DESs prepared by this method is pure in nature [30]. In freeze-drying method, aqueous solution of DESs or of the individual components are freeze-dried in order to sublimate the water to get solvent in its pure form [31]. Lastly, vacuum evaporation method in which HBA and HBD are mixed in water and evaporated at 50 °C with the help of rotator evaporator. The obtained solution is kept in charged desiccator until the solution reached a constant weight [8]. Irrespective of different preparation methods, high temperature results in degradation of DESs based on ChCl and carboxylic acids due to esterification reaction [32]. Additionally, no change in physicochemical properties of NADESs was found when prepared by three different methods i.e. heating and stirring, microwave and ultrasonication [28,33].

3. Physicochemical properties of DESs

Physicochemical properties of these newly generated solvents depend on their chemical nature as well as on their intermolecular interactions. Density, viscosity, polarity and surface tension of the extraction solvent plays an important role in mass transfer phenomenon, and it can be easily adjusted according to the need of an experiment. These following properties are discussed in this section.

3.1. Density

Density is a main property which controls the diffusivity and ability of solvent to miscible with other liquids [5]. It plays an important role due to its effect on the design and process operation as higher density of DESs during extraction process will require higher power consumption during agitation or mixing of contents using agitators or magnetic stirrers and also, during conveyance through pump from one place to another. Density of DESs is greatly affected by temperature, molar ratio of HBA and HBD, and pressure applied during preparation. Most DESs show higher densities (1.04–1.63 g/cm ^{3}) than water (1 g/cm^3) [34]. On contrary, Ribeiro et al. [35] prepared low density hydrophobic DESs by mixing DL-menthol as HBA and acetic acid, pyruvic acid, lactic acid (LA), lauric acid as HBD in different ratios. They observed low viscosity (5–100 cP) and density of hydrophobic DESs as compared to water. Similar results were observed by Martins et al. [6] on using terpenes and monocarboxylic acids based hydrophobic eutectic solvents. Leron et al. [36] found that density of ChCl: glycerol (Gly) decreases with increase in temperature due to thermal expansion whereas it increases with increase in pressure because of thermal compression. Same trend was observed by Sas, Fidalgo, Domínguez, Macedo and González [37] in ChCl: levulinic acid (LeA) as well as by Mjalli and Ahmed [38] in glyceline (ChCl: glycerol) and ethaline (ChCl: ethylene glycol). According to Shahbaz, Mjalli, Hashim and AlNashef [39], increase in temperature causes rapid motion of molecules and creates more space due to which density decreases. In line with the fact that density is also affected by molar ratio, Manurung, Simanjuntak, Perez, Syahputra, Alhamdi, Siregar and Syahputri Zuhri [40] firstly noted decrease in density with increase in concentration of ChCl salt in ChCl: D-glucose (Glu) DES but after molar ratio of 2:1 sudden increase in density of DES was observed which might be due to the presence of large number of halide anions extra salt in the DES. Additionally, decrease in density of ChCl: ethylene glycol (EG) DES was found with increase in concentration of ethylene glycol because of smaller density of EG than the density of ChCl. Yusof, Abdulmalek, Sirat and Rahman [41] conducted study to check the effect of HBD on density of DESs prepared by mixing tetrabutylammonium bromide (TBABr) with ethylene glycol, 1,3 propanediol and 1,5 pentanediol HBD which consist of two, three and five carbon chain, respectively. They noted decrease in the density of DESs with increase in the chain length of HBD as decrease in hydrogen bond interaction occur due to steric hindrance as a result free volume tends to increase and ultimately, density of DESs decrease.

3.2. Viscosity

Viscosity is a measure of internal friction of a flowing fluid which shows the resistance of a liquid to flow. Solvents with high viscosity are difficult to handle, transport from one place to another, stir, filter and therefore, this property plays an important role in the selection of appropriate solvent. Also, this physical characteristic of solvent aids in design of equipment and calculation of fluid flow. It depends on the nature of the HBA and HBD components, temperature, and percentage of water [7]. Hydrogen bonding, electrostatic and van der Waals interaction controls the viscosity of DESs [38]. They are 100–1000 times more viscous than organic solvents and water due to strong hydrogen bonds which results in lower mobility of free species within DESs [42,43]. Higher viscosity may hinder its utilization in some applications such as extraction [44]. Low viscous DESs were high in diffusivity that can further ameliorate the extraction capacity of synthetic pigments [45]. Viscosity and temperature were found inversely related to each other. Sugar based HBDs such as ChCl: Glu (molar ratio-1:1) was noted highly viscous (34,400 mPa) in nature at 323.15K whereas ChCl: Urea (molar ratio-1:2) had viscosity of 750 mPa at 298.15K [46].

Solvents prepared by polyalcohol were lower in viscosity than acid and sugar because of weaker molecular interaction of smaller molecules present in polyalcohol [47]. On the contrary, urea based DES showed larger viscosity due to the development of stronger hydrogen bonds than polyol based DESs [48]. Additionally, ChCl: diacid (oxalic acid) showed more viscosity than ChCl: monoacid (levulinic acid) which might be due to additional hydrogen bond formation [34]. Decrease in viscosity was detected with increase in mole fraction of HBD in allyl triphenyl phosphonium bromide (ATPPB) - diethylene glycol (DEG) DES (1:4–213.18, 1:10–70.916, 1:16–57.19 mPa s at 20 $^\circ$C) and ATPPB - triethylene glycol (TEG) DES (1:4–233.75, 1:10–95.287, 1:16–76.631 mPa s at 20 °C) due to OH bond stretching which results in weakening of hydrogen bond between salt (Br^-) and HBD (H^+) and therefore, decrease in viscosity. Furthermore, increase in molecular weight of DESs and increase in alkyl chain length of HBD (from DEG - (HOCH2CH2)2O to TEG- HOCH2CH2OCH2CH2OCH2CH2OH) cause enhancement in viscosity of DESs [49]. Higher viscosity can lead to many technical problems in decantation, dissolution and filtration [50] which is decreased by adding water in highly viscous DESs matrix by weakening the hydrogen bonds between the precursors [51]. Low viscosity DESs consisting of LeA, ethylene glycol or phenol were found incredible for practical use. Even 10 % of water can notably reduce the viscosity without affecting their solvation power [43]. However, addition of excess water or over-dilution (more than 50%) disturbs the hydrogen bonding in NADESs as a result, affecting its solubilization power adversely [24].

3.3. Polarity

Polarity is an important property that reflects the overall solvation capability of solvents which affects the extraction efficiency of a compound [52]. Change in polarity of Natural Deep Eutectic Solvents (NADESs) can take place by the addition of water [8]. Due to high polarity and intrinsic property of hydrophilic NADESs, it possesses great solubilising power for polar substances along with some water insoluble substances [7]. Organic acid based DESs are most polar (more than water) followed by amino acid and sugars based ones while polyalcohol based DESs are found least polar (close to menthol) [53]. Higher electronegativity and hydrogen bonding ability makes up the hydrophilic nature of most DESs and NADESs that shows its similarity with other polar solvents [47]. However, the polarity of DESs can be altered into polar or non-polar solvent that can further help to extract various kinds of phytochemical compounds. This property makes it highly effective over conventional solvents such as methanol, ethanol, water and acetone [54]. Formerly discovered DESs were mostly hydrophilic (water-soluble) in nature which hampered its utilization in non-water-soluble samples. Therefore, hydrophobic DESs got attention from researchers and scientists. Hydrophobic DESs was found first in 2015 and was used for the extraction of volatile fatty acids as well as for biomolecules like vanillin and caffeine [55]. Use of hydrophobic or hydrophilic DESs depends on the target compound to be extracted as well as on the type of food sample under consideration (solid or liquid). Successful extraction of organic as well as inorganic compounds can be carried out by using hydrophobic DESs and it is well-known for its solvation characteristics for both polar and non-polar compounds [56]. According to the law of similarity and inter-miscibility (i.e. like dissolves like), solvent polarity value near to the solute polarity value expected to perform superior and vice versa [57]. Xu, Ran, Chen, Fan, Ren and Yi [58] found poor extraction of citrus peel flavonoid by sugar based DESs as they have strong polarity whereas, flavonoids present in citrus peel are less polar in nature as it has multiple methoxy groups (R–O–CH3). Furthermore, ChCl: LeA was found most suitable for extracting flavonoid from citrus peel as it has lowest polarity among other tested DESs.

