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Review

Deep Eutectic Solvents (DESs) as Green Extraction Media of Beneficial Bioactive Phytochemicals

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Abstract: Deep eutectic solvents (DES) are a mixture of two or more components and are classified as ionic solvents with special properties such as low volatility, high solubility, low melting points, low-cost materials and are less toxic to humans. Using DES has been suggested as an eco-friendly, green method for extraction of bioactive compounds from medicinal plants and are a safe alternative for nutritional, pharmaceutical and various sector applications. Conventional solvent extraction methods present drawbacks such as long extraction period, safety issues, harmful to the environment, costly and large volume of solvents required. The extraction method with DES leads to higher extraction yield and better bioactivity results as compared to the conventional solvents. This review provides a summary of research progress regarding the advantages of using DES to extract bioactive compounds such as phenolic acid, flavonoids, isoflavones, catechins, polysaccharides, curcuminoids, proanthocyanidin, phycocyanin, gingerols, ginsenosides, anthocyanin, xanthone, volatile monoterpenes, tannins, lignin, pectin, rutin, tert-butyl hydroquinone, chlorogenic acids, resveratrol and others, as opposed to using conventional solvents. The bioactivity of the extracts is determined using antioxidant, antibacterial and antitumor activities. Hence, DESs are considered potential green media with selective and efficient properties for extracting bioactive ingredients from medicinal plants.

Keywords: medicinal plants; deep eutectic solvents; green extraction; phytochemical; bioactivity

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1. Introduction

Bioactive compounds of medicinal plants, such as phenolics, alkaloids, flavonoids, terpenoids, polysaccharides, lipids and peptides have several benefits, such as antioxidant, antibacterial and anti-inflammatory properties as well as protective effects against diseases [1,2]. These bioactive compounds are widely used in agrochemical, pharmaceutical and cosmetic industries [3] as well as in replacing synthetic material additives and improving quality of food products [4–6]. Natural bioactive compounds have been extracted from various living organisms, such as plants, fruits and algae. Different bioactive components require different extraction techniques [7]. The activity of these compounds also varies depending on many points under investigation; a study of the physiological effect of bioactive compounds on humans is thus required in the long term [1].

Extraction techniques are classified into two major types: conventional techniques include percolation, maceration, Soxhlet extraction and non-conventional techniques such as microwave-assisted extraction, ultrasound-assisted extraction and enzyme-assisted extraction [8,9]. The most bioactive compounds are extracted from plants by various

processes, mostly using different aqueous-organic solvents, such as hexane, methanol, benzene, chloroform, petroleum ether and acetone [10]. In general, non-conventional techniques have higher efficiency than conventional techniques because they require shorter extraction time, lower cost and significant purity of the compounds. Both techniques present several limitations, such as toxicity of traditional solvents (such as methanol and hexane), thermal instability, low bioactive compound recovery from traditional solvents and possible effects on the compound's chemical structures due to various pathways [11].

Water is the most commonly used medium in pharmaceutical, agrarian and nourishment businesses because its physical and chemical characteristics satisfy most of the compulsory conditions required by the U.S. Food and Drug Administration (FDA). However, water is only effective against polar compounds and has less effect on non-polar compounds [12]. In this regard, an appropriate extraction solvent that exerts less unfavorable impacts on the environment should be developed to replace ordinary chemical strategies. Utilization of green solvents to supplant certain conventional and dangerous solvents is wanted in industries [13].

Green solvents should have significant attributes, such as non-flammability, thermal stability, chemical soundness, low volatility and low toxicity and due to high environmental concerns, green solvents have received high scientific attention as a possible replacement for conventional organic solvents [14,15]. For instance, the use of deep eutectic solvent (DES) and ionic liquid (IL) in bioactive compound extraction is a green and successful technique [16,17]. However, ILs exert harmful effects on health and the environment and have high cost [18]. In this regard, scholars have focused on applications of DES because of their exceptional physicochemical properties, such as lower toxicity, higher biodegradability and lower cost than ILs [19–21]. In addition, researchers prefer the benefits of alternative solvents over conventional organic solvents to obtain the ultimate extract at specific and identical times. As such, alternative solvents that are not only ecological but also produce good quality and safe extracts have been developed [22]. Based on the combination of essential metabolites, recently developed DESs comprise sugar alcohols, sugars, amino acids and natural acids. This unused concept of DES has alluded to a "natural deep eutectic solvent" [23]. Many reports have revealed the selectivity of DES in extracting bioactive compounds, such as flavonoids, polyphenols, phenolic acids, saponins and anthraquinones, from different natural sources [4,24].

All the previous reviews included the usefulness of deep eutectic solvents in extracting bioactive compounds from medicinal plants and focused on the recovery amounts of bioactive compounds compared to conventional solvents [25–28]. However, this review aims to summarize the latest efforts dedicated to application of DES in extraction of bioactive compounds and examination of their biological activities, including antioxidant, antibacterial properties and anti-tumor activity.

2. Methodology

The review methodology was performed on published research in journals (Figure 1). The search process in relevant literature included articles from Science Direct and Scopus electronic databases by using "deep eutectic solvents" AND "plants extraction" as general keywords. The resulting articles were screened using accurate specific terms including "bioactivity," "bioavailability," "antioxidant," "antibacterial" and "In-vitro studies." The total articles obtained based on the keywords were $n = 185$. The search focused on specific terms used in obtained articles based on data validation. Consequently, 41 articles were used in this review.

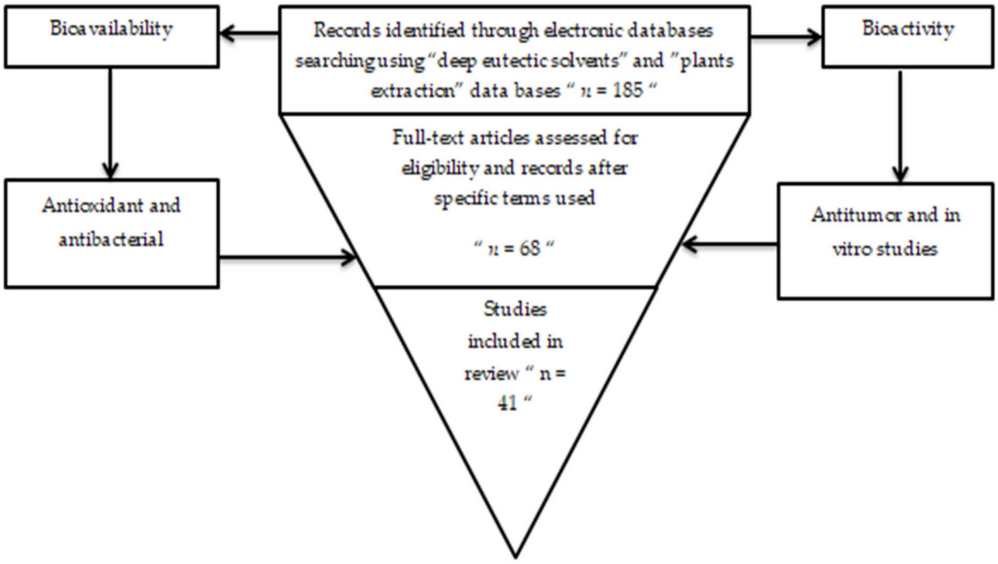

Figure 1. This is a figure for steps of the search process.

