Abstract: The acknowledgement that uncontrolled and excessive use of fossil resources has become a prime concern with regard to environmental deterioration, has shifted the orientation of economies towards the implementation of sustainable routes of production, through the valorization of biomass. Green chemistry plays a key role in this regard, defining the framework of processes that encompass eco-friendly methodologies, which aim at the development of highly efficient production of numerous bioderived chemicals, with minimum environmental aggravation. One of the major concerns of the chemical industry in establishing sustainable routes of production, is the replacement of fossil-derived, volatile solvents, with bio-based benign ones, with low vapor pressure, recyclability, low or no toxicity, availability and low cost. Glycerol is a natural substance, inexpensive and non-toxic, and it is a principal by-product of biodiesel industry resulting from the transesterification process. The ever-growing market of biodiesel has created a significant surplus of glycerol production, resulting in a concomitant drop of its price. Thus, glycerol has become a highly available, low-cost liquid, and over the past decade its use as an alternative solvent has been gaining unprecedented attention. This review summarizes the utilization of glycerol and glycerol-based deep eutectic mixtures as emerging solvents with outstanding prospect in bioactive polyphenol extraction.

Keywords: deep eutectic solvents; extraction; glycerol; green solvents; polyphenols

1. Introduction

Polyphenolic phytochemicals are substances originating from plant secondary metabolism, and they occur in a bewildering variety of structures in various foods of plant origin regularly consumed by human populations. Studies pertaining to polyphenol bioactivities have grown in number over the last decades, manifesting their importance as food constituents, pharmacological agents, and cosmetic ingredients [1,2]. The focusing of intense research on this family of metabolites arises from the accumulating evidence of their implication in battling several degenerative diseases (cardiovascular disorders, cancer), and of their unsurpassed ability to function as natural antioxidants in foods and biological systems [3,4].

Over the past few years, there has been a great raising of awareness about issues pertaining to natural resources misuse and depletion, excessive use of fossil fuels, and the environmental aggravation that accompany pertinent human activities. On this ground, it is becoming increasingly clear that orientation of the economy towards bio-based strategies is a dire necessity to establish sustainability in every aspect of industrial activity. The agri-food sector is responsible for the generation of a vast amount of biowastes, which must be properly and efficiently handled to prevent environmental pollution risks associated with their dumping. On the other hand, this waste biomass is more and
more recognized as being a bioresource that offers unprecedented opportunities for the production of a wide spectrum of high value-added products, in the framework of biorefinery concept [5–7].

The effective recovery and utilization of precious chemicals from biomass should also obey sustainability principles, and in this regard compliance with green chemistry principles is imperative in establishing eco-friendly process, that would aim at maximizing the valorization of side streams deriving from agri-food industries, without further waste generation [8]. Thus, technologies embracing minimization of energy requirements, short processing duration, and the use of recyclable, biodegradable and low-cost chemicals, are gaining high acceptance in both academia and industry. In this direction, there has been to-date a great deal of ongoing research related to the development of methodologies that would enable extraction of various high-value substances from agri-food waste biomaterials [9,10].

Cutting-edge technologies deployed to produce extracts from plant food processing residues aim at an assortment of objectives, including energy-efficient and cost-effective processes, and the use bio-based solvents that possess low boiling point, absence of toxicity, high extraction performance, recyclability and compatibility with foods/pharmaceuticals/cosmetics. All these objectives should be achieved without compromising end-product quality [11]. Thus, the search for solvents possessing such characteristics is of paramount significance in developing sustainable extraction procedures. Currently, much interest has focused on green liquids, such as water (pressurized, subcritical), bioethanol, deep eutectic solvents (DES), and supercritical fluids (e.g., CO$_2$) [12]. Yet, developments with other bio-derived materials are also gaining attention, and amongst them glycerol appears to have a prominent position. On this concept, this review summarizes the developments in polyphenol extraction using glycerol and glycerol-based DES.

2. Glycerol—Properties, Sources and Uses

Glycerol (1,2,3-propanetriol) is a viscous odorless and colorless liquid, with a syrupy sweet flavor that may derive from both renewable and fossil sources. Commodities traded under the name “glycerin” refer to commercial glycerol solutions and “crude glycerol” is a product containing 70–80% pure glycerol. This product may be concentrated to afford 95.5–99% pure glycerol [13]. The pure anhydrous glycerol has a density of 1.261 g mL$^{-1}$, a melting point of 18.2°C and a boiling point of 290°C, where it decomposes. Glycerol is a common constituent of foods, pharmaceuticals and cosmetics, with practically no toxicity and environmentally benign. It possesses three hydroxyl groups, which make it water-soluble and endow it with hygroscopicity. Glycerol molecules may associate with each other with an extended network of hydrogen bonds, lending it with unusually high boiling point and viscosity.