3.4. Surface tension

Surface tension is the tension created in the liquid surface due to cohesive nature of water molecules which allows it to resist an external force. This property plays important role in extraction, absorption, adsorption, heat exchangers, fluid flow piping, industrial processes design etc. [49]. Solvents having less surface tension penetrate easily in the solid matrix and therefore, enhance the extraction efficiency. Parameters such as alkyl chain length, temperature, hydrogen bond between HBA and HBD, molecular weight and viscosity affects the surface tension. Strong hydrogen bond form higher surface tension which generally gets disturbed at high temperature due to increase in kinetic energy and decrease in cohesion forces which ultimately results in reduction of surface tension [49,59]. Higher molar ratio of ChCl: glycerol decreases the surface tension of DESs as higher amount of ChCl reduces the interaction between HBA and HBD [60]. Firstly, Ghaedi, Ayoub, Sufian, Shariff and Lal [49] found lower value of surface tension in ATPPB-TEG than ATPPB-DEG DES as high OH covalent bond wave number of ATPPB-TEG depicts the weakening of hydrogen bond and hence, decrease in surface tension at all measured temperature and similar molar ratios. Secondly, due to decrease in DESs viscosity, reduction

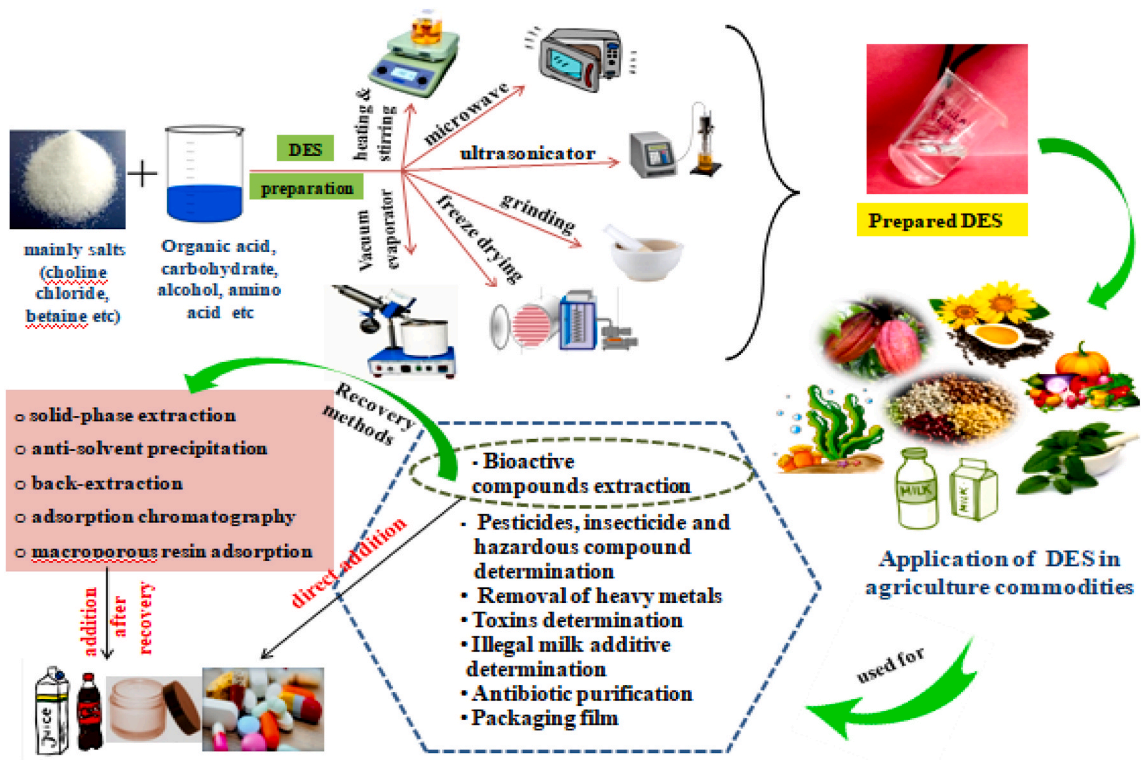

Fig. 1. Schematic representation of DESs preparation and its application in agriculture sector.

Table 1
Overview of various process parameters along with the yield for extraction of desired components from fruits, vegetables, cereals and pulses by using DESs.

Food material	Target component	Best DESs combination	Optimum molar ratio	DESs prepared method	Combined techniques for extraction	Yield	References
Banana puree	Soluble sugars	MA: β-alanine: water	1:1:3	H + S	MAE (2.45 GHz, 900 W, 25 °C, 30 min)	106.9 g/100 g	[71]
Myrciaria cauliflora	Anthocyanin and Pectin	a. ChCl: Prop (for anthocyanin) b. CA: Glu: water (for pectin)	1:2 1:1:3	H + S	Heating at 323K	279.45/100g anthocyanin 27.3% pectin	[72]
Mangifera pajang waste	Anti-oxidants	ChCl: AA	1:2	H + S	Incubator shaker (2 h at 51 °C), speed - 178 rpm	half-life values for the antioxidant-ChCl/AA was higher by 4.17–25% as compared to aqueous system	[73]
Garlic skin (GS) and green onion root (GOR)	Lignin isolation	ChCl: Gly: AlCl3.6H 2O	1:2:0.2	H + S	UAE (30 min in room temperature) and MAE (80 °C for 20 min)	lignin removal rate GS (90.14%) GOR (92.34 %)	[74]
Corn stalk, wheat straw, and rapeseed stem residues	Lignin	LA: ChCl (acidic DES) Gly: K2CO3 (alkaline DES)	5:1	H + S	Heating at 100 °C for 8 or 16 h or at 80 °C for 24 h	delignification yields 11.8–5.7 wt %	[75]
Apple, pear and orange	Diphenylamine	Menthol: n-octanoic acid	1:4	H + S	UAE (100 W at 20 °C for 1 min)	Extraction efficiency 94.4%	[76]
Fruit juices	Sulfonamides	TMA chloride: 2-Octanol	1:2	H + S	UAE (5 min)	Recovery88.09–97.84%	[77]
Fruit juices	Organophosphorus pesticides	ChCl: Phenol	1:2	H + S	UAE (12.31 min)	Recovery87.3–116.7 %	[78]
Blueberry	Anthocyanins	ChCl: Gly: CA	0.5:2:0.5	H + S	UAE (40 kHz, 2 min)	362.3 mg/100g	[79]
Apple pomace	Pectin	ChCl: LA	1:2	H + S	Heating in water bath (0.5–2h at 40–80 °C)	21.34% (w/w)	[80]
Mango Peel	Pectin	Betaine: CA ChCl: MA	1:2	H + S	water bath (90 °C)	36.76 % and 38.72 %	[81]
Olive pomace	Polyphenols	ChCl: CA ChCl: LA	1:2	H + S	HAE (30 min, 40 or 60 °C, speed - 4000 or 12,000 rpm), MAE (200 W at 40 or 60 °C for 30 min), UAE (30 kHz, 280 W, 40 or 60 °C for 30 min), HHPAE (room temperature, high pressure - 300 and 600 MPa for 5 and 10 min)	HAE18.30 mg/g (dw) MAE-9.49 mg/g (dw) UAE-2.51 mg/g (dw) HHPAE-5.31 mg/g (dw)	[82]
Lyciumbarbarum L.	Flavonoids	ChCl: *p*-toluenesulfonic acid	1:2	H + S	UAE (ambient temperature for 1.5 h)	Myricetin57.2 mg/g, morin-12.7 mg/g and rutin 9.1 mg/g	[83]
Buckwheat sprouts	Flavonoids	ChCl: TEG	1:4	H + S	UAE (700 W, 40 kHz, 40 °C for 40 min)	21.07 ± 1.23 mg RE/g	[84]
Citrus peel	Flavonoids	ChCl: LeA: N-MU	1:1.2:0.8	H + S	UAE (200 W, 35 kHz, 50 °C for 25 min)	65.82 mg/g	[58]
Grape skin	Phenolics	ChCl: Ox	1:1	H + S	MAE (50–90 °C for 15–90 min), UAE (30–90 °C for 15–90 min), fixed frequency - 35 kHz	5and 2-fold higher extraction yield than water and aqueous methanol for total anthocyanin content, respectively	[85]

(*continued on next page*)

Table 1 (*continued*)

Food material	Target component	Best DESs combination	Optimum molar ratio	DESs prepared method	Combined techniques for extraction	Yield	References
Grape pomace (GP), olive pomace (OP)	Polyphenolic compounds	ChCl: CA	2:1	H + S	Ultrasonic-microwave cooperative reactor (microwave power - 300 W, ultrasound power - 50 W for 10 min)	2892.07 ± 60.12 mg/kg dw (GP), 645.99 ± 64.8 mg/kg dw (OP)	[86]
Sour cherry pomace	Polyphenols	ChCl: MA	1:1	Microwave irradiation, US and H + S	Microwave irradiation (90 W for 15 s), UAE (40 °C for 30 min) and H + S (650 rpm, 40 °C for 30 min)	3238.32 μg total phenols/g, 2442.93 μg total anthocyanins/g, 418.00 μg total flavonoid/g, and 377.39 μg total phenolic acids/g in H + S method	[28]
Blueberry fruits	Phenolic compounds	ChCl: Gly:CA	0.5:2:0.5	H + S	UAE (40 kHz, 50 min, room temperature)	35-fold higher intestinal bioaccessibility for anthocyanin than organic solvent	[87]
Orange peel	Polyphenols	ChCl: EG	1:4	H + S	Shaking incubator (100 min, 313.15 K, 2800 rpm speed)	3.61 mg/g (for EG), 2.62 mg/g (for ethanolic solvent)	[88]
Mango Peel	Polyphenols	LA: Glu	5:1	H + S	UAE (30 min, 30 °C), CBE (400 rpm, 60 min, 50 °C), SE (reflux temperature of ethanol for 5 h)	1.4 times high phenolic content	[89]
Apple pomace	Bioactive compounds	ChCl: Gly, ChCl: LA, ChCl: CA	1:2 1:3 1:1	H + S	UAE (10–50 min, 20 kHz frequency, 400 W power and 70 % amplitude)	5105 μg/g (ChCl:Gly) 3448 μg/g (70 % ethanol)	[90]
Orange peel	Bioactive compounds	ChChl: Gly ChChl: MA	1:2 1:1	Water Bath	H + S (45 °C for 20 min)	ChChl:Gly (TPC 903 mg GAE/100 g, TFC 169 mg/100 g, AA 416 mg/100 g) ChChl: MA (TPC 1053 mg GAE/100 g, TFC -94.7 mg/100 g, AA -430 mg/100 g)	[91]