3. Deep Eutectic Solvents (DES): A Brief Overview

In 2003, Abbot et al. synthesized the first DES from a mixture of choline chloride (ChCl) and urea. In subsequent years, other DESs were discovered, including those synthesized by mixing choline chloride with various carboxylic acids (oxalic, malonic and succinic acids) [29]. The efficiency of DES for extraction of bioactive materials from plants was also investigated [30]. DES or NDES are easily prepared by mixing two or more components, such as choline chloride, maleic acid, citric acid, acetic acid, malic acid, fructose, sucrose, glucose, trehalose and water [31]. The mixture is mixed and stirred at a specific temperature until a clear homogeneous and viscous liquid is obtained [32]. The liquid is cooled to room temperature and is not subjected to any purification step. In general, DES is synthesized using different process times [33]. Choline chloride is the most widely used salt because it is inexpensive, used as a supporting nutrient in the poultry field and biodegradable [34]. Considering the various structural components of DES, scholars have studied their physicochemical properties, such as melting point, density, polarity, conductivity and viscosity. The melting points of the DES mixtures are lower than those of individual compounds [34]. The melting point is not fixed in all DES types but dependent on DES components, such as hydrogen bond donor (HBD), hydrogen bond accepter (HBA) and molar ratio. When choline chloride and urea are mixed in different molar ratios of 1:1 and 1:2, the freezing points of DES mixtures are >50 °C and 12 °C, respectively [35]. The melting point of DES is determined by the HBD ratio because the increased interaction between the salt anionic groups with the hydrogen bond will lead to decreased interactions with the salt cationic groups [36]. The DES density is an important physical property that has an estimated higher value than the water density value [37]. The notable variations in the DES mixtures in terms of density are due to their different individual molecular compositions, and their density is higher than that of their individual starting materials. This is most probably dependent on the concept of hole theory [36]. For instance, urea and acetamide have densities of 1.32 and 1.16 g cm^{-3}, respectively, while the DES of ZnCl2-acetamide (1:4) and ZnCl2-urea (1:3.5) have densities of 1.36 and 1.63 g cm^{-3}, respectively [35]. The densities of DES mixtures also have major effects on the molar ratios of their individual components [38].

The polarity of the compositions of DES mixtures is also a particularly important characteristic of the modulation mixture in extraction. Variations in DES polarity depend on individual compositions and are believed to be related to the molecular structure of HBD [13,39]. Moreover, the temperatures of DES are important given that increasing temperature leads to a decrease in the polarity of DES. In addition, increases in temperature

reduce the hydrogen-bond donating acidity of DES [40]. Most DES mixtures have viscosity greater than 100 cP at room temperature, which is higher than those of other solvents and traditional small molecule solvents [34–36]. The highly viscous nature is probably due to the presence of a huge network in the hydrogen bond of the compounds, resulting in decrease in the mobility of free species inside DES. Moreover, electrostatic interactions may contribute to the high viscosity of DES [35]. Although high viscosity can be very beneficial when processing single drop micro-extraction, it may negatively affect other extraction procedures. However, this defect is usually avoided by increasing the temperature during extraction or by adding water [3,41]. Conductivity is another physical property of DES. These solvents have poor conductivity, lower than 2 mS cm^{-1} at room temperature, due to their high viscosity [35]. Thus, elevated temperature will lead to a significant increase in DES conductivity due to the decline in viscosity [13,42]. A previous study reported that modification in the molar ratios of DES components affects the conductivity property; that is, increasing the amount of ChCl to glycerol will increase the conductivity (from 0.74 mS cm^{-1} for a molar ratio of 1:4 ChCl/glycerol to 1.30 mS cm^{-1} for a molar ratio of 1:2 ChCl/glycerol) [29,42]. Table 1 summaries the advantages and disadvantages of DESs from general perspective

Table 1. Main advantages and disadvantages of DESs.

Conditions	Advantages	Disadvantages	Ref
Synthesis	Simple preparation	Nil	[43]
Economy	Very low price and available	Nil	
Physiochemical properties	High reactivity, non-sensitive to water, non-flammability and thermal stability	High viscosity	[44]
Environmentally	Biodegradable, biocompatible, renewable and low toxicity	Some types have toxicity	[45]

4. Advance Plant Extraction Techniques by DES

The disadvantages of conventional plant extraction techniques are seen in the Soxhlet technique, whereby excessive volumes of solvent are used and time is wasted in plant extraction, resulting in lower volume yield. Advanced extraction techniques are known for their short extraction time, reduced volume of organic and hazardous solvents and simple operation, high extraction yield and low energy consumption; as such these techniques are categorized as "Green Extraction."

Ultrasound-assisted extraction (UAE) is used for extraction and analysis of different types of bioactive compounds and crude extract from a variety of plant materials [46]. This technique uses energy with low frequency (>20 kHz) and high power (80–200 W) and an ultrasonic bath or probe. The extraction principle depends on the cavitation phenomenon, which creates bubbles by disrupting and collapsing cell walls to release the target compounds and allow diffusion of solvents by working the UAE matrix; this technique is efficient and is time saving [47]. DES based on ultrasound-assisted extraction has been reported as a greener approach for bioactive compounds extraction than using conventional organic solvents [48]. Several types of DESs have been used in UAE to extract bioactive compounds from ginger. The extraction condition included 1:4 L-carnitine:1,3-butanediol at 40 °C for 30 min, resulting in higher yield of gingerols extracted than those of ethanol and water extraction; furthermore, UAE ginger extracts showed higher antioxidant capability [49].

Another advanced extraction method for bioactive compounds from biological matter is microwave-assisted extraction (MAE), which uses two types of equipment [50]. The principle of MAE depends on the use of electromagnetic radiation waves (typically 2.45 GHz) by direct interaction with the sample through heating and continuous dipole rotation. This process leads to the degradation of plant cell tissues and induces ion flow to release active compounds from the intracellular and cell membrane; MAE has high extraction efficiency [51]. The efficiency of this method depends on the nature of the sample and

solvent. Therefore, this type of extraction has low cost and saves solvent volume compared with traditional extraction techniques. Furthermore, industrial scale-up approaches of MAE have been developed due to its operational simplicity [52,53]. Five main flavonoids from sea buckthorn leaves were extracted by MAE using 12 kinds of DES (choline chloride as HBA) and 70% ethanol. Under the optimal condition of 64 °C for 17 min, this technique provides an improved performance, which is significantly superior to DES-HRE and DES-UAE and leads to a high extraction yield of 20.82 mg/g for target flavonoids within a short time. The extracted has also shown better antioxidant activity, while being low energy and eco-friendly [54].

In recent years, pressurized liquid extraction (PLE) has been commonly used [55]. This automated method uses a suitable solvent for bioactive compound recovery similar to how water depends on an increased temperature with high pressure to induce solvent diffusivity and enhance plant extraction. The process decreases pollution and converts waste into resources [56]. In 2009, a new kind of PLE was introduced with a cavitation method called negative-pressure cavitation extraction (NPCE) and another green technique known as subcritical water extraction (SWE) or pressurized hot water extraction (PHWE), which uses water under a critical boiling point [55]. Recently, green extraction was proposed to obtain flavonoids from *Equisetum palustre* L. by using nine types of DES-based negative pressure cavitation method (NPC and DES). The results showed higher extraction yield compared with methods using conventional ethanol solvents. Higher yields were observed when separating four main isoflavonoids from *Dalbergia odorifera* T. Chen leaves through negative-pressure cavitation-assisted extraction with 11 different types of green and efficient DESs [57,58]. Phenolic compounds were extracted from mangosteen pericarps by batch and semi-batch systems of subcritical water extraction, where the addition of DES at 10–30% volume results in high extraction yield and antioxidant activity [59].

Enzyme-assisted extraction (EAE) is another advanced green technique because it usually uses aqueous media that limit the amount of traditional solvents and reduces environmental effects [60]. The extraction principle depends on the effects of enzymatic activity on the cell wall integrity of plants and increases the permeability of the cell membrane, leading to efficient extraction of bioactive compounds. Most enzymes are derived from microbial organisms or different sources, such as plants and animals [61,62]. However, in recent studies, a combination of DES with enzyme activity is used in the so-called DES-based EAE, which is a suitable alternative for polysaccharide extraction from *Dendrobium officinale* (DOP), where different types of DESs were used. Choline chloride/glycerol-based EAE shows efficient DOP extraction when used with cellulose and pectinase, which also exhibit antioxidant scavenging activities [63].