Glycerol is one of the main constituents of triacylglycerols (triglycerides) occurring in living tissues and the major sources of glycerol are activities pertaining to transformation of animal fats and vegetable oils. Amongst them, the biodiesel industry plays a prominent role, since crude glycerol is generated in large amounts as a by-product of biodiesel production [14,15]. Traditionally, biodiesel manufacturing process involves transesterification reaction between triacylglycerols (e.g., vegetable oil) and methanol, catalyzed by KOH. In this process, treatment of 100 kg of oil affords 10.5 kg glycerol, and further purification requires refining steps to remove water and impurities, such as salt, methanol, and free fatty acids [14]. Glycerol refinement results in obtaining various degrees of purity required for applications in foods, pharmaceutical and personal care products, but it significantly increases the production cost.

As crude glycerol availability is tightly associated with the biodiesel production, the increases in the latter over the past 15 years have led to glycerol market saturation [14]. Yet the, food glycerin market is valued at 619.1 million USD in 2020, and it is expected to reach 874.5 million USD by the end of 2026, growing at a compound annual growth rate (CAGR) of 5.0% during 2021–2026 [16], and the global glycerol market size is expected to reach 3.5 billion USD by 2027, expanding at a CAGR of 4.0% [17]. Glycerol is mainly used in foods, pharmaceutical formulations, and cosmetics [14].
In cosmetics, glycerol is a very common ingredient (third after water and fragrance), functioning primarily as a humectant and skin protectant. Its pharmaceutical uses include applications in some over-the-counter drugs, such as ophthalmic and dermal products, and external analgesic. In food products, it is added usually as humectant and sweetener.

Glycerol is considered a renewable feedstock for the production of various chemicals [18,19], and a series of glycerol-derived liquids, such as 1,3-dialkoxy-2-propanols and 1,2,3-trialkoxy-propanes, have been tested as green solvents that could replace some petroleum-based ones [20]. The use of glycerol and glycerol-derived solvents as alternative media for organic reactions has emerged as a promising new field of research, opening new ways to revalorize glycerol for applications in synthetic organic chemistry, catalysis and biocatalysis [21]. In this concept, a series of glycerol applications, mainly in catalyzed synthesis, have been reviewed [22,23], providing data that are illustrative of the value of glycerol as a handful tool in synthetic organic chemistry. Likewise, the use of several glycerol-based solvents, such as glycerol carbonate, glycerol esters, ethers, and acetals, has been compiled to further bring out the significance of glycerol as a versatile solvent. The production of glycerol carbonate, glycerol acetates and glycerol reforming into hydrogen have also been proposed as very promising routes of crude glycerol purification and valorization [15].

3. Use of Glycerol in Solid-Liquid Extraction of Polyphenolic Phytochemicals

The use of glycerol as an extraction solvent or stabilizing agent has been sporadically documented for pollen extracts [24], grapefruit extracts [25], Echinacea purpurea extracts [26], epigallocatechin gallate [27], and Castanea sativa leaf extracts [28]. However, its systematic investigation as a solvent for polyphenol extraction was initiated by the study of Apostolakis et al., 2014 [29], who explicitly proposed water/glycerol mixtures as highly efficient media for polyphenol recovery from olive leaves. This report sparked off a series of following examinations, which demonstrated the potential of water/glycerol mixtures to effectively extract polyphenols from several plant materials, including various plant food processing by-products and botanicals.

3.1. Plant Food By-Products

The importance of glycerol as a green and high-performance solvent for the recovery of polyphenols and pigments from vinification solid wastes has been recently acknowledged [30]. However, glycerol has been tested on several plant food processing residues, as witnessed by studies published between 2014 and 2020. An overview of the studies reported so far is given in Table 1.