ChCl - – choline chloride, MA-malic acid, Prop - propylene glycol, Glu - glucose, LeA - levulinic acid, AA - ascorbic acid, Gly - glycerol, EG - ethylene glycol, LA – lactic acid, CA - citric acid, Ox - oxalic acid, MU - - methyl urea, TMA-trioctylmethylammonium, TEG - triethylene glycol, UAE-ultrasound assisted extraction, MAE-microwave assisted extraction, H + S - heating and stirring, HAE - homogenate assisted extraction, HHPAE - high hydrostatic pressure-assisted extraction, CBE - conventional batch extraction, SE - soxhlet extraction, dw - dry weight, RE –rutin equivalent, GAE - gallic acid equivalent, TPC- total phenol content, TFC - - total flavonoid content, AA - ascorbic acid.

in surface tension was observed with increase in concentration of HBD (i.e., DEG and TEG) in DESs. However, most importantly, while comparing the surface tension of two DESs (prepared from different components and same molar ratio), hydrogen bonding and alkyl chain should be considered the crucial parameter than viscosity. Even, at same molar ratio (1:4), ATPPB-DEG DES had less viscosity (150.76 mPa s at 25 °C) than ATPPB-TEG DES (166.52 mPa s at 25 °C) but the surface tension of former was higher i.e., 49.37 mN/m than latter one i.e. 48.25 mN/m at 25 °C. The major reason behind this was strong hydrogen bonding between HBA and HBD and small alkyl chain of ATPPB-DEG DES rather than viscosity. Also, lower molecular weight DES showed less surface tension at all temperature when prepared from same components. Chen, He, Fan and Song [61] noted higher and lower surface tension of betaine and chloride based DES, respectively than its pure substances. Hayyan, Mjalli, AlNashef, Al-Wahaibi, Al-Wahaibi and Hashim [62] found, at the same molar ratio of DESs, higher surface tension of Glu based DESs as compared to carboxylic acid-based ones. This might be due to large number of hydroxyl group (5-OH) in Glu based DESs which make the stronger hydrogen bond and therefore, results in higher surface tension. Bi, Tian and Row [63] found decrease in surface tension of alcohol based DESs in the following order: ChCl: 1,6 -hexanediol > ChCl: glycerol > ChCl: 1,4 butanediol > ChCl: 1,3 butanediol >2,3 butanediol >1,2 butanediol > ethyl glycol which were selected for extraction of flavonoids from *Chamaecyparis obtusa*.

4. Application of DESs in agricultural commodities and their by-products

Deep Eutectic Solvents (DESs) prepared by using various methods can be applied in fruits, vegetables, cereals, pulses, spices, herbs, plantation crops, oil seed crops, medicinal and aromatic plants, seaweeds and milk for different purposes such as extraction of bioactive compounds, removal of heavy metal etc. (Fig. 1).

4.1. Fruits and vegetables

Fruits and vegetables are the home of bioactive compounds and the by-products generated during its processing are also rich in these compounds as they are the part of it. Guo, Ping, Jiang, Wang, Niu, Liu and Fu [64] combined the homogenization and cavitation burst extraction technique developed in their laboratory for the mulberry anthocyanin extraction by using eighteen different Natural Deep Eutectic Solvents (NADESs). They revealed that ChCl: Gly NADES having molar ratio of 1:2 perform best as it extracted highest phenolic compounds (44.65 mg GAE/g) than molar ratio of 1:3 and 1:4. This is because, increase in concentration of Gly enhances the viscosity of NADES and therefore, create hindrance in mass transfer. Moreover, conventional solvents such as 70 % ethanol (29.96 mg GAE/g) and 80 % methanol (25.47 mg GAE/g) extracted lower phenolic compounds. Other optimum conditions for phenolic compounds extraction were temperature (60 °C), ultrasound amplitude (60 %), time (17.5 min), liquid-solid ratio (31.7 mL/g) and water content (33.5 %). Chen, Li, Liu, Wang, Yang, Zhang and Zhang [65] extracted flavonoid from *Rubia* species fruit by using DESs based ultrasonic assisted extraction (UAE). They found higher extraction i.e. 49.14 mg/g and 55.15 mg/g of total flavonoid from *Rubia truppeliana* and *Rubia cordifolia*, respectively when ChCl: LA was employed under following optimized conditions i.e. liquid: solid ratio - 30: 1 g/mL; extraction temperature - 70 °C and extraction time - 40 min. Additionally, extract obtained from NADES showed higher antioxidant activity and stability for flavonoid than ethanol extract which might be due to hydrogen bond between DES and the compound of interest that decrease the motion of interested compound. Similarly, Radošević, Ćurko, Gaurina Srček, Cvjetko Bubalo, Tomašević, Kovačević Ganić and Radojčić Redovniković [66] observed that NADESs proved to be efficient in isolating phenolic extracts of grape skin with improved biological activity as compared to organic solvents. Binary NADESs prepared from ChCl: Gly or ChCl: citric acid (CA) was similar in effectiveness as 80 % methanol for extracting anthocyanins from grape skin. Also, NADESs ensured the stability of extracted anthocyanins depicting its potential to be used in food, cosmetics and pharmaceuticals. Various other studies also came up that showed immense potential of NADESs as a solvent for extraction of anthocyanin components of grape skin, *Catharanthus roseus*, and wine lees (leftover dead yeast after wine fermentation) [67–69]. Apart from using NADESs as extracting solvent for bioactive compounds, they are also used for the determination of pesticides, sulphonamides, and diphenyl amides in various fruit juices (Table 1). NADESs has also been used in extracting several compounds from vegetables. Dai and Row [70] observed higher UAE efficiency of quercetin from onion and broccoli with betaine (Bet) based DESs than ChCl based ones. Bet: D-Mannitol showed the highest extraction recoveries (quercetin 95.75 %, isorhamnetin 93.82 %, and kaempferol 91.71 %) under the optimal conditions. A study was conducted on 17 types of NADESs which were based on different compounds like ChCl, acetyl ChCl, choline tartrate, Bet and carnitine in different ratios. Maximum flavonoids were extracted in acetyl ChCl: LA (2:1) based NADES (30 % water added) from various fruits, vegetables and spices such as grape, plum, orange peel, wolfberry, cranberry, onion, broccoli, rosemary, mustard and black pepper [29].

Fang et al. [92] revealed the potential of durian fruit seed gum (low viscosity and high water absorption property) in the edible food coating after tuning its properties using NADESs. Sousa, Lima, Silva, Moreira, Pintado and Silva [93] recommended the use of ChCl: oxalic acid and ChCl: ascorbic acid as a plasticizer in cassava starch-based film as it showed improvement in film characteristics in comparison to 40 % glycerol standard as plasticizer. Lijang, Wang, Wu, Cheng, Chen and Qi [94] analysis the interaction of organic salts with linalool and limonene present in citrus peel oil (CPO) by COSMO-RS (conductor-like screening model for real solvents) modeling. They separated terpenes (limonene) from terpenoids (linalool), as terpenes has no aroma as well as flavour and degrade in presence of light and heat, by associative extraction using DESs. Researchers observed that tetrabutylammonium chloride (TBAC) salt forms strong interaction with linalool and weak interaction with limonene. The high extraction of linalool (target substance) was due to in situ formation of deep eutectic solvent consist of TBAC as HBA and linalool as HBD. The COSMO-RS interaction analysis and the experimental data were noted in good agreement. Ultimately, the linalool was released for analysis using a gas chromatographer once the previously formed interaction was broken by the introduction of a strong HBD.