5. DES for Extraction of Bioactive Compounds

Different extraction methods were carried out using many types of DESs to obtain target bioactive compounds from various plants (Table 2). Current trends show that DESs are used to extract bi-compounds, tri-compounds and natural compounds, which cover most secondary metabolic plant materials, such as phenolics, flavonoids, isoflavonoids, terpenoids, alkaloids, anthocyanins, anthraquinones and polysaccharides.

5.1. Phenolic Compounds

Phenolic compounds consist of hydroxyl groups connected to an aromatic ring, and the main structure is known as the "phenol structure" [64]. Phenolic compounds are categorized as simple phenol, polyphenol, coumarins and others [65]. These compounds have garnered the interest of researchers in recent years due to their highly beneficial and significant results. Through various bioactivity assays, the benefits of these compounds include antibacterial, antioxidant and potential anti-cancer effects [64,66]. Studies used DES compounds for phenolic material extraction as an alternative to traditional alcoholic solvents [67]. For example, extraction of phenolic compounds by DES from *Carthamus tinctorius* uses proline:malic acid (PMH) and 25% of water; the method efficiently extracted

phenolics, such as hydroxysafflor yellow A (HSYA) and cartormin compounds [68]. Extraction of phenolic metabolites using DES and conventional organic solvents has been compared; using choline chloride:oxalic acids with 25% water from grape skin was highly effective for extraction [69]. The preparation of DES consists of choline chloride:citric acid at molar ratio of 2:1 with 30% water added to investigate the extraction of total polyphenolic compounds from grape pomace. Compared with traditional extraction systems, extraction using DES had higher total extraction yield (2892.07 $mg.g^{-1}$) and good bioactivity results, such as antioxidant activity by ORAC method and in vitro cytotoxicity by antiproliferative assay [70].

5.2. Flavonoid Compounds

Flavonoids are members of phenolic compounds with carbon as the main structure [71]. Flavonoids exhibit antioxidant, anti-microbial and antitumor properties associated with bladder cancer [72,73]. Traditional extraction of flavonoids has relied on different methods and conventional solvents due to difficulty in dissolving in aqueous solvents with time and amount loss. Recently, DES has been used as an alternative solvent; the method exhibits increased yield of flavonoids and is time and cost saving [74,75]. In addition, choline chloride:levulinic acid as DES can efficiently extract flavonoid glycosides and a glycones from *Platycladi cacumen* (myricitrin, quercitrin, amentoflavone, hinokiflavone) [76]. In 2015, bioactive compounds, such as rutin, were extracted from *Sophora japonica* by using 20 kinds of DES prepared from choline chloride and different HBD. The excellent properties of DES indicate that they have the potential to be used as solvents for extraction of rutin [30].

5.3. Alkaloids Compounds

Alkaloids are organic compounds that comprise complexes with a nitrogenous ring structure and are available in nature. These compounds exhibit important biological activities, such as anticancer [77]. Alkaloids are considered the most effective secondary metabolic material in Chinese medicinal plants and can be extracted using conventional and green solvents [78,79]. Alkaloid extraction by DES results in three different types of bioactive alkaloids from *Berberidis radix*. Choline chloride:levulinic acid and betaine:levulinic acid have higher alkaloid extractability compared with traditional solvents [80]. Three alkaloid compounds were extracted by choline chloride:fructose with 35% water from *Crinum powellii* bulb plant; this solvent had higher amounts of total alkaloids extracted than conventional solvents such as ethanol or methanol [81]. Furthermore, DES, which includes lactic acid:glucose:water (LGH) solvent, was used for alkaloid bio-extraction from *Larrea cuneifolia*; the extract showed significant antimicrobial activity against *Candida albicans* [82].

5.4. Other Bioactive Compounds

Several methods have improved the extraction of total anthocyanin compounds from herbal plants [83]. Ten different types of DES were screened for extraction of total anthocyanin; the citric acid:D-(+)-maltose as solvent exhibited 80% higher extraction yield than conventional methanol aqueous solvents. Moreover, the crude extract exerted antioxidant activity [84]. Bioactive components of plant polysaccharides possess bio-activities, such as anti-cancer, anti-virus and anti-oxidation [85,86]. The crude polysaccharide extract from *Camellia oleifera* abel was obtained using 17 types of DES as solvents; the optimal solvent system comprised choline chloride:ethylene glycol with 30% water, leading to a total yield of 152.37 $mg.g^{-1}$, which is higher than that of the control using aqueous extraction. Antioxidant activity was also markedly noticeable [87].

6. Biological Application of Plant Extracts Obtained Using DES

Table 2 summarizes the bioactivity effects including anti-oxidation, antibacterial and Antitumor activities of compounds extracted from plants by DES.

6.1. Antioxidant Activity

Studies in Table 2 used different antioxidant activity assays, such as DPPH free radical scavenging assay, ferric reducing antioxidant power (FRAP), hydroxyl radical (%OH) scavenging activity and ABTS. In the crude extraction of phenolic and flavonoid compounds from marjoram, the DES mixture used comprised lactic acid:glycine:water in the molar ratio of 3:1:3, which resulted in higher yields of phenolic and flavonoid compounds than 60% aqueous ethanol as solvent; the extract was subjected to DPPH assay and exhibited antiradical activity of 1950 µmol DPPH per gram dry weight [24]. Higher amounts of phenolic compounds were extracted from *Rosmarinus officinalis* L. when using choline chloride:lactic acid (1:3) compared with conventional 100% ethanol as solvent. After identifying the phenolic compounds in the extract, the ferric reducing antioxidant property was measured via FRAP assay and had a value of 183.82 mM trolox/g), which is higher than that obtained using ethanol extract [88]. Hence, different bioactive compounds with high antioxidation properties can be extracted from plants by using green solvents instead of traditional solvents. Given that plants contain high amounts of polyphenols, they may also have high antiradical scavenger activity due to molecular interaction between plant and DES; the reaction will lead to reduced oxidative degradation due to insufficient movement of solute molecules [23,89].

6.2. Antibacterial Activity

Bacterial growth inhibition assessment is a widely used method because it is inexpensive and time-saving process (one or two days). The effects of plant extracts obtained by DES extraction on bacterial growth were studied. Phycocyanin bioactive compound was extracted from *Arthrospira platensis*. The solvent system of xylose:glycerol in a 1:1 ratio was the most effective for extraction phycocyanin among five different DESs tested. The compound with the most efficient activity was determined using agar well diffusion, and the extract demonstrated strong activity against *Escherichia coli* and *Enterobacter aerogenes*, which showed wells with 17 and 16 mm diameter, respectively [90]. Other studies investigated the effects of the total polyphenol content extracted using malic acid:glucose:glycerol (1:1:1) from *Punica granatum* L. The antimicrobial activity of the extract was determined against Gram-positive *Staphylococcus aureus*; 90% inhibition was observed at 0.7 mg.mL^{-1} concentration. The result differed when ascorbic acid activity was used as control. This result confirms the interaction of polyphenols with the cell membrane of microorganisms, leading to microbial cell death or enzyme inhibition [91]. Flavonoids extracted from *Scutellariae* radix by ultrasound-assisted DES have been shown to possess equal anti-inflammatory activities to traditional solvents through inhibiting the release of nitric oxide production with the increase of extract concentration [92].