As mentioned earlier in the text, interest was stimulated by the study of Apostolakis et al., [29], who performed an optimization study, employing aqueous glycerol solutions with glycerol concentration varying from 7.5 to 10% (w/v). The authors demonstrated that at 80 °C, a glycerol aqueous mixture with a concentration of 9.3% outperformed a previously optimized method based on water/ethanol mixtures and carried out at 24 °C, providing almost 10% higher total polyphenol yield. Extraction kinetics was also faster with aqueous glycerol at 80 °C, compared to aqueous ethanol at 24 °C. However, in a study on apple waste peel polyphenol extraction, the rate constant found for the extraction with 70% (w/v) glycerol was significantly lower than those recorded with 50% (v/v) ethanol and 50% (v/v) butanediol, at 80 °C [31]. On the other hand, no important differences were seen for diffusivity (D_e).
| Plant Material                          | Glycerol Proportion | Extraction Mode          | Conditions                                      | Yield in Total Polyphenols (mg GAE g⁻¹) | Reference |
|----------------------------------------|---------------------|--------------------------|------------------------------------------------|----------------------------------------|-----------|
| Olive leaves                           | 9.3% (w/v)          | Stirred-tank             | \(T = 80 ^\circ \text{C}; t = 241 \text{ min}; R_{LS} = 60 \text{ mL g}^{-1}\) | 51.91                                  | [29]      |
| Apple peels                            | 70% (w/v)           | Stirred-tank             | \(T = 80 ^\circ \text{C}; t = 160 \text{ min}; R_{LS} = 100 \text{ mL g}^{-1}\) | 16.59                                  | [31]      |
| Onion solid wastes                     | 90% (w/v)           | Ultrasound-assisted      | \(T = 50 ^\circ \text{C}; t = 60 \text{ min}; R_{LS} = 90 \text{ mL g}^{-1}\) | 90.07                                  | [32]      |
| Red grape pomace                       | 90% (w/v)           | Ultrasound-assisted      | \(T = 45 ^\circ \text{C}; t = 60 \text{ min}; R_{LS} = 90 \text{ mL g}^{-1}\) | 66.70                                  | [33]      |
| Coffee brewing residues                | 3.6% (w/v)          | Ultrasound-assisted      | \(T = 45 ^\circ \text{C}; t = 175 \text{ min}; R_{LS} = 50 \text{ mL g}^{-1}\) | 8.15                                   | [34]      |
| Eggplant peels, potato peels, coffee brewing residues | 80% (w/v)        | Stirred-tank             | \(T = 80 ^\circ \text{C}; t = 180 \text{ min}; R_{LS} = 100 \text{ mL g}^{-1}\) | 5.63                                   | [35]      |
| Red grape pomace                       | 20% (w/v)           | Stirred-tank             | \(T = 23 ^\circ \text{C}; t = 180 \text{ min}; R_{LS} = 50 \text{ mL g}^{-1}\) | 5.63                                   | [36]      |
| Potato peels                           | 83% (w/v)           | Ultrasound-assisted      | \(T = 23 ^\circ \text{C}; t = 80 \text{ min}; R_{LS} = 81 \text{ mL g}^{-1}\) | 8.71                                   | [37]      |
| Eggplant peels                         | 90% (w/v)           | Ultrasound-assisted      | \(T = 50 ^\circ \text{C}; t = 90 \text{ min}; R_{LS} = 100 \text{ mL g}^{-1}\) | 13.51                                  | [38]      |
| Oak acorn husks                        | 60% (w/v)           | Stirred-tank, addition of 13% (w/v) HP-β-CD \(^1\) | \(T = 80 ^\circ \text{C}; t = 180 \text{ min}; R_{LS} = 50 \text{ mL g}^{-1}\) | 122.19                                 | [39]      |
| Olive leaves                           | 60% (w/v)           | Stirred-tank, addition of 7% (w/v) HP-β-CD \(^1\) | \(T = 60 ^\circ \text{C}; t = 180 \text{ min}; R_{LS} = 50 \text{ mL g}^{-1}\) | 54.33                                  | [40]      |
| Onion solid wastes                     | 60% (w/v)           | Stirred-tank, addition of 13% (w/v) HP-β-CD \(^1\) | \(T = 80 ^\circ \text{C}; t = 240 \text{ min}; R_{LS} = 50 \text{ mL g}^{-1}\) | 3.13                                   | [41]      |
| Rice bran                              | 19.5% (w/v)         | Orbital shaking          | \(T = 67 ^\circ \text{C}; t = 90 \text{ min}; R_{LS} = 33 \text{ mL g}^{-1}\) | 7.09                                   | [42]      |
| Rice bran                              | 15.9% (w/v)         | Orbital shaking          | \(T = 90 ^\circ \text{C}; R_{LS} = 31.6 \text{ mL g}^{-1}\) | 5.50                                   | [43]      |
| Grapefruit peels                       | 20% (w/v)           | Stirred-tank, HVED \(^3\) pretreatment | \(T = 70 ^\circ \text{C}; t = 60 \text{ min}\) | 19.3                                   | [44]      |
| Red grape pomace                       | 50% (w/v)           | Homogenizer-assisted     | \(R_{LS} = 22.4 \text{ mL g}^{-1}\) | 21.40                                  | [45]      |
| Mangosteen pericarp                    | 99% (w/v)           | Stirred-tank             | \(R_{LS} = 10 \text{ mL g}^{-1}\) | 4.00                                   | [46]      |
| Red grape pomace                       | 32.5% (w/v)         | Pressurized-liquid extraction | \(R_{LS} = 10 \text{ mL g}^{-1}\) | 4.00                                   | [47]      |