4.2. Cereals and pulses

Ochratoxin A (OTA) is a mycotoxin, produced by *Aspergillus* and *Penicillium*, mainly identified in wheat, wine, dried fruit etc., known to cause cancer in humans. Keeping this point in mind, Piemontese, Perna, Logrieco, Capriati and Solfrizzo [95] conducted study for determining OTA in wheat by using ChCl-based DESs of two different types (ChCl: Gly and ChCl: Urea) in the same ratio of 1:2. OTA was recovered up to 89 % which was close to the recovery from conventional solvent acetonitrile-water mixture (93 %). In another study, Huang, Feng, Chen, Wu and Wang [96] successfully removed the cadmium (Cd) from 51 % to 96 % by using ChCl based NADESs from rice flour which might be due to acidic nature of ChCl based NADESs that introduced H^+ ions into the system as a result Cd-rice flour complex disrupted whereas Gly based NADESs was unable to introduce H^+ ions into the system due to its alkaline nature. Additionally, when saponin (natural biodegradable surfactant and acidic in nature) was mixed with ChCl: L-(−)-Sorbose, synergistic effect was seen as it removed >99 % Cd from rice flour as saponin introduced more H^+ ions into the system and capture Cd^{2+} through micelle formation.

Huang, Feng, Jiang, Qiao, Wu, Voglmeir and Chen [50] observed that ChCl and glycerol based NADESs increases the solubility of rutin, a flavonoid, extracted from buckwheat hull by 660–1577 times as compared to water. ChCl based NADESs were more capable to extract high amounts of rutin than glycerol-based ones. Among all tested ChCl based NADESs, ChCl: Glycerol (1:1) with addition of 20 % water extracted the maximum amount of rutin i.e., 9.6 mg/g and further addition of water resulted in the reduction of it which might be due disruption of hydrogen bonds between the components of NADESs and therefore, loss in the supramolecular structure. Isoflavones, a type of polyphenols, act as antioxidant, anti-allergic, anti-cancerous, anti-inflammatory, anti-hyperglycemic, anti-hyperlipidemic and protect the nervous system. Viewing this, Shang, Dou, Zhang, Tan, Liu and Zhang [97] examined twenty different types of DESs by mixing various combinations of ChCl, Bet and L-proline as HBA with carboxylic acid, alcohols, sugars and amines as HBD for DESs-based UAE of isoflavones from chickpea sprouts. They concluded that ChCl: propylene glycol (1:1) gives highest (5.73 mg/g) whereas L-proline: DL-malic acid (1:1) produces the lowest amount of isoflavones. Under optimum conditions, yield of ononin, sissotrin, formononetin, biochanin A isoflavones and total flavonoid content were 0.55, 1.56, 1.71, 2.40 and 8.35 mg/g, respectively. Cui, Peng, Yao, Wei, Luo, Wang, Zhao, Fu and Zu [98] found that 1,6-hexanediol: ChCl (7:1) with 30 % of water content yields higher amount of bioactive compounds (genistin, genistein and apigenin) from pigeon pea roots and obtained higher extraction yield in DESs based microwave assisted extraction (MAE) followed by DESs based heat reflux extraction (HRE) and DESs based UAE. In the same year, Wei, Qi, Li, Luo, Wang, Zu and Fu [99] independently noticed that the yield of phenolic compounds from pigeon pea leaves was increased as ChCl: maltose ratio decreased from 1:1 to 1:2. However, extraction yield lessen when molar ratio changed from 1:2 to 1:4 because of high viscosity, increase in surface tension, and reduction in the reaction between chloride anion and desired compounds. Hence, they concluded that ChCl: maltose (1:2) NADES based MAE prepared with addition of 20 % water content was the best combination for the higher extraction of polar as well as weak polar phenolics (30.63 ± 0.98 mg/g) from pigeon pea leaves. Additionally, this was the first time that ultra performance liquid chromatography protocol was developed and successfully carried out for determination of fourteen different types of phenolics from pigeon pea leaves extracted by NADESs.

Nowadays, there is a huge demand of plant protein but the extraction of protein by conventional method (alkaline extraction-isoelectric precipitation) is time taking as well as laborious. Yue, Zhu, Yi, Lan, Chen and Rao [100] successfully extracted the protein from oat flour by using eighteen different DESs combinations containing ChCl with 1,4 butanediol, 1,2 butanediol and 2,3 butanediol in the presence or absence of water at various molar ratios. ChCl: 1,4 butanediol: water (1:3:1) showed highest protein content (55.28 %), foaming capacity, thermal stability (denaturation temperature - 105 °C–111 °C) and solubility. DES, in absence of water, showed higher total essential amino acid percentage than DESs containing water in the oat protein extracted by different DESs. Additionally, highest α-helix (45.55 %) was noted in 2,3 butanediol based DES/water binary mixture than 2,3 propanediol based DES

Table 2
Overview of DESs application in spices and herbs.

Samples	Target component	Best DESs combination	Optimum molar ratio	DESs preparation method	Combined techniques for extraction	Yield	References
Peppermint	Monoterpenes, phenolic compounds	ChCl: Glu	5:2	Freeze-drying	UAE (power −500 W, ambient temperature)	monoterpenes 0.479 mg/g to 1.253 mg/g total phenol content 55.23–98.27 mg/g total flavonoid content- 7.30–21.05 mg/g	[108]
Alkanet root	Phytochemicals	Sodium acetate: formic acid	1:4	H + S	UAE (25 °C for 20 min)	TPC 390.16 mg GAE/g, TFC 10.69 mg ECE/g and DPPH 444.68 mmol TE/g	[109]
Curcumae longae rhizome (CLR) or turmeric tea (TT)	Curcuminoids	TBA chloride: decanoic acid	1:1	H + S	Dispersive liquid-liquid microextraction based on solidification of floating DES drop	In CLR (mg/g)- bisdemethoxycurcumin-2.95, demethoxycurcumin- 2.42, curcumin-5.12 In TT (mg/g)- bisdemethoxycurcumin– 1.40, demethoxycurcumin - 1.54, curcumin – 4.15	[110]
Cumin	Essential oil	ChCl: L- LA	1:3	H + S	Microwave-assisted NADES pretreatment coupled with microwave hydrodistillation	2.22%	[111]
Vanilla pods	Vanillin	LA: fructose	5:1	H + S	Heating (50 °C for 1 h)	21.8 mg/g	[112]
Curcuma longa	Curcuminoids	ChCl: LA	1:1	H + S	UAE (30 °C for 20 min)	77.13 mg/g	[113]
Perillae Folium leaves	Essential oil	ChCl:MA	2:1	H + S	UAH (600 W for 20 min)	0.69 %	[114]
Caryophylli Flos	Bioactive compounds	1,3BD: LeA	1:3	H + S	UAE (30 min)	–	[115]

ChCl – choline chloride, Glu – glucose, MA-malic acid, TBA-tetrabutylammonium, LA – lactic acid, BD –butanediol, LeA – levulinic acid, H + S – heating and stirring, UAE-ultrasound assisted extraction, MAE -microwave assisted extraction, UAH– ultrasonic assisted hydrodistillation.

not containing water (43.80 %). On the other hand, DES/water binary mixture of 1,4 butanediol and 1,2 butanediol decreases the α-helix percentage in oat protein. Various hurdles are associated in the conventional method for the separation of cellulose and hemicelluloses from lignin which is a crucial step for the production of bioethanol. With the aim of solving this problem, for the first time, Kumar, Parikh and Pravakar [101] conducted study on the pre-treatment of lignocellulosic biomass rice straw by using NADESs followed by enzymatic hydrolysis of pre-treated biomass and observed that LA: ChCl (5:1) based NADES was capable to remove 60 ± 5% of lignin from biomass which was higher in amount than LA: Bet (2:1) based NADES (52 ± 6% lignin). After lignin removal, NADES-pretreated rice straw was subjected to enzymatic saccharification, and fermentable sugars were produced with a saccharification efficiency of 36.0 ± 3.2 %.

4.3. Spices and herbs

Spices and herbs are known for their high antioxidant content. Spices can be obtained from any part of the plant except its leaves whereas, herbs can be obtained only from the leaves of the plants [102]. Numerous research is carried out to extract compounds such as essential oil, vanillin, curcuminoids etc. from different spices and herbs (Table 2). Hsieh, Li, Pan, Chen, Lu, Yuan, Zhu and Zhang [103] performed UAE in ginger powder for extraction of gingerols by using 15 different alcohol based DESs. They concluded that Bet-1, 3-butanediol, L-carnitine –triethylene glycol as well as L-carnitine-1,3-butanediol in molar ratio of 1:4 and diluted with 75 % water before extraction shows higher extraction yield than traditional organic solvents. Additionally, suitable temperature for extraction of gingerols was found 50 °C (30 min) as beyond this temperature gingerols start degrading. Recently, Duru, Slesarev, Aboushanab, Kovalev, Zeidler, Kovaleva and Bhat [104] extracted isoflavones from kudzu roots and soy molasses waste by using UAE with NADESs and revealed that extract obtained from NADESs had higher antioxidant activity even the content of isoflavone was less as compared to methanolic extract. Additionally, less degradation rate of isoflavones was observed in NADESs extract. Turmeric is known as the queen

Table 3
Overview of DESs application in plantation and oil seed crops.