6.3. Antitumor Activity

Some researchers have discovered the cytotoxicity activity of medicinal plants extracted by DES in vitro by using MTS assay. Polyphenolic bioactive compounds were extracted from grape pomace by using choline chloride:citric acid (2:1) and tested against HeLa (cervical cancer) and MCF-7 (breast cancer) cell lines, with cell availability of 37.61% on cells lines at 5% (*v*/*v*) within 72 h. The compound extracted from olive pomace by using the same protocol showed clear results in the in vitro cytotoxicity (MTS) assay, with cell availability of 12.19% on cells lines at 5% (*v*/*v*) within 72 h [70]. Ginsenoside bioactive compound extracted from ginseng by using ternary DES (GPS-5) glycerol:l-proline:sucrose (9:4:1) as alternative solvent. Extract showed anti-tumor activity against human colorectal cancer cell lines at 58 µg mL; meanwhile, DES had no cytotoxic effects as determined via MTT assay [84]. All the above biological activities are presented in (Figure 2).

Table 2. Summary the application of the DES in medicinal plants extraction.

Plant Name	DES Type		Sample		Method of Extraction/Bioactive Compounds				Mode of Action	Ref.
	Composition	M.R	Parts	Amount	Technique	Type	Yield%	Instrumental		
Arthrospira platensis	xylose:glycerol	1:1	Powder	30 mg	MAE	Phycocyanin	85 μg.mL^{-1}	Spectrophotometer	Antibacterial activity: the phycocyanin fraction collected which obtained from extraction has activity against bacteria have been evaluated by agar well diffusion method with a zone inhibition against *Escherichia coli* is (17 mm) and against *Enterobacter aerogenes* is (16 mm). **Optimization condition (10 min, 348 k, CCD)**	[90]
Averrhoa bilimbi	choline chloride:citric acid monohydrate	1:3	Powder	10 mg	H and S	Total phenolic pectin	1.39% Gallic acid	Spectrophotometer	Antioxidant activity: the plant extracted has activity was evaluated by two methods: 1. DPPH free radical scavenging assay with value percentage (41.64%). 2. FRAP ferric reducing antioxidant power assay with value 1.15 Mm. **Optimization condition (150 min, 80 °C, BBD)**	[89]
Averrhoa bilmbi	choline chloride:citric acid monohydrate	1:3	Powder	1 g	H and S	Phenolic pectin	2.41% Gallic acid	Spectrophotometer	Antioxidant activity: the phenolic extracted from plant by DES has activity was evaluated by two assays: 1. Free radical scavenging DPPH assay: with highest value is (54.76%). 2. Ferric reducing antioxidant power (FRAP) assay: with value (1.34 Mm FeSO4).	[93]
Camellia sinensis	betaine, glycerol, and D-(þ)-glucose	4:20:1	Powder	100 mg	UAE	Catechins	100 mg.g^{-1}	LC-UV	The extract can be readily used in cosmetic products or pharmaceutical formulations for skin **Optimization condition (6.5 min, 37 °C, CCD)**	[94]
Camellia oleifera Abel.	choline chloride:ethylene glycol	1:2	Powder	0.1 g	UAE	Polysaccharides	152.37 mg.g^{-1}	ELASA	Antioxidant activity: the purity polysaccharides extracted by DES has activity was evaluated by two methods.	[87]
Cicer arietinum L.	choline chloride:propylene glycol	1:1	Powder	50 mg	UAE	Flavonoid isoflavones:	7.98 mg QE.g^{-1}	Spectrophotometer	Antioxidant activity: the extracted by DES was measured by two methods to determine the antioxidant ability: 1. DPPH free radical scavenging activity assay with clear result at (13%). 2. ABTS assay used to determine ability with result (16 μg QE.g^{-1} CPA). **Optimization condition (35 min, 59 °C, BBD)**	[95]

Table 2. *Cont.*

Plant Name	DES Type		Sample		Method of Extraction/Bioactive Compounds				Mode of Action	Ref.
	Composition	M.R	Parts	Amount	Technique	Type	Yield%	Instrumental		
Cyclocarya paliurus (Batal.)	choline chloride/ 1,4–butanediol	1:5	Leaves	40 mg	UAE	Flavonoid	7.1 mg.g^{-1}	LC-MS	The flavonoids extracted from the *C. paliurus* leaves have clear in vitro antioxidant activities in both DPPH with value (25.2 g/mL) and ABTS radical-scavenging assays with value (22.4 g/mL).	[96]
Curcuma longa	citric acid:glucose	1:1	Leaves	0.1 g	H and S	Curcuminoids	21.18 mg.g^{-1}	HPLC	Ant-oxidation assay: the DPPH free radical-scavenging capacity of plant pigments extracted by NDES was determined by according to a DPPH assay with radical scavenger activity percentage value (87.0%).	[97]
Dendrobium officinale	choline chloride:glycerol	1:2	Powder	0.3 g	EAE	Polysaccharides DOP-1DOP-2	34%	UV-VIS Spectra	The antioxidant scavenging activities of crude polysaccharide were performed by hydroxyl radical assay and DPPH activity assay with (40% and 50%) scavenging activity percentage respectively.	[63]
Dittany *Origanum dictamnus*	lactic acid:glycine:water	3:1:3	Hall plant	0.1 g	UAE	Total polyphenols	115.40 mg GAE.g^{-1}	Spectrophotometer	The crude plant extraction has antioxidant activity at (1100 µmol DPPH) per g of dry weight and (800 µmol AAE) per g of dry weight.	[24]
	lactic acid:glycine:water	3:1:3	Hall plant	0.1 g	UAE	Total flavonoids	18.52 mg RtE.g^{-1}	Spectrophotometer		
Eucalyptus globulus	choline chloride:ethylene glycol	1:2	Leaves	10 mL/g	H and S	Total phenolic	69.9 mg GAE.g^{-1}	Spectrophotometer	The plant extract has antioxidant ability was measured by three methods: 1. The radical scavenging was conducted by DPPH assay with value (68.0 mg TE.g^{-1}) per dry weight. 2. The trolox equivalent antioxidant capacity (TEAC) was evaluated through ABTS assay with value (89.9 mg TE.g^{-1}) per dry weight. 3. The ferric reducing antioxidant power (FRAP) assay was used to determine this activity with value (66.3 mg TE.g^{-1}) per dry weight.	[98]
	choline chloride:ethylene glycol	1:2	Leaves	10 mL/g	H and S	Total flavonoid	45.4 mg RtE.g^{-1}	Spectrophotometer		
Fennel *Foeniculm vulgare*	Lactic acid: choline chloride	3:1	Hall plant	0.1 g	UAE	Total polyphenols	18.60 mg GAE.g^{-1}	Spectrophotometer	The crude plant extraction has antioxidant activity at (150 µmol DPPH) per g of dry weight and (140 µmol AAE) per g of dry weight.	[24]
	Lactic acid: choline chloride	3:1	Hall plant	0.1 g	UAE	Total flavonoids	9.75 mg RtE.g^{-1}	Spectrophotometer		
	Lactic acid:glycine:water	3:1	Hall plant	0.1 g	UAE	Total polyphenols	34.72 mg GAE.g^{-1}	Spectrophotometer	The crude plant extraction has antioxidant activity at (230 µmol DPPH) per g of dry weight and (100 µmol AAE) per g of dry weight.	
	Lactic acid:glycine:water	3:1	Hall plant	0.1 g	UAE	Total flavonoids	7.96 mg RtE.g^{-1}	Spectrophotometer		