Notes: \(^1\) 2-Hydroxypropyl β-cyclodextrin; \(^2\) Refers to total anthocyanin pigments (expressed as cyanidin 3-O-glucoside equivalents); \(^3\) High-voltage electric discharges; \(^4\) Not reported as sum.
A subsequent examination of red grape pomace extraction employing water/glycerol solutions showed that yield in total polyphenols, total flavonoids and total pigments peaked at a glycerol concentration of 20% (w/v). Incorporation of tartaric acid in this solvent up to 2% (w/v) disfavored increases in extraction yield and antioxidant activity of the extracts [36]. However, homogenizer-assisted extraction of red grape pomace indicated 50% (w/v) glycerol concentration as being the optimum for maximizing total polyphenol, total flavonoid and pigment extraction yield [45]. A concomitant maximization was also seen for the antioxidant activity of the extract obtained. Likewise, pressurized liquid extraction of red grape pomace at 150 °C demonstrated 50% glycerol to be the most suitable solvent for flavanol, stilbene and phenolic acid extraction, but flavonol extraction was favored with a 32.5% solution [47].

For other waste material tested, the optimum glycerol concentration displayed significant differences, stressing the importance of the nature of phenolics to be extracted, but also the extraction conditions. Huang et al., [42] reported that rice bran polyphenol extraction required 19% glycerol, at a temperature of 67 °C. A latter investigation on rice bran was in line with this outcome, suggesting an optimum concentration of 16%, at 90 °C [43]. A similar level of 20% (w/v) was also proposed for the extraction of polyphenols from grapefruit peels, which had been pretreated with high-voltage electric discharges [44].

When tested pure, glycerol was also shown to be more effective than ethanol and water, but less so compared to propylene glycol, in the extraction of mangosteen (Garcinia mangostana Linn) pericarp polyphenols [46]. In investigations involving fixed level of glycerol concentration (no optimization), 80% (w/v) glycerol was demonstrated to perform equally compared to 50% aqueous methanol and 50% aqueous ethanol, in extracting total polyphenols from potato peels, eggplant peels and coffee brewing residues, at 80 °C [35]. Yet, the hydroglycerolic solvent was significantly more efficient in total flavonoid extraction. Nevertheless, for apple waste peels a 70% (w/v) glycerol solution at 80 °C was found to be of comparable efficiency with 50% (w/v) ethanol and 50% (v/v) butanediol [31].

Apart from traditional stirred-tank extraction, ultrasound-assisted extraction (UAE) has also been implemented in combination with hydroglycerolic solvents, providing in some cases outstanding yields in total polyphenols and pigments. The first report on such an attempt was on polyphenol recovery from coffee brewing residues, where incorporation of glycerol at a rather low level (3.6% w/v) resulted in 7.4% increase in total polyphenol yield [34]. Kinetic investigation also demonstrated that extraction obeyed a second-order model, being faster with water compared to water/glycerol mixture. However, $D_e$ was higher in water/glycerol than in pure water. Response surface optimization of the UAE of eggplant (Solanum melongena) peel polyphenols using water/glycerol solutions indicated that effective extraction would require 90% (w/v) glycerol, at 50 °C, whereas identical total polyphenol yields were attained with 40% (v/v) ethanol, at 80 °C [38]. Under these conditions, extraction with both solvents followed second-order kinetics, with the water/ethanol extraction displaying higher extraction rate and $D_e$. In the same line, Paleologou et al., [37] showed that potato peel extraction with water/glycerol and with water/ethanol solutions was optimal with a glycerol concentration of 83% (w/v), at 80 °C, and ethanol concentration of 59% (v/v), at 77 °C, respectively. No statistical difference was found in the total polyphenol yields achieved using either solvent. In this case too, extraction was effectively described by a second-order model. Furthermore, water/ethanol extraction exhibited higher extraction rate and higher $D_e$.