Samples	Target component/ extracted component	Best DESs combination	Optimum molar ratio	DESs prepared method	Other combined techniques for extraction	Extraction yield/ efficiency	References
Rapeseed cake (RC) and evening primrose (EC) cake	Protein rich precipitate	ChCl: Gly	1:2	H + S	Heating (140 °C for 2 h)	19.9 g/100 g RC, 34.2 g/100 g EC	[121]
Edible oil (sunflower oil, baby oil, trout oil, waste frying oil, syrup soaked pastry oil)	Separation and preconcentration of lead, copper, nickel, manganese	ChCl: Ur	1:2	H + S	Flame atomic absorption spectrometry	Recovery greater than 95%	[122]
Spent coffee grounds	Phenolic compounds	Bet:1,2 BD	1:7	H + S	Thermoshaker (500 rpm, 50 °C, 60 min)	31.67 mg GAE/g	[123]
Peanut roots	Resveratrol	ChCl: 1,4 BD	1:3	H + S	UAE (40 kHz and 400 W, 55 °C, 40 min)	38.91 mg/kg	[124]
Peanut hull	Quercetin	Imidazole: LA	1:1	H + S	MAE (323 K, 8 min)	430 μg QE/g	[125]
Palm oil	Palmitic acid	Bet monohydrate: Gly	1:8	H + S	hotplate (40 °C, 2h, agitation- 250 rpm)	Efficiency of palmitic acid extraction −34.14%, amount of antioxidant preserved in the refined palm oil up to 99%.	[126]
Olive, almond, sesame, cinnamon	Ferulic, caffeic, cinnamic acid	ChCl: EG	1:2	H + S	5 min in ultrasonic bath	Recovery 94.7–104.6%	[127]
Spent coffee grounds	Chlorogenic acids, flavonoids	1,6-hexanediol: ChCl	7:1	H + S	UAE (ambient temperature for 45 min)	TPC 17.0 mg GAE/g, DPPH 26.2 mg TE/g, FRAP 32.9 mg TE/g	[128]
Date palm seed	Bioactive compounds	ChCl: LA	1:2	H + S	UAE (35 and 40 °C, 15 min)	TPC 145.54 mg GAE/g DPPH 719.19 mmol TE/ g	[129]
Coffee husk waste	Phenolic compounds	ChCl: proline	1:1	H + S	H + S (80 °C, 120 rpm, 30 min)	10.07 mg GAE/g	[130]

ChCl - choline chloride, Gly - glycerol, Ur – urea, Bet – betaine, BD - butanediol, LA - lactic acid, Glu - glucose, EG - ethylene glycol, H + S - heating and stirring, UAE-ultrasound assisted extraction, MAE - - microwave assisted extraction, GAE - gallic acid equivalent, QE - quercetin equivalent, TE - trolox equivalent.

Table 4
Overview of DESs application in medicinal and aromatic plants.

Samples	Target/extracted component	Best DESs combination	Optimum molar ratio	DESs prepared method	Other combined techniques for extraction	Extraction yield/efficiency	Therapeutic properties	Ref.
Rhodiola rosea rhizome	Phenyletanes and Phenylpropanoid	LA: Fru: water	5:1:11	H + S	UAE (50 W, 35 kHz, 36 °C, 60 min)	26.10 mg/g	Treat depression, fatigue, weakness and anxiety	[140]
Dittany (Dt), fennel (Fe), marjoram (Mj), mint (Mi) and sage (Sa)	Polyphenol	LA: glycine: water	3:1:3	H + S	UAE (80 °C, 90 min, power - 140W, frequency - 37 kHz)	TPC (mg GAE/g dw) Dt 115.40, Fe 34.72, Mj - 137.36, Mi 109.67, Sa114.92 TFC (mg RtE/g dw) Dt 18.52, Fe 7.96, Mj - 21.70, Mi 17.12, Sa 24.29	Antioxidant, antimicrobial chemoprotective potency	[141]
Ligusticum chuanxiong Hort	Ferulic acid	ChCl: 1,2 Prop	1:2	H + S	MAE (60 °C, 15 min)	2.32 mg/g	Antioxidant, antibacterial, anticancer and promote blood circulation	[142]
Stevia rebaudiana leaves	Stevioside and rebaudioside A	TEA chloride: EG	1:2	H + S	UAE (59.4 °C, 70 min)	Three times higher steviol glycosides in UAE than conventional method	Antibacterial, hypotensive, diuretic, anti-tumors, anti-inflammatory	[143]
Polygonum cuspidatum	Resveratrol	ChCl: Ox	1:1	H + S	UAE (75 °C, 80 min, 250 W)	12.31 mg/g	Antioxidant, anti-viral, anti-inflammatory, anti-diabetes and antitumor activities	[144]
Kinkeliba (C. micranthum)	Phenolic compounds	ChCl: LA	1:2	H + S	UAE (40 kHz, 296 W, 25 °C, 30 min), HAE (100 rpm, 25 °C, 30 min), ME (25 °C, 12 h)	TPC 21.12–23.62 mg GAE/g, TFC 4.38–5.01 mg ECE/g	Antioxidant, nephroprotective activity, anti-tyrosinase, anti-inflammatory, anti-diabetic, anti-microbial	[145]
Centella asiatica	Asiaticoside	Bet: LeA	1:2	H + S	UAE (36 °C, 32 min, 140 W)	229.92 mg/g	ulcerative colitis, wound, atopic dermatitis,	[146]

ChCl - choline chloride, LA - lactic acid, Fru – fructose, EG-ethylene glycol, Prop – propanediol, TEA – Tetraethylammonium, Ox – oxalic acid, Bet – betaine, LeA – levulinic acid, H + S - heating and stirring, UAE-ultrasound assisted extraction, MAE -microwave assisted extraction, HAE – homogenate assisted extraction, ME – maceration extraction, GAE - gallic acid equivalent, RtE – rutin equivalent, ECE - epicatechin equivalent.

of spices and contains the natural polyphenol, curcumin. Accordingly, a new method was developed by Altunay, Elik and Gürkan [105] for extraction of curcumin via vortex-assisted alcohol-based DESs microextraction. They found higher extraction efficiency when betaine hydrochloride (BetCl): Gly (1:3) based DES was used due to strong hydrogen bonding, ion-dipole and dipole-dipole interactions of BetCl- Gly with curcumin. Other optimum parameters were: pH 6.0, sample volume of 50 mL, aprotic solvent (acetone, 300 μL), vortex time of 2 min and speed of 3000 rpm. Guo, Zou, Li, Kou, Liu and Fu [106] extracted and recovered the linarin from *Chrysanthemum indicum* flowers, which is used as a herb, spice as well as one of the constituent for medicinal products, by using DESs. They observed highest yield (14.23 mg/g) of linarin, 1.21 times more than 80% ethanol extraction, under optimal extraction conditions i.e., ChCl: ethylene glycol (1:2), water content of 30 %, liquid-solid ratio of 32 mL/g, extraction power of 340 W and extraction time of 32 min. Furthermore, they recovered 81.55 % linarin by macroporous resin method. Barbieri, Goltz, Batistão Cavalheiro, Theodoro Toci, Igarashi-Mafra and Mafra [107] conducted a study on the extraction as well as stabilization of phenolic compounds from rosemary in different DESs prepared by heating ChCl as HBA with various HBDs (glycerol, Ox acid, LA, 1,2-propanediol). They obtained higher total phenolic content (62.21 mg/g) in ChCl: 1,2-propanediol based DESs extract whereas, ChCl: Gly based DESs showed higher value for DPPH (155.83 mM trolox equivalent/g) which was found 4–18 % higher than ethanol (132.53 mM trolox equivalent/g). In addition, DESs extracted phenolic compounds were observed to be more stable in comparison to ethanol extracts due to the interaction between solvent and phenols present in rosemary extract that results in reduction in the movement of solute molecules, less contact time with oxygen and therefore, decrease in oxidative degradation.