Table 2. *Cont.*

Plant Name	DES Type		Sample		Method of Extraction/Bioactive Compounds				Mode of Action	Ref.
	Composition	M.R	Parts	Amount	Technique	Type	Yield%	Instrumental		
Ginkgo biloba	choline chloride:malonic acid	1:2	Leaves	100 mg	WBS	Proanthocyanidin (PAC)	22.19 mg.g^{-1}	Spectrophotometer	The PAC extracted has antioxidant activity was measured by: 1. Total reduction capability: IC_{50} is (53.68 µg.mL^{-1}) and after recovered IC_{50} is (52.24 µg.mL^{-1}). 2. DPPH free radical scavenging capability: IC_{50} is (136.71 µg.mL^{-1}) and after recovered IC_{50} is (128.38 µg.mL^{-1}). 3. ABTS free radical scavenging capability: IC_{50} is (4.77 µg.mL^{-1}) and after recovered IC_{50} is (8.06 µg.mL^{-1}). **Optimization condition (53 min, 65 °C, CCD)**	[99]
Ginger	L-carnitine:1,3-butanediol	1:4	Powder	30/1 ratio	UAE	Gingerols	3.82 mg.g^{-1}	HPLC	Antioxidant activity: the plant extracted with DES has activity was measured by two assays with RSM optimization: 1. FRAP assay: the greatest value was determined at (20.36 mg TE.g^{-1}). 2. ABTS assay: the largest value was determined at (24.40 mg TE g^{-1}). **Optimization condition (30 min, 50 °C, CCD)**	[49]
Ginseng	glycerol:l-proline:sucrose	9:4:1	Powder	100 mg	UAE	Total ginsenosides	8 mg.g^{-1}	LC-UV	The Total ginsenosides have anti-tumor activity through used Human colorectal cancer cell lines at (58 µg mL) and the DES had no cytotoxic effects was determined with MTT assay. **Optimization condition (45 min, 60 °C, CCD)**	[84]
Grape pomace	choline chloride:citric acid	2:1	Powder	0.5 g	UAE	Total polyphenolic	2892.07 mg/kg per dw	HPLC	Antioxidant capacity of polyphenolic extract was evaluated through oxygen radical absorbance capacity assay (ORAC) with value (2189.97 µmolTE g^{-1} dw). Antiproliferative activity of polyphenolic extract was evaluated by in vitro cytotoxicity (MTS) assay with cell availability (37.61%) on cells lines at 5% (*v*/*v*) through 72 h.	[70]

Table 2. *Cont.*

Plant Name	DES Type		Sample		Method of Extraction/Bioactive Compounds				Mode of Action	Ref.
	Composition	M.R	Parts	Amount	Technique	Type	Yield%	Instrumental		
Grape skins	choline chloride:malic acid	1:1	Powder	0.1 g	ultrasonic bath	Total phenolic content	91 mg.g^{-1}	Spectrophotometer	The antioxidant activity of crude extraction is (371 µmol TE) per g of dry weight was determined by the oxygen radical absorbance capacity (ORAC) method. The choline chloride: malic acid NDES has antiproliferative activity against MCF-7 and HeLa cells at 18 and 23 cell viability, respectively was evaluated by WST-1 cell proliferation assay.	[100]
	choline chloride:malic acid	1:1	Powder	0.1 g	ultrasonic bath	Total anthocyanin content	24 mg.g^{-1}	Spectrophotometer		
Grape skin	citric acid:D-(+)-maltose	4:1	Powder	100 mg	UAE	Total anthocyanins content (TAC)	63.36 mg.g^{-1}	Spectrophotometer	The relative TAC extraction with radical scavenging activity (RSA) at the same level (59% per g) of dry weight by using DPPH assay	[101]
Green coffee beans	Glycerol:betaine	1:2	Powder	0.4 g	H and S	Phenolics (chlorogenic acids)	7.37%	HPLC	The plant extract with phenolics compound has biochemical activity was determined by In vivo assay with rats.	[102]
Ixora javanica	choline chloride:propylen eglycol	1:1	Flowers	0.05 g	UAE	Total flavonoid content	13.5 mg QE.g^{-1}	Spectrophotometer	Antioxidant activity: The activity of the extract was determined by its DPPH radical scavenging assay with highest inhibition value (83%). Tyrosinase inhibitory activity: The activity of the extract was determined by Mushroom tyrosinase solution with highest inhibition value (49%). **Optimization condition (5 min, 57 °C, CCD)**	[103]
	choline chloride:propylen eglycol	1:1	Flowers	0.05 g	UAE	Total anthocyanin content	12 mg CGE.g^{-1}	Spectrophotometer		
Lemon waste peels	glycerol:choline chloride	3:1	Powder	0.1 g	UAE	Total polyphenols	53.76 mg GAE.g^{-1}	Spectrophotometer	Antioxidant activity: the plant extracted with DES has antioxidant activity was measured by two assays: 1. Antiradical activity A_{AR} at (230 µmol DPPH) per g of dry weight. 2. Reducing power P_R at (65 µmol AAE) per g of dry weight.	[104]
	glycerol:choline chloride	3:1	Powder	0.1 g	UAE	Total flavonoid	19.42 mg RtE.g^{-1}	Spectrophotometer		
Mangosteen pericarp	citric acid:alanine	1:1	Powder	2.5 g	Batch system	Total phenolic content	179.54 mg.g^{-1}	Spectrophotometer	The total crude plant of extract has Antioxidant Activity measured by DPPH free radical scavenger assay with IC50 inhibition percentage is (46 µg.mL^{-1}).	[59]
	citric acid:alanine	1:1	Powder	2.5 g	Batch system	Xanthone	24.87 mg.g^{-1}	Spectrophotometer		
Marjoram *Origanum majorana*	lactic acid:glycine:water	3:1:3	Hall plant	0.1 g	UAE	Total polyphenols	137.36 mg GAE.g^{-1}	Spectrophotometer	The crude plant extraction has antioxidant activity at (1950 µmol DPPH) per g of dry weight and (900 µmol AAE) per g of dry weight.	[24]
	lactic acid:glycine:water	3:1:3	Hall plant	0.1 g	UAE	Total flavonoids	21.70 mg RtE.g^{-1}	Spectrophotometer		

Table 2. *Cont.*

Plant Name	DES Type		Sample		Method of Extraction/Bioactive Compounds				Mode of Action	Ref.
	Composition	M.R	Parts	Amount	Technique	Type	Yield%	Instrumental		
Mentha piperita	choline chloride:D-(+)-glucose	5:2	Leaves	100 mg	UAE	Total phenolic content	98.27 mg GAE.g^{-1}	Spectrophotometer	The antioxidant properties of the peppermint extracts was analyzed by the three methods: 1. DPPH assays: extracted has activity at (93.50 mg TE.g^{-1}). 2. ABTS assays: extracted has activity at (142.29 mg TE.g^{-1}). 3. FRAP assays: extracted has activity at (191.49 mg TE.g^{-1}). **Optimization condition (25 min, CCD)**	[105]
	choline chloride: D-(+)-glucose	5:2	Leaves	100 mg	UAE	Total flavonoid content	21.05 mg CE.g^{-1}	Spectrophotometer		
	choline chloride:D-(+)-glucose	5:2	Leaves	0.1 mg	UAE	Volatile monoterpenes	600 mg.g^{-1}	GC-MS		
Mint *Mentha. spicata*	lactic acid:choline chloride	3:1	Hall plant	0.1 g	UAE	Total polyphenols	99.17 mg GAE.g^{-1}	Spectrophotometer	The crude plant extraction has antioxidant activity at (600 µmol DPPH) per g of dry weight and (950 µmol AAE) per g of dry weight.	[24]
	lactic acid:choline chloride	3:1	Hall plant	0.1 g	UAE	Total flavonoids	24.89 mg RtE.g^{-1}	Spectrophotometer		
	lactic acid:glycine:water	3:1:3	Hall plant	0.1 g	UAE	Total polyphenols	109.67 mg GAE.g^{-1}	Spectrophotometer	The crude plant extraction has antioxidant activity at (2500 µmol DPPH) per g of dry weight and (950 µmol AAE) per g of dry weight.	
	lactic acid:glycine:water	3:1:3	Hall plant	0.1 g	UAE	Total flavonoids	17.12 mg RtE.g^{-1}	Spectrophotometer		
Olea europaea	glycerol:glycine: water	7:1:3	Leaves	1.56 g	H and S	Total polyphenol	106.25 mg GAE.g^{-1}	Spectrophotometer	The DES crude plant extracted has antiradical activity was detected by two assays: 1. Antiradical activity (A_{AR}) with exhibited (1097.8 µmol DPPH per g of dw). 2. Ferric reducing power (P_R) with exhibited (445.1 µmol AAE per g of dw). **Optimization condition (280 min, 70 °C, CCD)**	[106]
	glycerol:glycine: water	7:1:3	Leaves	1.56 g	H and S	Total flavonoid	32 mg RtE.g^{-1}	Spectrophotometer		
Olive leaves	glycerol:choline chloride	3:1	Powder	0.1 g	UAE	Total polyphenols	36.75 mg GAE.g^{-1}	Spectrophotometer	Antioxidant activity: the plant extracted with DES has antioxidant activity was measured by two assays: 1. Antiradical activity A_{AR} at (250 µmol DPPH) per g of dry weight. 2. Reducing power P_R at (280 µmol AAE) per g of dry weight.	[104]
	glycerol:choline chloride	3:1	Powder	0.1 g	UAE	Total flavonoids	1.29 mg RtE.g^{-1}	Spectrophotometer		