On the other hand, in a study on UAE of polyphenols from onion solid wastes, a different outcome was reached [32]. Although extraction optimization suggested 90% (w/v) as being the most appropriate solvent composition, the kinetic assay performed showed that extraction of both total polyphenols and total pigments followed first-order kinetics. In addition, it was evidenced that increasing temperature from 50 to 80 °C was not favorable for total polyphenol extraction, as opposed to total pigment yield, which displayed an increasing trend. Likewise, optimization of UAE of red grape pomace once again proved 90% (w/v) glycerol to be the highest-performing solvent for total polyphenol and total pigment extraction, which obeyed a first-order kinetic model [33]. For both total polyphenol and total
pigment extractions, the rate constant and $D_e$ increased by raising the temperature from 50 to 80 °C. An investigation on UAE of flavonoids from onion solid wastes and red grape pomace using 90% (w/v) glycerol did confirm that first-order kinetic model could effectively describe the extraction behavior from both plant materials [48].

Combination of water/glycerol solutions with cyclodextrin as co-solvent for the recovery of polyphenolic substances have also been reported. Using oak (Quercus robur) acorn husks as plant matrix, polyphenol yield was optimized with 60% (w/v) glycerol and 13% (w/v) 2-hydroxypropyl β-cyclodextrin (HP-β-CD), at 80 °C [39]. Identical values for glycerol, HP-β-CD and temperature were also determined for the optimization of pigment (anthocyanin) extraction from onion solid wastes [41]. The extract thus generated was successfully used as a natural yogurt colorant. Finally, optimization of olive leaf polyphenol extraction demonstrated 60% (w/v) glycerol and 7% (w/v) HP-β-CD to be the most efficient combination, at 60 °C [40].

### 3.2. Medicinal and Aromatic Plants (MAPs)

Typical examples of MAP extraction using glycerol or glycerol-based mixtures are given in Table 2 [49–57]. The evidence emerged from early studies [58] indicated that mixtures of ethanol/glycerol (1–20%) were more effective for the extraction of phenolics such as carvacrol and rosmarinic acid from Origanum onites L.; Origanum vulgare spp. hirtum and Origanum vulgare L. than mixtures of ethanol/propylene glycol. A solvent of water/ethanol (1/1) that contained 30% (w/v) glycerol was also significantly more efficacious that water/ethanol (1/1) in extracting polyphenols from Origanum onites L [55]. Moreover, simple maceration with 95% glycerol was found to be a convenient means of producing polyphenol-enriched extracts from Thymus vulgaris and Origanum vulgare [57]. Contrary to those, a more recent investigation demonstrated higher efficiency of alkanediols including 1,2-ethanediol, 1,2-propanediol and 1,3-propanediol, compared to glycerol, towards recovery of polyphenols from Juglans regia L [54]. All these solvents were tested as water mixtures, at solvent/water proportion of 8/2 (w/w).

Regarding hydroglycerolic mixtures, the first report on their use for polyphenol extraction from MAPs was by Karakashov et al., [49], who showed that 10% (w/v) glycerol was significantly more effective than water for the extraction of Hypericum perforatum (St John’s wort). In line with results from plant food by-products previously mentioned, extraction kinetics, which obeyed second-order model, was faster with water than with 10% (w/v) glycerol, at optimum temperature of 70 °C. The authors attributed this finding to the increased viscosity of water/glycerol mixtures compared to pure water. Results drawn from a similar study on Hypericum triquetrifolium were alike [50], showing the supremacy of water/glycerol over pure water in achieving higher total polyphenol extraction yields, in spite of the slower extraction rate seen with the water/glycerol solvent.