4.4. Plantation and oil seed crops

Various compounds are extracted by using DESs as extracting solvent from plantation and oil seed crops (Table 3). Yuniarti, Saputri and Mun'im [116] optimized the method for extraction of caffeine and chlorogenic acid (CGA) from green coffee beans of Coffea canephora by using ChCl: sorbitol based Natural Deep Eutectic Solvent (NADES) in different molar ratios (2:1, 4:1 and 6:1) and observed highest yield of caffeine (5.87 mg/g) and CGA (12.24 mg/g) with ChCl: sorbitol ratio of 4:1, extraction time of 60 min and liquid-solid ratio of 1:30 g/mL. Moreover, the yield of CGA was found 297% higher than that by maceration method. Procentese and Rehmann [117] concluded that pretreatment of coffee silverskin (CS), which is a by-product of coffee industry, from ChCl: Gly (1:2) was found as an effective DES for higher sugar yield (0.24 $g_{glucose}/g_{biomass}$) and lesser fermentation inhibitors. Tea contains numerous types of polyphenols (catechins) which is known for its antioxidant property and hence, shows positive effect in human health and extension of shelf-life of food products. Considering this, Bajkacz, Adamek and Sobska [118] conducted study to extract the catechins from tea by using DESs prepared by mixing Girard's reagent T (GrT) with ChCl as well as with some organic acids (CA, malic acid, LA) in different proportions. They concluded that DESs-solid-liquid extraction is a promising technology for extraction of bioactive compounds as higher yield was found in malic acid: GrT (2:1) based DES as compared to ILs and conventional solvents. Deeper comprehension of the extraction procedures and the interaction between the solute and solvent is made possible by the COSMO-SAC model's that saves money and time. Hijo, Alves, Farias, Peixoto, Meirelles, Santos and Maximo [119] experimentally observed higher extraction efficiency of polyphenols from mate leaves by using ionic liquid (monoethanolammonium (MEA): acetic acid (AA) with 25 % water) and DES (ChCl: AA with 25 % water) than conventional solvents (ethanol). They confirmed these experimental results by using COSMO-SAC model in which they noted a greater number of regions available to form hydrogen bonding in MEA, AA and ChCl components by σ-profile than ethanol. Additionally, activity coefficient in infinity dilution ($\ln \gamma^{\infty}$) of target compounds (i.e. caffeic acid, chlorogenic acid and quercetin) also supported that 25 wt% of water in ionic liquid/DES enhanced the extraction values. ChCl: formic acid (1:5) based DES was one of the eco-friendly methods for extracting lignin from sugarcane bagasse than sulfite-pulping, kraft procedure and organic solvent process [120].

Liu, Zhang, Yang and Yu [131] observed higher extraction yield of lignans (sesamol, sesamin and sesamolin) from sesame oil when ChCl and phenols-based DES was used in ultrasonic-assisted liquid-liquid microextraction as it extracted both polar as well as non-polar lignan instead of polyols based DESs that extracted only polar lignans. Shabani, Zappi, Berisha, Dini, Antonelli and Sadun [132] developed a novel electro analytical method for the determination of polar antioxidant compounds from extra virgin olive oil (EVOO) and they successfully used LA: Glu (6:1) based DES for the extraction of polar antioxidants from EVOO, without using toxic organic solvent. Manuela, Drakula, Cravotto, Verpoorte, Hruškar, Radojčić Redovniković and Radošević [133] found highest extraction of polyphenol from cocoa waste by employing Bet: Glu (1:1) and for the first time in the NADESs history, NADES extract (which contained polyphenol) was further incorporated by this research group for the preparation of polyphenol enriched chocolate milk drink. They observed a 2-fold increase in polyphenol amount after adding 1 % of this extract in the drink and further concluded that on the basis of sensory evaluation by electronic tongue, 1–10 % addition of Bet: Glu or ChCl: Glu based NADESs extract in chocolate milk was acceptable except 10 % ChCl: Glu ones that might be due to high concentration of ChCl which is responsible for displeasing odor as well taste in the final product.

4.5. Medicinal and aromatic plants

Countless number of plants are present on the earth which exhibit active components beneficial for human health (Table 4). *Pooria cocos*is an edible fungus generally seen on dead barks as well as roots of pine trees and its polysaccharides are known for its remarkable therapeutic properties such as anti-hyperglycemia, anti-tumor, anti-inflammatory etc. Considering these extraordinary biological activities, Zhang, Cheng, Zhai, Sun, Hu, Pei and Chen [134] studied different DESs combinations for the extraction of polysaccharides from *Pooria cocos* and found the highest yield by ChCl: Oxalic acid (1:2) based DES (46.24 %) which was 8.6 times higher than yield of hot water extraction (5.40 %). Similarly, *Satureja montana* is another plant whose parts are used as traditional medicine for various diseases. Considering this, Jakovljević, Vladić, Vidović, Pastor, Jokić, Molnar and Jerković [135] conducted a study to extract rutin and rosmarinic acid from *Satureja montana* and found both ChCl: LA (1:2) as well as ChCl: LeA (1:2) based DESs most suitable for rutin extraction whereas, ChCl: Urea (1:2) based DES was found better for rosmarinic extraction. Additionally, ChCl: Urea (1:1) based DES extracts exhibited best antioxidant activity at 30 °C and 50 % water content. Wang, Jiao, Gai, Wang, Guo, Niu and Fu [136] used tailor-made DESs for extraction of bioactive compounds from fig leaves having therapeutic properties and observed higher extraction yield when glycerol: xylitol: fructose (molar ratio- 3:3:3) DES used as solvent in UAE and MAE as compared to UAE and MAE extraction based on methanol. Moreover, DES-MAE gave higher extraction yield than DES-UAE. Phenolics of *Moringa oleifera* leaves (MOLs) are also widely known for their therapeutic properties in various diseases such as cancer [137]. Wu, Li, Chen, Wang and Lin [138] developed an UAE method to extract phenolic compounds from MOLs by preparing 13 different DESs combinations using ChCl, Bet and L-proline as HBA and amides, acids and alcohols as HBD. They revealed that L-proline: Gly (2:5) based DES showed higher extraction of total phenol content (TPC - 29.8 mg GAE/g DW) at optimal processing parameters (37% water content, 144 W ultrasonic power, 40 °C ultrasonic temperature). Moreover, they concluded that phenol extraction by this method showed higher TPC, total flavonoid content and antioxidant activity than heating and maceration extraction method with water and ethanol. Wojeicchowski, Ferreira, Abranches, Mafra and Coutinho [139] used COSMO-RS (conductor-like screening model for real solvents) in screening of DESs for extraction of antioxidants from rosemary. In σ-profiles of target solutes (i.e. carnosol and carnosic acid) of rosemary showed non-polar nature which helped the researchers to directly came into the decision that DESs composed of hydrophobic HBA and HBD will be best to dissolve these target solutes (based on the principle of like dissolves like) and also, the solubility of solute will be negatively impacted by the addition of water. Finally, they observed 15 wt % of tetrapropylammonium chloride, 55 wt % of 1,2-propanediol, and 30 wt % of water mixture best for extraction of these target compounds.

Ocimum sanctum (OS)*, Terminalia bellerica* (TB) and *Terminalia chebula* (TC) are medicinal plants commonly used in Indian System of Medicine. OS leaf extracts known for antidiabetic and antioxidant properties whereas TB and TC are used in the preparation of triphala that cure various diseases. Keeping this in view, Choudhary, Guleria, Sharma, Salaria, Chalotra, Ali and Vyas [147] evaluated different ChCl based NADESs for extracting polyphenolic compounds from three above mentioned medicinal plants and observed that ChCl: Malic acid (1:2) with 30 % water content was most effective in extracting total phenolic content (mg GAE/g dw) from OS (161.59), TB (650.72) and TC (819.18) than methanolic extract (OS- 109.65, TB- 450.56 and TC- 614.05). The reason may be that organic acid based NADESs are more polar in nature, however, sugar and polyalcohol based NADESs are less polar, with polarity close to that of methanol. Additionally, extract obtained from this NADESs combination showed highest α-glucosidase inhibitory activity which may be because of higher phenolic content. *Rosa roxburghii* Tratt (RRT) is a traditional medicinal plant whose fruits and leaves are known to be high in antioxidant activity. Zhao, Wang, Yan, Cai, Fu, Gu, Liu, Jin and Fu [148] developed active food packaging film by incorporating RRT leaves extract, prepared by using NADESs as a solvent, in chitosan/zein matrix. Prepared film showed better water vapor permeability, mechanical property and light barrier property and also, having high antioxidant and antimicrobial activity which successfully increased the shelf life of cherry tomatoes and blueberries.

Aggarwal, Singh, Gupta and Sharma [149] pre-treated the dried powder of *Ageratina adenophora* flowers, an aromatic weed plant, by ultrasound assisted extraction using mixture of ChCl: LA based NADES and water followed by hydro distillation for extraction of essential oil. They found 4.76 times increase in the yield of essential oil by employing ChCl: LA (1:3) NADES as compared to treated ones without NADES. Also, IC_{50} value of NADES treated sample was found better than control (without NADES treated). Interestingly, isolation of new 5,11-epoxycadin-3,4-en-8-one sesquiterpene crystal was found in essential oil obtained from NADES-treated samples. Both, essential oil as well as isolated new molecule showed anti-acetylcholinesterase activity, which might be due to binding of enzyme with volatile aromatic compounds, that can be useful for treating Alzheimer disease. Sharma, Arokiyaraj, Anmol, Rana, Sharma and Reddy [150] found the effective insecticidal property of essential oil obtained from roots of *Nardostachys jatamansi* by using water and ChCl: Ox (1:1), ChCl: LA (1:1) and ChCl: LA (1:2) NADESs against sap-sucking pest of leguminous crops (i.e. cowpea aphid) and plantation and fruit crops (cacao mealybug) due to presence of valeranone, nerolidol, viridiflorol, β-patchoulene and α–cadinol compounds. However, maximum yield of essential oil was noted in ChCl: MA (2:1) NADES than other NADES combinations.