Table 2. *Cont.*

Plant Name	DES Type		Sample		Method of Extraction/Bioactive Compounds				Mode of Action	Ref.
	Composition	M.R	Parts	Amount	Technique	Type	Yield%	Instrumental		
Olive pomace	choline chloride:citric acid	2:1	Powder	0.5 g	UAE	Total polyphenolic	645.99 mg/kg per dw	HPLC	Antioxidant capacity of polyphenolic extract was evaluated through Oxygen radical absorbance capacity assay (ORAC) with value (453.10 μmolTE g−1 dw). Antiproliferative activity of polyphenolic extract was evaluated by in vitro cytotoxicity (MTS) assay with cell availability 12.19% on cells lines at 5% (*v/v*) through 72 h.	[70]
Onion solid wastes	glycerol:choline chloride	3:1	Powder	0.1 g	UAE	Total polyphenols	82.94 mg GAE.g^{-1}	Spectrophotometer	Antioxidant activity: the plant extracted with DES has antioxidant activity was measured by two assays: 1. Antiradical activity A_{AR} at (618.55 μmol DPPH) per g of dry weight. 2. Reducing power P_R at (700.79 μmol AAE) per g of dry weight.	[104]
	glycerol:choline chloride	3:1	Powder	0.1 g	UAE	Total flavonoid	80.68 mg RtE.g^{-1}	Spectrophotometer		
Onion peels	choline chloride:urea:water	1:2:4	Powder	1 g	H and S	Phenolics	64.23 mg GAE.g^{-1}	Spectrophotometer	Antioxidant activity: the phenolic extract by DES and through in vitro Ferric Reducing Antioxidant Power (FRAP) assay has activity in highest PR value 1457.19 μmol AAE g of dry weight	[107]
	choline chloride:sucrose:water	4:1:8	Powder	1 g	MAE	Phenolics	48 mg GAE.g^{-1}	Spectrophotometer	Antioxidant activity: the phenolic extract by DES and through In vitro Radical Scavenging Activity (AAR) assay has activity in highest value 79.81%.	
Orange peelwaste	choline chloride:ethylene glycol	1:4	Powder	0.5 g	SLE	Total phenolic content	3.61 mg GAE.g^{-1}	Spectrophotometer	The Orange peel waste extracted has antioxidant activity was estimated by DPPH free radical scavenger assay obtained IC_{50} (30.6 μg.mL^{-1}).	[2]
Picea abies bark	choline chloride:lactic acid	1:1	Powder	1 g	H and S	Total phenolic content	100 mg GAE.g^{-1}	Spectrophotometer	The bark crude extraction has free radical scavenging activity RSA (16%) at 30 min and (16.59%) after 30 min by DPPH assay	[108]
Propolis	choline chloride:tartaric acid	2:1	Powder	1 g	UAE	Flavonoid	46.0 mg CE.g^{-1}	Spectrophotometer	Antioxidant activity: the plant extracted has antioxidant capacity was evaluated by DPPH scavenging ability assay with 62.2 IC_{50} in μg.mL^{-1}. **Optimization condition (10 min, CCD)**	[109]
	choline chloride:tartaric acid	2:1	Powder	1 g	UAE	Tannins	2.40 mg CE.g^{-1}	Spectrophotometer		

Table 2. *Cont.*

Plant Name	DES Type		Sample		Method of Extraction/Bioactive Compounds				Mode of Action	Ref.
	Composition	M.R	Parts	Amount	Technique	Type	Yield%	Instrumental		
Punica granatum L.	malic acid:sucrose	1:1	Powder	1 g	IRE	Total polyphenol content	75 mg GAE.g^{-1}	Spectrophotometer	Antiradical activity: the extracted polyphenols was evaluated by the free radical scavenging activity DPPH assay with (339 μMTE.g^{-1} of DM). Antioxidant activity: the extracted polyphenols was evaluated by phosphomolybdenum reduction assay with (45 mg AA eq.mL^{-1}). Antimicrobial activity: the extracted polyphenols by DES was estimated against the bacterial gram+ *Staphylococcus aureus* at 0.7 mg/mL concentration with inhibition result (90%). Antimicrobial activity: the extracted polyphenols by DES was estimated against the bacterial negative, *Escherichia coli* at 0.7 mg/mL concentration with inhibition result (90%).	[91]
	malic acid:glucose:glycerol	1:1	Powder	1 g	IRE	Total polyphenol content	152 mg GAE.g^{-1}	Spectrophotometer		
	glucose:tartaric acid	1:1	Powder	1 g	IRE	Total polyphenol content	90 mg GAE.g^{-1}	Spectrophotometer		
Rice straw	lactic acid:choline chloride	5:1	Powder	5% solids loading	Incubation and agitation	Lignin	68.1 mg.g^{-1}	Spectrophotometer	The crude cellulase enzyme has activity (13 U/mL) at 0.5% of NDES concentrations was measured using filter paper assay method.	[110]
	choline chloride:malic acid	1:1	Powder	5% solid loading	Incubation	Lignin	8.1 mg.g^{-1}	Spectrophotometer	The acidic green solvent has antimicrobial growth activity against *Clavispora* NRRL Y-50464 when measured at 660 nm through 24 h.	[111]
Rosmarinus officinalis	glycerol:choline chloride	1:2	Leaves	150	UAE	Total phenolic content	22.53 mg GAE.g^{-1}	Spectrophotometer	Antioxidant activity: the final plant extracted by DES has activity was measured by DPPH free radical photometric assay with value (155.83 mMtrolox.g^{-1}).	[88]
	lactic acid:choline chloride	1:3	Leaves	150	UAE	Total phenolic content	59.85 mg GAE.g^{-1}	Spectrophotometer	Antioxidant activity: the final plant extracted by DES has activity was measured by Ferric reducing antioxidant property (FRAP assay) with value (183.82 mMtrolox.g^{-1}).	
Sage *Salvia officinali*	lactic acid:glycine:water	3:1:3	Hall plant	0.1 g	UAE	Total polyphenols	114.92 mg GAE.g^{-1}	Spectrophotometer	The crude plant extraction has antioxidant activity at (2294 μmol DPPH) per g of dry weight and (950 μmol AAE) per g of dry weight.	[24]
	lactic acid:glycine:water	3:1:3	Hall plant	0.1 g	UAE	Total flavonoids	24.29 mg RtE.g^{-1}	Spectrophotometer		
	lactic acid:choline:chloride	3:1	Hall plant	0.1 g	UAE	Total polyphenols	100.90 mg RtE.g^{-1}	Spectrophotometer	The crude plant extraction has antioxidant activity at (1000 μmol DPPH) per g of dry weight and (1041 μmol AAE) per g of dry weight.	
	lactic acid:choline:chloride	3:1	Hall plant	0.1 g	UAE	Total flavonoids	23.56 mg RtE.g^{-1}	Spectrophotometer		