The optimization of polyphenol extraction from two Artemisia species [51] demonstrated that maximum total polyphenol yield could be achieved with 90% (w/v) glycerol, in absolute accordance with the results reported by Philippi et al., [38], Katsampa et al., [32] and Trasanidou et al., [33]. The implementation of the second-order kinetic model also revealed that both extraction rate constant and $D_e$ increased as a response to increasing temperature, up to 80 °C. The increases in total polyphenol yield as a function of increasing temperature were accompanied by concomitant enhancement of both antiradical activity and ferric-reducing power. Extracts from licorice with an optimum glycerol content of 85% were also shown to possess excellent antiradical and Fe$^{2+}$-chelating properties, as well as tyrosinase and elastase inhibitory activity and anti-inflammatory activity [53]. The authors supported that, on this evidence, licorice hydroglycerolic extracts might have excellent anti-aging properties, making them promising constituents of specialized cosmeceutical formulations.
Table 2. Representative examples of total polyphenol recovery from botanicals using aqueous glycerol mixtures.

| Plant Material                      | Glycerol Proportion | Extraction Mode                  | Conditions                        | Yield in Total Polyphenols (mg GAE g⁻¹) | Reference |
|-------------------------------------|---------------------|----------------------------------|-----------------------------------|----------------------------------------|-----------|
| Hypericum perforatum                | 10% (w/v)           | Stirred-tank                     | T = 70 °C; t = 69 min<br>R_L/S = 50 mL g⁻¹ | 89.90                                  | [49]      |
| Hypericum triquetrifolium Turra     | 10% (w/v)           | Stirred-tank                     | T = 70 °C; t = 73 min<br>R_L/S = 50 mL g⁻¹ | 54.83                                  | [50]      |
| Artemisia arborescens               | 90% (w/v)           | Stirred-tank                     | T = 80 °C; t = 160 min<br>R_L/S = 100 mL g⁻¹ | 48.45                                  | [51]      |
| Artemisia inculta Delile            |                     |                                  |                                   |                                        |           |
| Salvia triloba (fruticosa)          | 40–75% (v/v)        | Ultrasound-assisted, Pressurized-liquid<br>R_L/S = 40 mL g⁻¹ (UAE) | T = 25 °C; t = 88 min<br>T = 70 °C; t = 20 min | nr                      | [52]      |
| Glycyrrhiza glabra                  | 85% (w/w)           | Ultrasound-assisted              | R_L/S = 50 mL g⁻¹                  | nr                                     | [53]      |
| Juglans regia                       | 20% (w/w)           | Stirred-tank                     | T = 50 °C; t = 120 min<br>R_L/S = 33 mL g⁻¹ | 18.30                                  | [54]      |
| Origanum amites                     | 30% (w/v)           | Stirred-tank<br>Stirred-tank, ultrasonication<br>pretreatment | R_L/S = 30 mL g⁻¹                  | 59.11                                  | [55]      |
| Salvia fruticosa Mill               | 60% (w/v)           | Stirred-tank<br>Stirred-tank, ultrasonication<br>pretreatment | T = 50 °C; t = 150 min<br>R_L/S = 25 mL g⁻¹ | 92.00                                  | [56]      |
| Origanum vulgare                    | 95% (w/w)           | Maceration                       | T = 55 °C; t = 10 days<br>R_L/S = 19 mL g⁻¹ | 47.85                                  | [57]      |
| Thymus vulgaris                     |                     |                                  |                                   |                                        |           |
In a more recent study, a blend of ultrasonication pretreatment and hydroglycerolic solvent was found to be a convenient means of producing *Salvia fruticosa* (otherwise known as *S. triloba* L.) with high polyphenol concentration and enhanced antioxidant activity [56]. Maximum yield was achieved with 40 min ultrasonication and subsequent batch stirred-tank extraction with 60% (w/v) aqueous glycerol, at 50 °C. By contrast, aqueous extracts of *S. triloba* L. generated with pressurized liquid extraction were shown to be richer in polyphenols and displayed stronger antioxidant effects compared to extracts produced with various water/glycerol combinations [52].