4.6. Seaweeds

Saccharina japonica was studied for seaweed polysaccharides extraction through DESs combined with subcritical water extraction. The effects of DESs forms, DESs molar ratio, water content, liquid-solid ratio, extraction temperature, and extraction pressure on polysaccharide extraction yield were examined. Experiments revealed the optimum conditions for the extraction of a high quantity of alginates (28.1 %) and fucoids (14.93 %) at a temperature of 150 °C, pressure of 19.85 bar, water content of 70 % and an L/S ratio of 36.81 mL/g. In addition, the obtained polysaccharides exhibited unpretentious antioxidant activity [151]. Das, Sharma, Mondal and Prasad [152] found that hydrated form of DESs were highly efficacious in extracting the κ-carrageenan from *Kappaphycus alvarezii* as compared to non-hydrated form of DESs. Additionally, κ-carrageenan obtained from DESs was found at par in physicochemical and rheological characteristics with κ-carrageenan extracted from conventional methods and found better as compared to water extracted κ-carrageenan. DESs are considered as appropriate solvents in comparison to tedious conventional methods for the simplistic polysaccharide extraction from seaweed.

4.7. Milk

Milk has been known as complete food as it contains good amount of protein, fat, vitamins and minerals such as selenium (Se), calcium (Ca) and magnesium (Mg). Various diseases such as depression, cardiovascular disease, tumor, thyroid dysfunction and viral spread are associated with deficiency of Se [153]. It is available in the milk in the form of seleno-amino acids (such as selenocysteine or selenomethionine). Highest concentration of Se was noted in casein and whey whereas lowest in fat [154]. The remaining Se is found as free Se-amino acids in the water-soluble portion of milk [155]. Prior to extraction of free Se-amino acid by using conventional solvent requires numerous extraction steps (like separation of fat and precipitation of protein) which is laborious and time taking. In order to rectify this problem, López, D'Amato, Trabalza-Marinucci, Regni, Proetti, Maratta, Cerutti and Pacheco [156] developed single-step procedure for Se-amino acid analysis by using lactic acid: Glu (5:1) NADES in which fats and proteins are separated simultaneously. Researchers successfully used this method to extract free Se-amino acid in free dried Se-biofortified sheep milk, CRM ERM-BD 150 skimmed milk powder and cow's milk powder samples. This developed method avoids the use of harmful chemicals as well as saves energy and generate less waste as compared to traditional solvents.

DESs can also be used in quality control laboratories as it helps to detect hazardous components present in food samples (Table 5). Like phthalate acid esters (PAEs) used as plasticizers in polymers like polyvinyl chloride plastics (as it gives softness effect) which further used in packaging of food products. PAEs can easily be leached out from packaging towards the food materials as it is not chemically bound to polymers and disturbs the endocrine system of humans [157]. Keeping this in mind, Wang, Lu, Shi, Yang and Yang [158] explored a new procedure for determination of PAEs in packed milk samples based on liquid-liquid microextraction technique using DESs and reported highest recovery (%) of phthalates in menthol: lauric acid (1:1) based hydrophobic DES. This method was found green, fast and simple for detecting PAEs in milk samples.

Likewise, Sereshti, Semnani Jazani, Nouri and Shams [165] concluded that a green method can be developed for the detection of tetracycline (an antibiotic) in milk samples by applying hydrophobic DESs as an extraction solvent in dispersive liquid-liquid microextraction technique. Ramezani, Ahmadi and Absalan [166] revealed that ChCl: ethylene glycol-based NADES improves the chromatographic behaviour and helps in convenient analysis of melamine, an illegal milk additive, in milk samples.

5. Recovery of bioactive compounds from DESs

Recovery of bioactive compounds from DESs is a major issue due to the low vapor pressure of these solvents and higher miscibility of DESs with water. Various methods have been used by researchers for separating bioactive compound from DESs such as solid phase extraction, anti-solvent precipitation, back-extraction, adsorption chromatography and macroporous resin adsorption. Chen, Jiang, Yang, Bi and Liu [124] uses the macroporous resin adsorption for separating Ginkgo flavonoids from DESs extract solution and reach to the result that use of AB-8 resin give maximum adsorption yield i.e. 93.7 % as compared to D101 (yield- 85.2%) and HPD450, HPD417, ADS-17 and DM130 (yield lower than 60%). In Hibiscus flower, Liu, Lyu, Fu, Jiang and Cui [167] successfully recovered 88.45 %–92.02 % of natural antioxidants from DESs by employing macroporous resin and concluded that recycled DESs can be used maximum of four times for further extraction of antioxidant from hibiscus flower. Zhuang, Dou, Li and Liu [168] also carried out macroporous resin method for separating flavonoid from *Platycladi Cacumen* but most of the resin (AB-8, X-5, HP-20, HPD- 750, LX-5 and LX- 38) used by this group was different from previous study and found that LX-38 gave higher yield than other resins. Panić, Gunjević, Cravotto and Radojčić Redovniković [169] found that by diluting the ChCl: CA NADES containing grape-pomace extract with 80 % of water before adsorption chromatography recovered the highest anthocyanin i.e. 99.46 % than without diluting one which was only 70.36%. It might be because of breakage of bond between NADES and anthocyanin as water content was greater than 50 % disrupt the NADES structure. Furthermore, they also recycled the NADES by evaporating water fraction under vacuum and recovering the ChCl: CA up to 96.8 %. However, recycled NADES gave less extraction efficiency than freshly prepared NADES. Xu, Ran, Chen, Fan, Ren and Yi [58] successfully performed two step back extraction method by using ethyl acetate and *n*-butanol as back extraction solvents for recovery of polymethoxylated flavonoids and glycosides of flavonoids from citrus peel with recovery of greater than 86 %. This group also tried the anti-solvent precipitation method, but this method yields less than 17.27 % of citrus flavonoids. Depending on the type of NADESs, Doldolova, Bener, Lalikoğlu, Aşçı, Arat and Apak [170] recovered curcuminoids from NADESs extracts in a range of 37.5–41.1 % by using water as anti-solvent. This lower recovery might be due to the solubility of curcuminoids in NADESs. Suresh, Singh, Anmol, Kapoor, Padwad and Sharma [171] successfully used HP-20 microporous resin to recover steroidal saponins of *Trillium govanianum* (a medicinal plant) from extract prepared by using ChCl: LA (1:1) NADES. Protodioscin, a steroidal saponins, exhibited the

Table 5
Overview of DESs application in milk samples.

Samples	Purpose of use of DESs	Analyte	Best DESs combination	Optimum molar ratio	Ref.
Bovine Milk	Extraction solvent	Non-steroidal inflammatory drugs (NSAIDs)	in situ DESs formation between Menthol and analyte	–	[159]
Milk	Chelating agent and extraction solvent	Heavy metals (Cadmium, copper, lead)	Menthol: sorbitol: mandelic acid	1:2:1	[160]
Milk	Extraction and preconcentration	Lead	ChCl: phenol	1:2	[161]
Milk	Extraction solvent/dispersive solvent	Pesticides	ChCl: ethylene glycol, ChCl: decanoic acid	1:2	[162]
Milk	Extraction agent	Chloromycetin, thiamphenicol	ChCl: glycerol	1:2	[163]
Powdered milk and baby formula	Extraction	Zinc	ChCl: oxalic acid	2:1	[164]

highest yield (i.e., 39.5 mg/g) among all the targeted compounds. Furthermore, extraction yield of steroidal saponins was decreased (46.86 %) in recovered ChCl: LA based NADES than fresh ones. This time Suresh, Singh, Sharma and Sharma [172] utilized HP-20 microporous resin to recover steviol glycosides of *Stevia rebaudiana* (calorie free sweetener) from two different multicomponent NADESs i.e., LA: Gly: MA: Glu (1:1:1:1) and ChCl: LA: Ox: Gly (2:2:1:1). Similar to above (and previous) study, less extraction yield was measured from both the recovered NADESs as compared to their fresh ones which might be due to alteration in initial molar ratios of NADESs components by the metabolic intermediate's impurities of stevia tissues.

Even though the researchers recovered the target compound from NADESs by using macroporous resin or back extraction method, but use of organic solvent cannot be neglected in these methods whereas the main motto behind the use of DESs/NADESs was to eliminate use of organic solvents. Along with it, they are costly and time-consuming methods. There is a need to discover such methods in which use of organic solvents will be eliminated without affecting the recovery yield of target compounds.