Table 2. *Cont.*

Plant Name	DES Type		Sample		Method of Extraction/Bioactive Compounds				Mode of Action	Ref.
	Composition	M.R	Parts	Amount	Technique	Type	Yield%	Instrumental		
Satureja thymbra	glycerol:tri-sodium citrate.	15:1	Powder	36.2 mL/g	H and S	Total polyphenol	186.95 mg GAE.g^{-1}	Spectrophotometer	The antiradical activity (AAR) of plant crude extracted was evaluated by the DPPH probe with result (705.16 µmol DPPH g dw) and ferric reducing power (P_R) activity with result (695.96 µmol AAE g dw).	[112]
	glycerol:sodium acetate trihydrate	3:1	Powder	36.2 mL/g	H and S	Total polyphenol	185.19 mg GAE.g^{-1}	Spectrophotometer	The antiradical activity (AAR) of plant crude extracted was evaluated by the DPPH probe with result (1270.15 µmol DPPH g dw) and ferric reducing power (P_R) activity with result (535.09 µmol AAE g dw).	
	glycerol:choline chloride	3:1	Powder	36.2 mL/g	H and S	Total polyphenol	171.48 mg GAE.g^{-1}	Spectrophotometer	The antiradical activity (AAR) of plant crude extracted was evaluated by the DPPH probe with result (1268.90 µmol DPPH g dw) and ferric reducing power (P_R) activity with result (1193.44 µmol AAE g dw). **Optimization condition (200 min, 80 °C, BBD)**	
Sea buckthorn leaves	1,4-butanediol:choline chloride	3:1	Leaves	1 g	MAE	Flavonoids	20.82 mg.g^{-1}	HPLC	The flavonoid extraction from leave has antioxidant activity was measured by DPPH assay with IC_{50} value (0.074 mg.mL^{-1}) and ABTS radical-scavenging activity assay with value (0.662 mmol.g^{-1} trolox) while reducing power assay (P_R) with IC_{50} value (0.127 mg.mL^{-1}). **Optimization condition (17 min, 64 °C, BBD)**	[54]
Sophora japonica	choline chloride: triethylene glycol	1:4	Powder	1 g	Water bath and stirring	Rutin	279.8 mg.g^{-1}	HPLC	The rutin extracted by DES has antioxidant activity through measured by three methods: 1. The radical scavenging activity (RSA) of rutin is (5.68 µg.mL^{-1}) by DPPH radical scavenging assay. 2. The radical scavenging activity (RSA) of rutin is (0.19 µg.mL^{-1}) by Superoxide radical scavenging assay. 3. The radical scavenging activity (RSA) of rutin is (0.28 µg.mL^{-1}) by Hydroxyl radical scavenging assay. **Optimization condition (23 min, 70 °C, BBD)**	[113]
Soybean oil	choline chloride:ascorbic acid	2:1	Oil	0.10 g	UALLME	(TBHQ) tert-Butylhydroquinone	73.07 mg.kg^{-1}	HPLC	The TBHQ extracted from oil sample by Vc-based DES showed a protection ability for antioxidant activity	[114]

Table 2. *Cont.*

Plant Name	DES Type		Sample		Method of Extraction/Bioactive Compounds				Mode of Action	Ref.
	Composition	M.R	Parts	Amount	Technique	Type	Yield%	Instrumental		
Spent coffee grounds	1,6-hexanediol: choline chloride	2:1	Powder	50 mg	UAE	Total chlorogenic acids	19.6 mg 3-CQA.g^{-1}	UHPLC	The plant extracted by DES has antioxidant capacity was determined by three methods: 1. DPPH assay: used to evaluated the antioxidant activity at 21.2 mg TE.g^{-1} 2. FRAP assay: used to evaluated the antioxidant activity at 31.3 mg TE.g^{-1} 3. ABTS assay: used to evaluated the antioxidant activity at 30.7 mg TE.g^{-1} **Optimization condition (45 min, 60 °C, CCD)**	[115]
	1,6-hexanediol:choline chloride	2:1	Powder	50 mg	UAE	Total phenolic content	15.1 mg GAE.g^{-1}	Spectrophotometer		
	1,6-hexanediol:choline chloride	2:1	Powder	50 mg	UAE	Total flavonoid content	18.7 mg CE.g^{-1}	Spectrophotometer		
Spent filter coffee	glycerol:choline chloride	3:1	Powder	0.1 g	UAE	Total polyphenols	22.59 mg GAE.g^{-1}	Spectrophotometer	Antioxidant activity: the plant extracted with DES has antioxidant activity was measured by two assays: 1. Antiradical activity A_{AR} at (80 µmol DPPH) per g of dry weight. 2. Reducing power P_R at (140 µmol AAE) per g of dry weight.	[104]
	glycerol:choline chloride	3:1	Powder	0.1 g	UAE	Total flavonoid	0.57 mg RtE.g^{-1}	Spectrophotometer		
	glycerol:sodium–potassium tartrate:water	5:1:4	Powder	0.1 g	UAE	Total polyphenols	11.58 mg GAE.g^{-1}	Spectrophotometer	Antioxidant activity: the plant extracted with DES has antioxidant activity was measured by two assays: 1. Antiradical activity A_{AR} at (60 µmol DPPH) per g of dry weight. 2. Reducing power P_R at (290 µmol AAE) per g of dry weight.	
	glycerol:sodium–potassium tartrate:water	5:1:4	Powder	0.1 g	UAE	Total flavonoid	1.42 mg RtE.g^{-1}	Spectrophotometer		
Vitis vinifera,	1,2-Propanediol–choline chloride–water	1:1:1	Powder	100 g	agitation and magnetic stirrer	Resveratrol	10.982 µg.mL^{-1}	UPLC-UV	MTT cytotoxicity assay used to determine the activity of 2% NADES/PCW THP-1 and HUVEC cell line with the results showed that at concentration exhibited high deleterious impact on respective viability of 71 and 85%, respectively.	[116]

Table 2. *Cont.*

Plant Name	DES Type		Sample		Method of Extraction/Bioactive Compounds				Mode of Action	Ref.
	Composition	M.R	Parts	Amount	Technique	Type	Yield%	Instrumental		
Wheat bran	glycerol:choline chloride	3:1	Powder	0.1 g	UAE	Total polyphenols	17.8 mg GAE.g^{-1}	Spectrophotometer	Antioxidant activity: the plant extracted with DES has antioxidant activity was measured by two assays: 1. Antiradical activity A_{AR} at (240 µmol DPPH) per g of dry weight. 2. Reducing power P_R at (25 µmol AAE) per g of dry weight.	[104]
	glycerol:choline chloride	3:1	Powder	0.1 g	UAE	Total flavonoids	7.27 mg RtE.g^{-1}	Spectrophotometer		
	glycerol:sodium–potassium tartrate:water	5:1:4	Powder	0.1 g	UAE	Total polyphenols	1.53 mg GAE.g^{-1}	Spectrophotometer	Antioxidant activity: the plant extracted with DES has antioxidant activity was measured by two assays: 1. Antiradical activity A_{AR} at (50 µmol DPPH) per g of dry weight. 2. Reducing power P_R at (75 µmol AAE) per g of dry weight.	
	glycerol:sodium–potassium tartrate:water	5:1:4	Powder	0.1 g	UAE	Total flavonoids	0.79 mg RtE.g^{-1}	Spectrophotometer		