4. Glycerol-Based Deep Eutectic Solvents (DES) in Polyphenol Extraction

Deep eutectic solvents (DES) are neoteric designer liquids, which over past five years have been a subject of intensive research as very promising solvents. DES are usually composed of two constituents, one hydrogen bond donor and one hydrogen bond acceptor (HBA), which upon heating they form hydrogen bond-based mixtures exhibiting a eutectic point. Numerous of these mixtures are liquid under regular atmospheric conditions and may be used as green, high-performance solvents for the extraction of a variety of bioactive substances, including terpenoids, alkaloids and polyphenols [59–61]. Ever since its introduction as a DES constituent [62,63], the interest on glycerol as hydrogen bond donor (HBD) has been increasingly high. The physical-chemical properties of several glycerol-based DES have been extensively tested [63–68], while glycerol-based DES are now being widely used in polyphenol extraction (Table 3) [69–76], a fact highlighting their importance and prospects [76–79].

4.1. Glycerol as Hydrogen Bond Donor

Albeit glycerol is a common HBD of numerous DES reported in the literature, there is only a few examinations pertaining to the systematic testing of glycerol as HBD, in combination with various HBA, for the development of polyphenol extraction methodologies. Mouratoglou et al. [69] were the first to report synthesis of novel, glycerol-based DES, using sodium acetate and sodium-potassium tartrate as HBAs. The authors demonstrated that aqueous mixtures of these DES may in some instances significantly outperform water and aqueous ethanol in extracting polyphenols from several plant food wastes. A similar outcome was seen for the extraction of olive leaf polyphenols, indicating a glycerol/sodium-potassium tartrate/water DES to be equally effective with aqueous glycerol [70].

Likewise, glycerol-based DES with choline chloride were shown to be particularly effective in extracting specific bioactive substances, such as oleuropein from olive leaves [71]. Glycerol-based DES with choline chloride, sodium acetate and trisodium citrate were shown to be highly effective for polyphenol extraction from *Satureja thymbra*. In that study, it was also reported for the first time the unusual decrease in the extraction rate as a function of temperature [72]. In those examinations, the importance of HBD/HBA molar ratio was also stressed with regard to DES stability, since below a certain HBD/HBA ratio, DES were unstable at ambient temperature, a fact manifested with HBA crystallization. This phenomenon was further confirmed by following studies employing glycerol/glycine DES [80]. Testing of several DES for rutin extraction from tartary buckwheat suggested glycerol/choline (1/1) as the highest-performing solvent [81].

Some other investigation highlighted the role of the molar ratio HBD/HBA in the extraction performance of glycerol-based DES. In particular, maximization of polyphenol extraction from *Moringa oleifera* Lam. leaves was shown to occur with glycerol/sodium acetate at a molar ratio of 6 [82], whereas lower or higher molar ratios were not favorable in this regard. Such a behavior was confirmed by several following studies employing DES composed of glycerol/L-alanine [74], glycerol/nicotinamide [76], glycerol/sodium propionate [75] and glycerol/citrates [83]. Finally, another study on glycerol-based DES with sodium acetate, sodium propionate and sodium butyrate, illustrated that the longer the carbon chain length of the HBA, the higher the amount of water required in the DES/water mixture to attain maximization of polyphenol extraction from *Origanum dictamnus* [73].
| Plant Material       | HBA                        | Extraction Mode         | Conditions                                      | Yield in Total Polyphenols (mg GAE g⁻¹) | Reference |
|----------------------|----------------------------|-------------------------|-------------------------------------------------|----------------------------------------|-----------|
| Various plant food wastes | Sodium acetate             | Ultrasound-assisted     | \( T = 80 \degree C; t = 90 \text{ min} \) \( R_{L:S} = 100 \text{ mL g}^{-1} \) | 1.53–88.03                        | [69]      |
|                      | Sodium-potassium tartrate  | Ultrasound-assisted     | \( T = 73 \degree C; t = 60 \text{ min} \) \( R_{L:S} = 45 \text{ mL g}^{-1} \) | 26.75                                 | [70]      |
|                      | Choline chloride           | Ultrasound-assisted     | \( T = 50 \degree C; t = 200 \text{ min} \) \( R_{L:S} = 45 \text{ mL g}^{-1} \) | 171.48–186.95                        | [71]      |
| Olive leaves         | Sodium-potassium tartrate  | Ultrasound-assisted     | \( T = 50 \degree C; t = 200 \text{ min} \) \( R_{L:S} = 45 \text{ mL g}^{-1} \) | 64.99–76.79                          | [73]      |
| Satureja thymbra     | Trisodium citrate dihydrate | Stirred-tank            | \( T = 80 \degree C; t = 180 \text{ min} \) \( R_{L:S} = 59 \text{ mL g}^{-1} \) | 118.97                               | [74]      |
| Origanum dictamnus   | Sodium propionate          | Stirred-tank            | \( T = 80 \degree C; t = 150 \text{ min} \) \( R_{L:S} = 100 \text{ mL g}^{-1} \) | 137.50                               | [75]      |
| Humulus lupulus      | Glycine                    | Ultrasound-assisted pretreatment Stirred-tank | \( T = 80 \degree C; t = 180 \text{ min} \) \( R_{L:S} = 100 \text{ mL g}^{-1} \) | 82.87                               | [76]      |
| Onion solid wastes   | Sodium propionate          | Stirred-tank            | \( T = 80 \degree C; t = 150 \text{ min} \) \( R_{L:S} = 100 \text{ mL g}^{-1} \) | 137.50                               | [75]      |
| Moringa oleifera    | Nicotinamide               | Ultrasound-assisted pretreatment Stirred-tank | \( T = 80 \degree C; t = 180 \text{ min} \) \( R_{L:S} = 100 \text{ mL g}^{-1} \) | 82.87                               | [76]      |
4.2. Glycerol vs. Other Hydrogen Bond Donors