6. Implementation of DESs in analytical methods in food samples

Zinc is an essential micronutrient for human body whose deficiency can cause various problems such as decrease in fertility, reduction in healing process etc. Estimation of zinc in food samples is difficult due to its low concentration which is below the limit of detection of instrument. Keeping this in mind, Haq, Balal, Castro-Muñoz, Hussain, Safi, Ullah and Boczkaj [173] successfully developed a green method by using ChCl: phenol (molar ratio 1:2) DES for the preconcentration of zinc before its analysis by flame atomic absorption spectroscopy. This study recommended that developed method is appropriate for routine fish and eel analysis. With a pre-concentration factor (PF) of 25 and a relative standard deviation (RSD) of 1.7 %, the limit of detection (LOD) and limit of quantification (LOQ) were determined to be 0.041 μg/kg and 0.136 μg/kg, respectively. Similarly, Elahi, Arain, Ali Khan, Ul Haq, Khan, Jan, Castro-Muñoz and Boczkaj [174] discovered method for the simultaneously pre-concentration as well as determination of nickel and zinc in edible oils, milk and fishes by using tetrabutylammonium chloride and decanoic acid (molar ratio - 1:2) DES. LOD was noted 0.029 μg/kg and 1.5 μg/kg for nickel and zinc, respectively.

Faraz, Haq, Balal Arain, Castro-Muñoz, Boczkaj and Khan [175] developed low-cost method (compared to GC and HPLC) for the pre-concentration and spectrophotometric determination of Niclosamide in wastewater and pharmaceutical samples. Niclosamide was found to be toxic for fish species, cause health problems in humans at high concentration and, therefore, it has been important to monitor its presence in environment. This method was found highly sensitive as its LOD and LOQ were noted around 0.112 and 0.374 mg/L, respectively. Ul Haq, Bibi, Balal Arain, Safi, Ullah, Castro-Muñoz and Boczkaj [176] discovered new method for the determination of lead (II) ions from various commercial edible oil products. For lead (II) extraction, DES based on ChCl: phenol in a molar ratio of 1:2 showed the highest recovery. This study concluded that silver nanoparticles may adsorb lead (II) and help it to move from the aqueous phase into the DES phase. Because the sorption kinetics of the nanoparticles are so good, this stage happens extremely quickly. LOD and LOQ were 0.28 μg/L and 0.94 μg/L, respectively. The established approach includes all expected lead concentration levels in oil samples, from parts per billion to higher levels. This method is far more sensitive and many times faster (only 6.5 min/sample) than previously published methods.

Elik, Fesliyan, Gürsoy, Haq, Castro-Muñoz and Altunay [177] given a novel extraction and preconcentration method using a hydrophobic magnetic deep eutectic solvent for the analysis of melamine (inappropriately used as additive) in milk and milk-based products. Air-assisted hydrophobic magnetic DES based dispersive liquid phase extraction approach had the lowest RSD (1.3%), highest PF (160), and shortest extraction time (3 min). LOD (0.9 ng/mL) observed in this method was lower than that of majority of techniques that have been published which is claimed that this method was cheaper than HPLC-UV and HPLC-PDA methods. Synthetic dyes used in industries such as food, textile, leather etc. are known to cause pollution in wastewater discharged from these industries that can further cause problems in aquatic plants and, to human health. Keeping this in view, Ullah, Haq, Salman, Jan, Safi, Arain, Khan, Castro-Muñoz and Boczkaj [178] successfully discovered a method for extraction of Nile red dyes from aqueous medium by using ChCl: phenol (molar ratio 1:2) DES. The results showed that the LOD and LOQ were 2.2 μg/L and 7.3 μg/L, respectively, with an enrichment factor of 40 and an RSD value of 1.35–1.5 %. The developed method benefits were validated by comparing it with existing analytical processes such as reduction in analysis time, sensitive, robust, easy instrumentation, and environmentally friendly.

7. Safety regulations, cytotoxicity, and provisions for commercial use of DESs

Choline is naturally present in various types of food such as egg, meat etc. which is required for various functions of the body. It produces acetylcholine (neurotransmitter) that helps in storage of memory, control of muscle etc. [179]. Excessive secretion of saliva and sweating, fish like body odor, low blood pressure, diarrhea and destruction to liver are some adverse effects of higher intake of choline. Adequate intake (AI) for choline is 550 mg/day and 425 mg/day for men and women, respectively. Tolerable upper intake level is 3500 mg/day for adults [180]. Choline (not less than 32 mg/100g in infant milk) and its salt i.e. ChCl are recommended for use in infant milk by FSSR, 2011. Additionally, ChCl can also be used as an additive whose technical functionality is to increase emulsification in food products. Similarly, there are other NADES components available that are similar to choline chloride in structure and function that may be used as solvents for extraction of bioactive compounds from different sources according to their suitability.

Suresh, Singh, Anmol, Kapoor, Padwad and Sharma [171] checked the cytocompatibility of fifteen different NADESs on animal cell lines (i.e., NRK-52E and IEC-6) and found high cell viability at different concentrations (10, 50, 100 and 200 μg/mL) after 24 and 48 h which showed the non-toxic behavior of NADESs. ChCl: Resorcinol (1:1) NADES expressed slight cytotoxicity on IEC-6 cell lines at 48 h whereas, ChCl: oxalic acid (1:1) NADES showed at higher concentration (200 μg/mL) due to formation of crystals. Macário, Oliveira, Menezes, Ventura, Pereira, Gonçalves, Coutinho and Gonçalves [181] checked the cytoxicity of HBA (choline chloride, tetramethylammonium chloride and tetrabutylammonium chloride), HBD (ethylene glycol, 1-propanol, butanoic acid, hexanoic acid and urea) and the DESs prepared from the combination of these HBA and HBD at molar ratio 1:1 on two human cell lines i.e. HaCaT and MNT-1. Toxic effect of tetrabutylammonium chloride and DES formed by this HBA showed cytotoxicity whereas, choline chloride, tetramethylammonium chloride and the DESs prepared from these two HBA were observed harmless for the cell lines even at high concentration (500 μg/mL). They suggested the potential use of these non-toxic DESs in cosmetics and pharmaceutical industries. Mitar, Panić, Kardum, Halambek, Sander, Zagajski Kučan, Radojcic Redovnikovic and Radošević [182] tested cytotoxicity of eight organic acid based DESs i.e. choline chloride: malic acid (1:1), proline: malic acid (1:1), choline chloride: proline: malic acid (1:1:1), betaine: malic acid (1:1), malic acid: glucose (1:1), malic acid: glucose: glycerol (1:1:1), choline chloride: citric acid (2:1); betaine: citric acid (1:1) on human cell lines (HEK-293T, HeA and MCF-7). They found no growth inhibition of cell lines by DESs even at higher concentration (2000 mg/l) and therefore, they were considered eco-friendly for environment and human beings.

For betaine, maximum consumption of 400 mg/day (i.e. 6 mg/kg body weight per day) is considered safe [183]. Food Safety and Standard Authority of India (FSSAI) drafted regulations on October 29, 2020 for the amendment of Food Safety and Standards (Health Supplements, Nutraceuticals, Food for Special Dietary Use, Food for Special Medical Purpose, Functional Foods and Novel Foods) Regulations. In this new draft, they included betaine (N,N,N,-trimethylglycine) in the list of ingredients as nutraceuticals whose permitted range is 600–650 mg/day [184]. Naturex, Avignone (France) is a botanical company that manufactures and sells plant extracts, and it is the only company till date that commercially produces NADESs based extracts. These extracts are available in the market and its use is only confined to cosmetic products [133]. So far, after exhaustive reviewing to the best of our knowledge, no commercial use of NADESs based extracts is seen in food related products.

8. Conclusions

Eco-benign DESs replacing the conventional solvent has been easily prepared by heating and stirring method. DESs are non-toxic, biodegradable, easily tunable, versatile, eco-friendly, and inexpensive in nature. Also, these solvents showed higher extraction efficiency, enhanced biological activity of bioactive compounds and greater stability in DESs when subjected to various storage conditions makes it superior than conventional solvents. DESs are successfully employed in extraction of bioactive compounds, removal of heavy metals, determination of pesticides, insecticides, toxins, hazardous compounds and illegal milk additives, extraction of Nile red dye from wastewater and in purification of antibiotics. Density, polarity, viscosity, and surface tension are some important properties that should be kept in mind while choosing suitable DESs for the respective work. Scanty number of research is conducted related to application of bioactive compounds rich NADESs extract in the food and examination of its stability. As NADESs is prepared from natural compounds it can be directly added into the food and eliminates the expensive and time-consuming step i.e., separation of target compounds. But it is suggested that the toxicity of final product, after the addition of NADESs based extract, should be tested before releasing the product for human consumption. Also, FSSAI and other government bodies should set the regulations for use of NADESs based extract further in food as it will make easy channelizing of its use in commercial food products.

CRediT authorship contribution statement

Taru Negi: Writing – original draft, Visualization, Software, Conceptualization. **Anil Kumar:** Writing – review & editing, Visualization, Supervision, Resources. **Satish Kumar Sharma:** Validation, Supervision, Resources. **Neha Rawat:** Writing – original draft, Conceptualization. **Deepa Saini:** Writing – original draft, Conceptualization. **Ranjna Sirohi:** Writing – review & editing. **Om Prakash:** Supervision. **Ashutosh Dubey:** Supervision. **Anuradha Dutta:** Supervision. **Navin Chand Shahi:** Supervision.

Declaration of competing interest

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

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