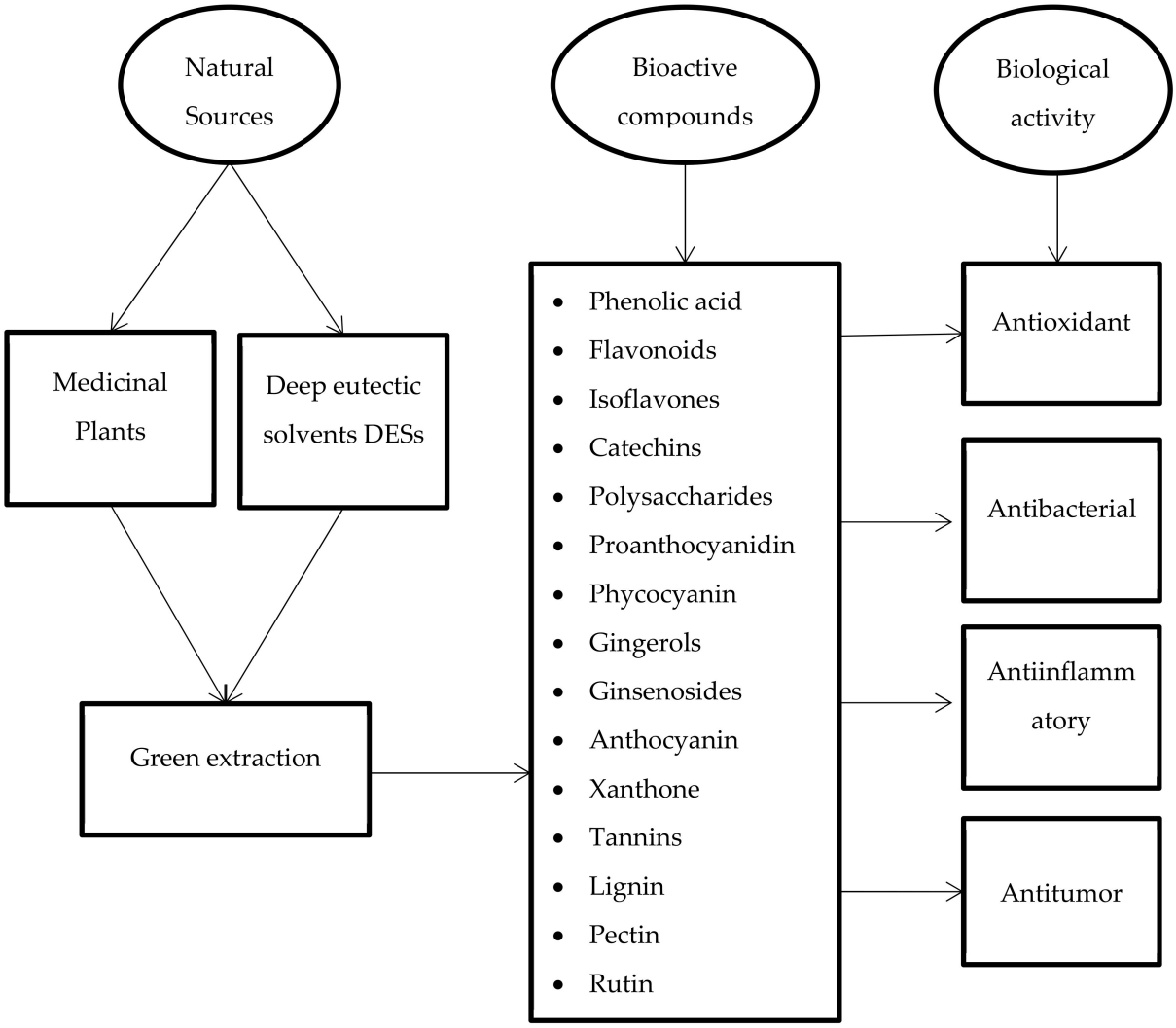

Figure 2. Steps for the green extraction media of beneficial bioactive compounds.

7. DES as Eco-Friendly Medium of Extraction

Eco-friendly solvents should have characteristically low toxicity and acceptable high levels of biodegradability; scholars have studied these characteristics for types of DES and most studies that have biodegradability assessment for DESs are to be considered "easily biodegradable" [43,117,118]. Most DES mixtures have good environmental aspects such as choline chloride (ChCl), the main compound used in different DESs [119]. NADES have similar eco-friendly characteristics as well as these constituents being synthesized by natural components and having no draw back effect [120]. All mixtures are not expensive, have good recyclability and are compatible with industry products, such as pharmaceutical and cosmetic products [42].

In a previous work, the closed bottle test method was used to assess the biodegradability for three types of choline chloride-based DES in wastewater aqueous media containing microorganisms [121]. The same method was used to determine the biodegradability of 20 types of DES. These solvents included amine-based DES, sugar-based DES, alcohol-based DES and acid−based DES; the solvent was observed within 28 days and measured for oxygen demand every seven days. Amine-based DES exhibited the highest value of biodegradability, whereas acid-based DES had the lowest value. DES have higher

biodegradability than the conventional solvents tested. The primary reason could be the permeability of the cell membrane in different ways [30].

Many authors determined that DESs and NDESs have low toxicity characteristic for human health and the environment [43,122]. The variation of DESs' toxicity is dependent on the main structure compounds [123].

8. Conclusions and Future Perspectives

Using DES as medium for extraction of bioactive compounds from medicinal plants is superior to methods utilizing conventional solvents and is a green and environment-friendly approach. The green properties of DESs are due to their low toxicity, eco-friendliness, biodegradability, shorter time and wider ability to solubilize compounds with different polarities. In this regard, DESs have been increasingly applied in green extraction of plants. Toxicity investigations are needed, and several factors, such as molar ratio mixture, water content and temperature as well as physiochemical properties should be explored. These factors will increase the yield and lead to broad and different bioactivities. Nonetheless, additional experimental works should be carried out using DESs as potential extractive agents, and their toxicity should be evaluated. Given their potential use as antioxidants, antibacterial agents, new therapeutic agents and in vitro activity, further investigations for alternative extraction using DESs that are safe for human consumption need to be explored before they are applied in the food or pharmaceutical industries.

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Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

AAE	Ascorbic acid equivalents
A_{AR}	Antiradical activity
BBD	Box–Behnken design
BI	Bacterial inhibition
CCD	Central composite design
CHCL	Choline chloride
COS	Conventional organic solvents
DES	Deep eutectic solvents
DPPH	2,2-Diphenyl-1-picrylhydrazyl
EAE	Enzyme-assisted extraction
ELISA	Enzyme-linked immunosorbent assay
FRAP	Ferric reducing antioxidant power
GAE	Gallic acid equivalents

HBA	Hydrogen-bond acceptor
HBD	Hydrogen-bond donor
H and S	Heating and stirring
HPLC	High performance liquid chromatography
ILs	Ionic liquids
IRE	Infra extraction
LGH	Lactic acid-glucose
MAE	Microwave-assisted extraction
NADES	Natural deep eutectic solvent
MBC	Minimum bacterial concentration
MIC	Minimum inhibitory concentration
M.R	Molar ratio
NPCE	Negative pressure cavitation extraction
PHWE	Pressurized hot water extraction
PLE	Pressurized liquid extraction
P_R	Reducing power
RtE	Rutin equivalents
SLE	Super liquid extraction
SWE	Subcritical water extraction
UAE	Ultrasound-assisted extraction
UV-VIS	Ultraviolet-visible spectrophotometry
WBS	Water bath system
UALLME	Ultrasound assisted liquid liquid microextraction

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