An issue of high significance pertaining to polyphenol extraction efficiency was raised by studies on testing glycerol, as well as other HBDs, on a comparative basis. Sodium acetate-based DES demonstrated to be more efficient solvents for the recovery of polyphenols from red grape pomace when combined with L-lactic acid as the HBD, whereas combinations with glycerol were of lower efficiency. Yet, glycerol/sodium acetate (5/1) outperformed L-lactic acid/sodium acetate (5/1) in total flavonoid extraction [84]. In another study, a series of DES based on glycerol and L-lactic acid as HBDs, and sodium citrate salts as HBAs, were synthesized and screened for their efficiency in extracting polyphenols from Salvia fruticosa Mill [83].

It was concluded that L-lactic acid was a more efficacious HBD, providing significantly higher total polyphenol yield. The same conclusion was reached when a glycerol/citric acid DES was compared with an ethylene glycol/citric acid DES, at identical HBD/HBA ratio, for the extraction of Hibiscus sabdariffa anthocyanins [85]. In opposition to these findings, a series of glycerol/sodium propionate DES were consistently more efficient in polyphenol extraction from onion solid wastes compared to L-lactic acid analogues [75].

5. Future Perspectives

By virtue of its low price, high availability, absence of toxicity, absence of flammability and absence of volatility, glycerol and glycerol-based DES appear as the ideal candidates for the development of polyphenol extractions processes with a strong sustainable profile. The evidence accumulated so far dictates that glycerol has a great potential in this regard and it could play key roles in pertinent industrial applications. On the other hand, constructive criticism associated with disadvantages that would possibly hamper a wide applicability of glycerol is of undisputed value, in fully assessing its usefulness as extraction solvent.

An issue that should be addressed is the high viscosity of glycerol and glycerol-based DES, which could lend handling of extracts problematic on industrial scale. Such a drawback could be overcome using water mixtures, and presumably blends with other eco-friendly solvents (e.g., ethanol). Such an approach would enable suitable fine-tuning of solvent viscosity with obvious practical benefit, since it could also regulate extraction selectivity, and hence purity of the product, without compromising extraction yield. Another shortcoming linked to glycerol is its low vapor pressure, which does not allow for solvent removal through evaporation, as in cases of volatile solvents. Although techniques such as solid-liquid extraction using e.g., resins or molecular sieves might appear attractive, the incorporation of additional unit operations in an extraction process would entail the risk of increased cost and energy, thus abrogating the green character of the whole procedure.

At this point, a “heretic” option of completely abolishing downstream processing might represent a strategy that should not be overlooked. Should glycerol be used first, as the extraction solvent and second, as part of the final product formulation, then solute recovery could be very effectively by-passed, offering a straightforward valorization of the extract. In this fashion, polyphenol-enriched extracts could be directly incorporated into foods/pharmaceuticals/cosmetics, the appropriate composition and concentration provided. This philosophy would become even more appealing, considering that current trends suggest ingredient production based on functionality rather than purity. Therefore, the extracts thus produced could be destined for specific applications rather than for general use. Advancement of research on such a conceptual basis might offer unprecedented opportunities for alternative glycerol uses and development of processes which can be effectively scaled-up to deliver neoteric industrial products through both profitable and sustainable routes.

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